Neuropsychiatric Symptoms and the Risk of Institutionalization and Death: The Aging, Demographics, and Memory Study

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OBJECTIVES: To examine the association between neuropsychiatric symptoms and risk of institutionalization and death.

DESIGN: Analysis of longitudinal data.

SETTING: The Aging, Demographics, and Memory Study (ADAMS).

PARTICIPANTS: Five hundred thirty-seven adults aged 71 and older with cognitive impairment drawn from the Health and Retirement Study (HRS).

MEASUREMENTS: Neuropsychiatric symptoms (delusions, hallucinations, agitation, depression, apathy, elation, anxiety, disinhibition, irritation, and aberrant motor behaviors) and caregiver distress were identified using the Neuropsychiatric Inventory. A consensus panel in the ADAMS assigned cognitive category. Date of nursing home placement and information on death, functional limitations, medical comorbidity, and sociodemographic characteristics were obtained from the HRS and ADAMS.

RESULTS: Overall, the presence of one or more neuropsychiatric symptoms was not associated with a significantly higher risk for institutionalization or death during the 5-year study period, although when assessing each symptom individually, depression, delusions, and agitation were each associated with a significantly higher risk of institutionalization (hazard rate (HR) = 3.06, 95% confidence interval (CI) = 1.09–8.59 for depression; HR = 5.74, 95% CI = 1.94–16.96 for clinically significant delusions; HR = 4.70, 95% CI = 1.07–20.70 for clinically significant agitation). Caregiver distress mediated the association between delusions and agitation and institutionalization. Depression and hallucinations were associated with significantly higher mortality (HR = 1.56, 95% CI = 1.08–2.26 for depression; HR = 2.59, 95% CI = 1.09–6.16 for clinically significant hallucinations).

CONCLUSION: Some, but not all, neuropsychiatric symptoms are associated with a higher risk of institutionalization and death in people with cognitive impairment, and caregiver distress also influences institutionalization. Interventions that better target and treat depression, delusions, agitation, and hallucinations, as well as caregiver distress, may help delay or prevent these negative clinical outcomes. **J Am Geriatr Soc 59:473–481, 2011.**

Key words: neuropsychiatric symptoms; caregiver distress; institutionalization; mortality

Neuropsychiatric symptoms such as agitation, depression, apathy, delusions, and hallucinations are highly prevalent in older adults with dementia and milder forms of cognitive impairment.[1–4] Population-based studies have estimated that 40% to 50% of individuals with cognitive impairment without dementia (CIND) or mild cognitive impairment (MCI) and 50% to 60% of those with dementia have at least one neuropsychiatric symptom, compared with 10% to 20% of those with normal cognitive function.[1–4] The pattern of presentation of individual neuropsychiatric symptoms differs between those with CIND and those with dementia, with psychotic symptoms and aberrant motor behaviors being more prevalent in people with dementia.[4] A greater number of neuropsychiatric symptoms was independently associated with functional limitations in those with CIND and dementia, even after controlling for severity of cognitive impairment and other potentially confounding factors.[4]

Neuropsychiatric symptoms have important implications for patients, families, and policymakers because they may lead to greater caregiver distress,[5,6] functional decline,[7–9] earlier institutionalization,[8–12] higher healthcare costs,[13–16] and greater risk of mortality.[8,17] One study found that the

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presence of any difficult symptoms or behaviors (e.g., psychotic symptoms, aggressive behaviors, wandering, waking up the caregiver at night) increased the likelihood of nursing home placement over 3 years of follow-up.[12] Other characteristics, including African-American race, Hispanic ethnicity, living alone, activity of daily living (ADL) limitations, and advanced cognitive impairment also increased the risk of nursing home placement. This study did not examine whether specific individual neuropsychiatric symptoms are more or less strongly associated with the risk of institutionalization. Other studies have suggested that agitation, hallucinations, and aberrant motor behaviors are associated with a higher risk of institutionalization, but these studies are difficult to interpret because of lack of adjustment for co-occurring symptoms.[8–11]

The results of studies examining the association between neuropsychiatric symptoms and mortality are mixed, probably because of differences in methodology.[8,9,11,17,18] Some studies suggest that hallucinations,[8] depression,[17] and wandering[18] are associated with higher mortality, although other studies did not find these associations.[9]

To better assess the relationship between neuropsychiatric symptoms and institutionalization and death, the current study used a nationally representative sample of older Americans to examine whether the presence of any neuropsychiatric symptoms, or particular individual symptoms, were associated with a higher risk of nursing home placement and death over 5 years of follow-up. It was hypothesized that the presence of particular individual symptoms, such as depression[17] and aberrant motor behaviors,[18] would be associated with these negative clinical outcomes, independent of the level of cognitive impairment.

METHODS

Conceptual Model for Higher Risk of Institutionalization in Older Adults with Neuropsychiatric Symptoms

The conceptual model underlying the analysis of the risk of institutionalization in older adults with neuropsychiatric symptoms is shown in Figure 1. Neuropsychiatric symptoms are common in people with CIND or MCI and dementia[1–4] and are probably associated with the brain pathology causing cognitive impairment.[19,20] Cognitive impairment and medical comorbidities in older adults are strongly associated with a higher risk of limitations in ADLs, which in turn are associated with greater risk of nursing home placement.[12] Neuropsychiatric symptoms may also be associated with a higher risk of functional limitations independent of cognitive impairment and chronic medical conditions.[4] It was hypothesized that neuropsychiatric symptoms lead to greater supervision time and emotional distress in family caregivers,[5,6] which may accelerate nursing home placement,[12] independent of the severity of functional limitations. Sociodemographic factors, including race and ethnicity, wealth, and insurance coverage for long-term care, may also increase the likelihood of nursing home placement.[12]

A similar conceptual model was developed for the possible association between neuropsychiatric symptoms and death (figure not shown). It was hypothesized that neuropsychiatric symptoms are associated with a higher risk of functional limitations,[4] risky behaviors, and eating problems, which may lead to greater risk of death, independent of cognitive impairment and medical comorbidities.

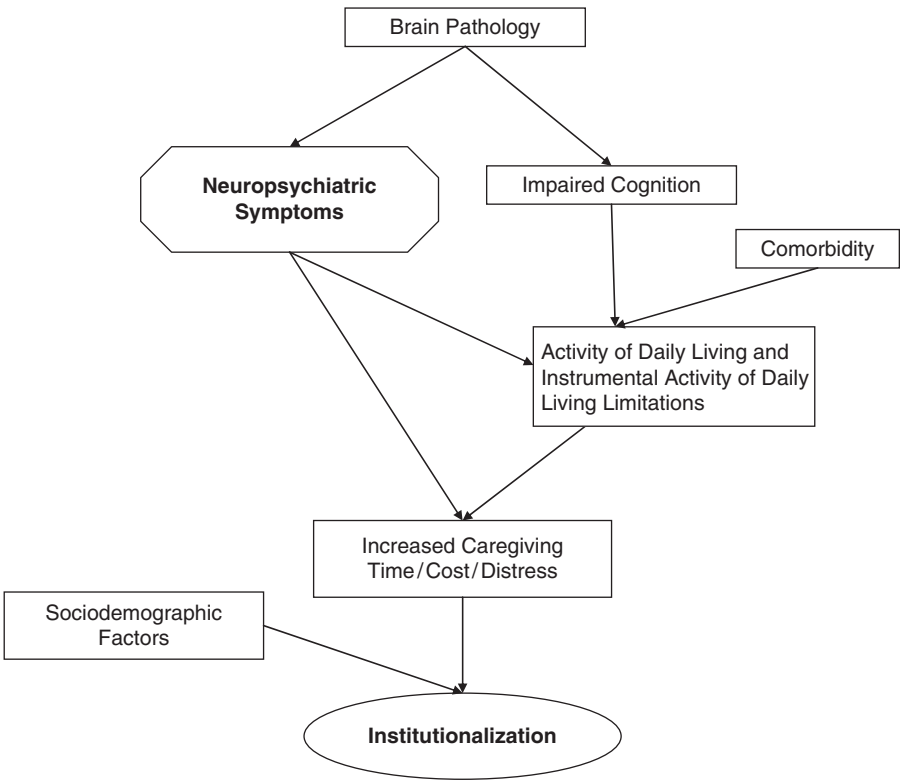

Figure 1. Conceptual model of higher risk of institutionalization in older adults with neuropsychiatric symptoms.

Sample

Data from the Aging, Demographics, and Memory Study (ADAMS) and the 2000, 2002, 2004, and 2006 waves of the Health and Retirement Study (HRS) were used. The HRS is an ongoing biennial longitudinal survey of a nationally representative cohort of more than 20,000 U.S. adults aged 51 and older who reside in the community and in nursing homes throughout the 48 contiguous United States.[21] The HRS sample is selected using a multistage area probability sample design, and population weights are constructed so that valid inferences can be drawn for the entire U.S. population aged 51 and older. Weights are constructed in a two-step process, in which the first step develops poststratified household weights using the initial sampling probabilities for each household, as well as birth year, race and ethnicity, and sex of household members. The second step uses these household weights to construct poststratified respondent-level weights scaled to yield weight sums corresponding to the number of individuals in the U.S. population as measured by the U.S. Census Bureau Current Population Survey for March in the year of data collection.[22] The National Institute on Aging sponsors the HRS, and the Institute for Social Research at the University of Michigan conducts is.

The ADAMS is a substudy of the HRS focused on identifying the prevalence and outcomes of cognitive impairment and dementia. The ADAMS sample was a stratified random subsample of 1,770 individuals aged 71 and older from five cognitive strata based on scores on the 35-point HRS cognitive scale (HRS cog)[23] or proxy assessments of cognition from the 2000 or 2002 wave of the HRS.[24] The ADAMS further stratified the three highest cognitive strata according to age (71–79 vs $\geq$80) and sex to ensure adequate numbers in each subgroup.[24] One hundred nine individuals (13%) in the ADAMS sample resided in nursing homes at the time of the ADAMS assessment. Population weights for nursing home residents were derived using data from the 2000 Census and the Centers for Medicare and Medicaid Services Minimum Data Set.[24] Full details of the ADAMS sample design and selection procedures are described elsewhere.[24–26] The initial assessments of ADAMS subjects occurred between July 2001 and December 2003, on average 13.3 $\pm$ 6.9 months after the most recent HRS interview. The study flow and additional details on participation rates have been reported previously.[26] A total of 856 of the 1,770 individuals selected for the sample (mean age 81.5) completed the initial ADAMS assessment (56% of subjects who were still alive). Sixteen individuals for whom the Neuropsychiatric Inventory (NPI) was not completed and 303 individuals with normal cognition (n = 537 for current analyses) were not included. To minimize the potential bias due to selective nonparticipation, a response propensity analysis was performed, and nonresponse adjustments to the ADAMS sample selection weights were developed.[24] Population sample weights were then constructed to take into account the probabilities of selection in the stratified sample design and to adjust for differential nonparticipation in the ADAMS.[24]

The ADAMS data are publicly available and can be obtained from the HRS Web site (http://hrsonline.isr.umich.edu). The institutional review boards at Duke University Medical Center and the University of Michigan approved all study procedures, and study participants or their surrogates provided informed consent.

Measurements

Cognitive Evaluation

In the ADAMS, a nurse and a neuropsychology technician assessed all participants at their residence for cognitive impairment. The full details of the assessment and diagnostic procedures are described elsewhere.[25,26] During the assessment, participants completed a battery of neuropsychological measures; a self-reported depression measure; a standardized neurological examination; a blood pressure measurement; collection of buccal deoxyribonucleic acid samples for apolipoprotein E (*APOE*) genotyping; and a 7-minute, videotaped segment covering portions of the cognitive status and neurological examinations. Proxy informants provided information about participants' cognitive impairment, functional limitations, neuropsychiatric symptoms, and medical history. Informants were usually spouses or children (73%) and lived with the participant in 53% of the cases. The ADAMS consensus expert panel of neuropsychologists, neurologists, geropsychiatrists, and internists reviewed all information collected during the in-home assessment and assigned cognitive diagnoses. Diagnoses were within three cognitive categories: normal cognitive function, CIND, and dementia. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised*,[27] and *Diagnostic and Statistical Manual of Mental Disorder, Fourth Edition*[28] criteria were used for diagnosis of dementia. CIND was defined as mild cognitive or functional impairment reported by the participant or informant that did not meet criteria for dementia or performance on neuropsychological measures that was below expectation and at least 1.5 standard deviations below published norms on any test within a cognitive domain (e.g., memory, orientation, language, executive function, praxis).

Participants with dementia were classified according to stage or severity using the Clinical Dementia Rating Scale (CDR),[29–31] a widely used assessment tool that stages the severity of dementia based on information obtained from the participant and informant during the evaluation. As in prior studies,[3,32] mild dementia was defined as CDR stage 0.5 or 1, moderate dementia as CDR stage 2, and severe dementia as CDR stages 3 to 5.

Neuropsychiatric Symptoms

The ADAMS assessed neuropsychiatric symptoms using the NPI. The NPI is a widely accepted measure of neuropsychiatric symptoms associated with cognitive impairment.[33,34] It collects information on symptoms during the past month in 10 domains—delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, and aberrant motor behaviors—using a structured interview of a knowledgeable informant. For each symptom reported by the informant, additional information is obtained on the frequency (4-point scale) and severity (3-point scale) of the symptom. Symptoms were defined as clinically significant if the product of the frequency and severity score of the reported symptom was 4 or higher.[35] Psychometric properties of the NPI have been previously

reported.[33] The NPI has been validated in prior studies and has been shown to have good reliability (Cronbach alpha 0.88 for internal consistency reliability).[33]

Caregiver Distress

In the NPI, caregivers were asked to rate the emotional or psychological distress they experienced in relation to each symptom they reported on a 6-point scale: 0 (not at all distressing), 1 (minimally distressing), 2 (mildly distressing), 3 (moderately distressing), 4 (severely distressing), 5 (very severely or extremely distressing).[34] The total score was used to identify overall caregiver distress and was included in the analytical models. Caregiver distress was categorized into four ordinal levels based on total score (0, 1–5, 6–10, $\geq$11). The psychometric properties (e.g., reliability, validity) of this scale have been assessed previously and found to be adequate.[34]

Determining Institutionalization, Mortality, and the Date of Outcomes

For respondents who reported living in a nursing home at the time of a follow-up survey, the time to admission was established by calculating the time from the ADAMS assessment until nursing home admission. Only the first nursing home admission was evaluated, so multiple nursing home stays were not addressed. In addition, admissions to a nursing home that were brief enough to be completed between surveys were not included.[36] Because older adults with terminal illness may enter a nursing home just before death, six participants who entered a nursing home within 1 month of death were excluded from the institutionalization analysis. The same method was used to compute the time from the ADAMS assessment until death. Participants were censored after 5 years of follow-up or at death.

Sociodemographic Characteristics

Data were obtained on participant age (71–79, 80–89, $\geq$90), sex, race (white, black, other), and years of formal education ($<$12, 12, $>$12 years) from the ADAMS. Household net worth was categorized according to quartile, and marital and living status (married or partnered living together, unmarried living with other, unmarried living alone, living in nursing home) were determined using data from the 2000 and 2002 waves of the HRS. Whether respondents had Medicaid or long-term care insurance was determined using data from the 2000 or 2002 waves of the HRS.

Functional Limitations

The ADAMS assessed the number of limitations in ADLs and instrumental ADLs (IADLs) using an informant questionnaire. ADLs assessed were getting across a room, dressing, bathing, eating, transferring, and toileting. IADLs assessed were preparing meals, going grocery shopping, making telephone calls, taking medications, and handling finances. The number of limitations was categorized using three ordinal levels (0, 1–2, 3) for ADLs and IADLs.

Chronic Medical Conditions

The HRS collects data on the presence of chronic medical conditions (heart disease, chronic lung disease, diabetes mellitus, cancer, musculoskeletal conditions, stroke, and psychiatric problems) in each wave of the survey.[37] Respondents report whether a physician has ever diagnosed each condition. Data on chronic conditions from the 2000 or 2002 wave of the HRS were used and included in the analysis as dichotomous variables.

Other Covariates

The ADAMS obtained detailed information regarding the medications that respondents were taking at the time of the interview. Antipsychotics, antidepressants, and cholinesterase inhibitors were chosen as medications potentially associated with nursing home placement and death, and dichotomous variables indicating their current use were included in the analyses.

Statistical Analysis

Sociodemographic characteristics, total number of neuropsychiatric symptoms and presence of individual neuropsychiatric symptoms were compared according to cognitive category using chi-square tests. Because one goal of the analysis was to identify whether the presence of any neuropsychiatric symptoms was independently associated with risk of institutionalization or death, separate Cox proportional hazards models with nursing home placement and death as the dependent variables were estimated to determine adjusted hazard ratios (HRs) for these outcomes over 5 years of follow-up. The analysis for the risk of institutionalization was adjusted for sociodemographic characteristics, long-term care insurance, and cognitive category. Whether caregiver distress mediated the significant relationship between neuropsychiatric symptoms and institutionalization and whether functional limitations confounded the relationship was also examined by also controlling for these variables. The analysis for mortality was adjusted for sociodemographic characteristics, medical comorbidities, relevant medications, and cognitive category. Similar Cox models were then estimated to examine whether individual neuropsychiatric symptoms were associated with higher risk of these clinical outcomes, adjusting for other co-occurring symptoms. Adjusted HRs were computed to compare the relative strength of the association of each neuropsychiatric symptom with 5-year institutionalization or death. To test the hypothesis that the level of cognitive impairment modifies the relationship between neuropsychiatric symptoms and these clinical outcomes, significant interactions between cognitive category and neuropsychiatric symptoms (e.g., total number of neuropsychiatric symptoms $\times$ cognitive category, presence of delusions $\times$ cognitive category) were tested for. None of these interaction terms was statistically significant, so they were not included in the final regression models. The analysis was repeated with the variables for clinically significant neuropsychiatric symptoms (frequency score times severity score $\geq$4), and these results were compared with those from the previous analyses for the presence or absence of any neuropsychiatric symptoms.

The proportional hazards assumption was assessed with graphical and goodness-of-fit testing procedures, and it was confirmed that it was not violated.[38] All analyses were weighted and adjusted for the complex sampling design (stratification, clustering, and nonresponse) of the ADAMS and the HRS.[23] STATA version 10.1 (Stata Corp, College Station, TX) was used for data analysis. All reported *P*-values are two-tailed, and $P<.05$ was considered statistically significant.

RESULTS

Characteristics of Study Sample

Table 1 shows the sociodemographic characteristics and the presence of neuropsychiatric symptoms of the study sample

Table 1. Sample Characteristics According to Cognitive Category

Characteristic	Cognitive Impairment without Dementia	Dementia			*P*-Value*
		Mild	Moderate	Severe	
	N (Weighted %)				
Sample†	238 (61.6)	153 (21.1)	64 (6.9)	82 (10.4)	
Age					<.001
71–79	94 (42.9)	36 (24.5)	13 (26.3)	10 (10.2)	
80–89	109 (44.7)	83 (61.3)	26 (35.5)	45 (70.1)	
≥90	35 (12.4)	34 (14.2)	25 (38.2)	27 (19.7)	
Sex					.006
Female	120 (54.5)	92 (58.1)	49 (77.7)	67 (83.1)	
Male	118 (45.6)	61 (41.9)	15 (22.3)	15 (16.9)	
Race					.16
White	173 (85.6)	105 (79.1)	49 (86.8)	64 (77.3)	
Black	52 (10.4)	42 (16.3)	11 (9.4)	14 (7.9)	
Other	13 (4.0)	6 (4.6)	4 (3.8)	4 (14.8)	
Education, years					.09
<12	143 (42.7)	100 (58.1)	34 (38.6)	40 (39.2)	
=12	53 (30.5)	33 (27.5)	14 (22.0)	21 (29.4)	
>12	42 (26.8)	20 (14.4)	16 (39.4)	21 (31.4)	
Household net worth quartile					.18
1 (low)	110 (37.5)	77 (53.2)	38 (45.1)	42 (56.7)	
2	60 (21.9)	37 (21.6)	11 (18.6)	15 (18.8)	
3	41 (21.5)	23 (14.6)	6 (24.7)	13 (11.0)	
4 (high)	27 (19.1)	15 (10.6)	9 (11.5)	12 (13.5)	
Living situation					<.001
Alone	79 (32.5)	53 (41.1)	19 (24.6)	11 (17.4)	
With spouse	105 (43.2)	46 (29.2)	11 (11.4)	11 (12.4)	
With others	44 (19.5)	40 (20.5)	16 (18.6)	18 (21.0)	
Nursing home	10 (4.8)	14 (9.2)	18 (45.4)	42 (49.2)	
Number of Neuropsychiatric Inventory symptoms					.002
0	151 (55.4)	71 (53.7)	17 (24.0)	21 (28.7)	
1	42 (21.1)	31 (20.9)	14 (21.7)	18 (17.4)	
≥2	45 (23.5)	51 (25.4)	33 (54.3)	43 (53.9)	
Delusions	7 (4.0)	16 (6.6)	21 (39.7)	20 (27.6)	<.001
Hallucinations	6 (2.2)	13 (6.8)	13 (30.6)	22 (20.6)	<.001
Agitation	27 (13.5)	29 (12.9)	20 (24.0)	34 (41.3)	.003
Depression	51 (29.5)	45 (25.1)	22 (35.9)	16 (28.9)	.77
Apathy	23 (14.4)	24 (13.2)	15 (24.7)	29 (42.0)	.001
Elation	1 (0.1)	0 (0)	0 (0)	4 (5.9)	<.001
Anxiety	19 (9.1)	29 (12.5)	20 (29.8)	12 (11.2)	.07
Disinhibition	9 (9.6)	14 (5.9)	11 (31.5)	10 (8.6)	.04
Irritation	29 (16.0)	23 (11.1)	13 (17.4)	17 (15.5)	.65
Aberrant Motor Behaviors	4 (2.4)	13 (10.7)	11 (13.0)	24 (31.0)	.001

* *P*-values were derived from the chi-square test for association between the indicated variable and the cognitive category.

† Values in parentheses are weighted percentages derived using the Aging, Demographics, and Memory Study (ADAMS) sample weights to adjust for the complex sampling design of the ADAMS.

stratified according to cognitive category (CIND, mild dementia, moderate dementia, severe dementia). Participants with more-advanced cognitive impairment were older, more likely to be female, and more likely to live in a nursing home. More-severe cognitive impairment was associated with greater risk of neuropsychiatric symptoms.

Neuropsychiatric Symptoms and 5-Year Risk of Institutionalization

Eighty-four individuals already living in a nursing home at the time of the ADAMS assessment were excluded from the present analyses, leaving a sample size of 453. Table 2 shows the results of Cox proportional hazards regression for the association between any neuropsychiatric symptoms (total number of symptoms, individual symptoms) and 5-year risk of institutionalization in participants with CIND and dementia. The first column of the table shows the adjusted HRs for 5-year risk of institutionalization in participants with neuropsychiatric symptoms compared with those without. Based on all NPI responses, participants with one or more neuropsychiatric symptoms did not have a significantly higher risk of institutionalization over the 5-year period than those without neuropsychiatric symptoms. Regarding specific neuropsychiatric symptoms, participants with depression had a significantly higher risk of institutionalization, controlling for the other co-occurring symptoms. This association was not diminished even after controlling for caregiver distress (second column). HRs of participants with delusions and depression increased substantially after controlling for functional limitations (third column).

Table 3 shows the results of Cox proportional hazards regression for the association between clinically significant neuropsychiatric symptoms and 5-year risk of institutionalization in participants with CIND and dementia. Regarding specific neuropsychiatric symptoms, participants with clinically significant delusions and agitation had a significantly higher risk of institutionalization, controlling for the other co-occurring symptoms. HRs of participants with clinically significant delusions and agitation were substantially lower after controlling for caregiver distress, suggesting mediation of this relationship through caregiver distress, whereas the HRs increased substantially after controlling for functional limitations (second and third columns, respectively).

Neuropsychiatric Symptoms and 5-Year Risk of Death

Table 4 shows the results of Cox proportional hazards regression for the association between neuropsychiatric symptoms and 5-year risk of death in participants with

Table 2. Presence of Any Symptoms and 5-Year Risk of Institutionalization

Characteristic	HR* (95% Confidence Interval)		
	Base Model	Adjusted for Caregiver Distress	Adjusted for Functional Limitations
Analysis for number of NPI symptoms			
0 NPI symptom	Reference	Reference	Reference
1 NPI symptom	2.55 (0.89–7.24)	3.20 (0.92–11.15)	2.47 (0.88–6.91)
≥2 NPI symptoms	2.81 (0.91–8.58)	4.36 (0.75–25.32)	2.71 (0.77–9.53)
Cognitive category	1.84 (1.15–2.49)	1.86 (1.19–2.93)	1.71 (1.06–2.77)
Caregiver distress	—	0.77 (0.43–1.36)	—
ADL limitations	—	—	0.73 (0.42–1.27)
IADL limitations	—	—	1.23 (0.77–1.99)
Analysis for individual NPI symptoms			
Delusions	2.95 (0.59–14.72)	2.93 (0.52–16.30)	4.26 (1.29–14.05)
Hallucinations	0.06 (0.01–0.75)	0.06 (0.00–0.73)	0.05 (0.00–0.62)
Agitation	1.27 (0.41–3.88)	1.26 (0.42–3.73)	1.52 (0.50–4.56)
Depression	3.06 (1.09–8.59)	3.03 (1.00–9.84)	3.47 (1.06–11.29)
Apathy	1.47 (0.24–8.83)	1.45 (0.17–11.83)	1.54 (0.42–5.64)
Elation†	—	—	—
Anxiety	0.33 (0.06–1.75)	0.33 (0.06–1.78)	0.10 (0.00–1.37)
Disinhibition	0.39 (0.07–1.95)	0.39 (0.06–2.33)	0.74 (0.17–3.09)
Irritation	0.81 (0.39–1.68)	0.79 (0.33–1.91)	1.18 (0.64–2.19)
Aberrant motor behaviors	3.76 (0.49–28.41)	3.73 (0.50–27.69)	4.78 (0.69–33.1)
Cognitive category	1.79 (1.06–3.03)	1.78 (1.12–2.84)	1.54 (0.88–2.68)
Caregiver distress	—	1.02 (0.43–2.41)	—
ADL limitations	—	—	0.58 (0.33–1.00)
IADL limitations	—	—	1.46 (0.87–2.45)

The model adjusted for cognitive category (cognitive impairment without dementia; mild, moderate, or severe dementia), sociodemographic characteristics, and long-term care insurance.

*Hazard ratio (HR) derived using a Cox proportional hazards regression model with 5-year risk of institutionalization as the dependent variable.

†Unable to estimate because of small sample size.

NPI = Neuropsychiatric Inventory; ADL = activity of daily living; IADL = instrumental activity of daily living.

Table 3. Clinically Significant Symptoms and 5-Year Risk of Institutionalization

Characteristic	HR* (95% Confidence Interval)		
	Base Model	Adjusted for Caregiver Distress	Adjusted for Functional Limitations
Analysis for number of NPI symptoms			
0 Clinically significant symptom	Reference	Reference	Reference
≥1 Clinically significant symptoms	2.36 (0.87–6.42)	2.77 (0.36–21.36)	2.30 (0.86–6.18)
Cognitive category	1.77 (1.27–2.47)	1.78 (1.27–2.50)	1.67 (1.08–2.57)
Caregiver distress	—	0.90 (0.40–2.01)	—
ADL limitations	—	—	0.75 (0.43–1.30)
IADL limitations	—	—	1.21 (0.79–1.85)
Analysis for individual NPI symptoms			
Delusions	5.74 (1.94–16.96)	3.87 (0.96–15.58)	7.13 (2.67–19.02)
Hallucinations	0.14 (0.01–2.68)	0.25 (0.00–8.75)	0.18 (0.01–4.36)
Agitation	4.70 (1.07–20.70)	3.41 (0.85–13.58)	5.77 (1.00–33.51)
Depression	2.09 (0.30–14.47)	1.41 (0.11–17.15)	1.44 (0.10–19.42)
Apathy	0.24 (0.08–0.74)	0.15 (0.04–0.60)	0.22 (0.08–0.63)
Elation†	—	—	—
Anxiety	0.32 (0.04–2.33)	0.21 (0.02–1.56)	0.24 (0.03–1.95)
Disinhibition	0.08 (0.00–1.40)	0.06 (0.00–0.74)	0.22 (0.02–1.91)
Irritation	0.52 (0.16–1.66)	0.35 (0.08–1.39)	0.49 (0.11–2.03)
Aberrant motor behaviors	2.99 (0.47–19.01)	2.37 (0.34–16.17)	3.29 (0.44–24.18)
Cognitive category	1.93 (1.27–2.93)	1.89 (1.27–2.81)	1.83 (1.13–2.98)
Caregiver distress	—	1.67 (0.71–3.95)	—
ADL limitations	—	—	0.94 (0.43–2.02)
IADL limitations	—	—	1.03 (0.60–1.76)

Clinically significant symptoms defined as a frequency score times severity score ≥4.

The model adjusts for cognitive category (cognitive impairment without dementia; mild, moderate, or severe dementia), sociodemographic characteristics, and long-term care insurance.

*Hazard ratio (HR) derived using a Cox proportional hazards regression model with 5-year risk of institutionalization as the dependent variable.

†Unable to estimate because of small sample size.

NPI = Neuropsychiatric Inventory; ADL = activity of daily living; IADL = instrumental activity of daily living.

CIND and dementia. The first column of the table shows the adjusted HRs for 5-year risk of death in participants with neuropsychiatric symptoms compared with those without. The second column of the table shows the adjusted HRs for 5-year risk of death in participants presenting with clinically significant symptoms compared with those without clinically significant symptoms. Based on all NPI responses, participants with one or more neuropsychiatric symptoms, even clinically significant symptoms, did not have a significantly higher 5-year risk of death than those without neuropsychiatric symptoms. Participants with the specific symptom of depression and those with clinically significant hallucinations had a significantly higher 5-year risk of death, controlling for the other co-occurring symptoms.

DISCUSSION

In this study using a nationally representative sample of older adults with CIND and dementia, total number of neuropsychiatric symptoms, even clinically significant symptoms, was not associated with risk of institutionalization or death over 5 years of follow-up, after adjusting for potentially confounding factors including severity of cognitive impairment, although as hypothesized, several particular neuropsychiatric symptoms—depression, delusions, and agitation—were strongly associated with a higher risk of nursing home placement or death, even after adjusting for the other co-occurring symptoms.

Regarding the association between neuropsychiatric symptoms and risk of institutionalization, these results are different from those of some prior studies, probably because of methodological differences. Two studies reported that participants with one or more difficult behaviors had a significantly higher risk of institutionalization (HR = 1.47, 95% CI = 1.10–1.97;[9] HR = 1.30, 95% CI = 1.11–1.52[12]) during their study periods (4.4 years;[9] 3 years[12]). These prior studies assessed the presence of fewer difficult behaviors (e.g., psychotic symptoms, wandering, and aggression) that might be more strongly associated with risk of institutionalization. In addition, less-complete adjustment for confounders and more statistical power in those prior studies may have contributed to the detection of a significant relationship. To the knowledge of the authors, the current study is the first one to examine the association between individual neuropsychiatric symptoms and risk of institutionalization while adjusting for other co-occurring symptoms. Prior studies suggested that hallucinations[8] and wandering[9] are associated with higher risk of nursing home placement.

The current study highlights the possible mediating roles of caregiver distress and functional limitations in the

Table 4. Neuropsychiatric Symptoms and 5-Year Risk of Death

Characteristic	Presence of Any Symptoms	Clinically Significant Symptoms*
	HR† (95% Confidence Interval)	
Analysis for number of NPI symptoms		
0 NPI symptom	Reference	Reference
1 NPI symptom	0.79 (0.53–1.17)	1.03 (0.73–1.45)
≥2 NPI symptoms	1.00 (0.66–1.51)	
Cognitive category	1.73 (1.47–2.02)	1.69 (1.42–2.02)
Analysis for individual NPI symptoms		
Delusions	0.88 (0.48–1.62)	0.84 (0.42–1.66)
Hallucinations	1.24 (0.74–2.07)	2.59 (1.09–6.16)
Agitation	0.91 (0.64–1.29)	0.95 (0.50–1.82)
Depression	1.56 (1.08–2.26)	1.61 (0.95–2.74)
Apathy	1.18 (0.65–2.16)	1.45 (0.83–2.52)
Elation	—	—
Anxiety	0.67 (0.35–1.27)	0.98 (0.52–1.86)
Disinhibition	0.57 (0.24–1.34)	0.38 (0.08–1.74)
Irritation	1.24 (0.73–2.11)	1.03 (0.57–1.86)
Aberrant motor behaviors	0.92 (0.50–1.66)	0.86 (0.48–1.56)
Cognitive category	1.77 (1.50–2.10)	1.65 (1.38–1.97)

The model adjusts for cognitive category (cognitive impairment without dementia; mild, moderate, or severe dementia), sociodemographic characteristics, relevant medications, and medical comorbidities.

* Clinically significant symptoms defined as a frequency score times severity score ≥4.

† Hazard ratio (HR) derived using a Cox proportional hazards regression model with 5-year risk of death as the dependent variable.

Unable to estimate because of small sample size.

NPI = Neuropsychiatric Inventory.

association between neuropsychiatric symptoms and risk of institutionalization. Depression was found to be associated with greater risk of institutionalization independent of caregiver distress, whereas caregiver distress mediated the association between clinically significant delusions and agitation and institutionalization. These findings suggest that some neuropsychiatric symptoms may increase the risk of institutionalization independent of the distress they cause caregivers. Functional limitations may confound the association bewteen some neuropsychiatric symptoms and the risk of institutionalization, probably because of their independent association with particular symptoms.[4]

The independent association between depression and institutionalization highlights the importance of identification and treatment of depression in older adults with cognitive impairment and dementia. The mediating role of caregiver distress between agitation and delusions and institutionalization suggests that interventions targeted at supporting caregivers and reducing caregiver burden when agitation and delusions are present in care recipients may be valuable to caregivers and patients.

Depression has been shown to be associated with greater risk of death.[17,39] The current study provides additional confirmation of this relationship, using the NPI to determine presence of depression. Cognitive impairment and depression may combine to increase mortality risk in older adults through pathways that include failure to thrive, frailty, poor chronic disease management, and social isolation.[17,40] Impairment of visuospatial and executive function have been shown to be associated with greater mortality and perhaps to mediate the association between depression and mortality through autonomic dysfunction.[41,42] As a prior study suggested, the current study found that clinically significant hallucinations were associated with mortality. This may be due to a residual confounding effect of severity of cognitive impairment or presence of delirium[43,44] and to greater mortality risk associated with dementia with Lewy bodies, a subtype of dementia characterized by frequent hallucinations.[45]

The strengths of this study include a nationally representative population-based sample that included the range of cognition in people with CIND or dementia, the use of a well-validated comprehensive assessment of neuropsychiatric symptoms, and the ascertainment of the date of important clinical outcomes by using longitudinal data from the HRS. A number of potential limitations should also be considered when interpreting the results. For the neuropsychiatric symptoms with low prevalence, a significant association may not have been detected because of low statistical power. There may be residual confounding due to omission of unmeasured factors related to neuropsychiatric symptoms and the outcomes, even though a wide range of potentially confounding factors were included. Measurement error may have occurred even though the NPI, which has good psychometric characteristics, was used.[33] Ascertainment of date of nursing home admission may also be subject to measurement error due to suboptimal reliability and recall bias.

In summary, these findings suggest that depression, delusions, and agitation are associated with greater risk of institutionalization in people with CIND and dementia, whereas depression and hallucinations are associated with greater risk of death. The association between delusions and agitation and risk of institutionalization may depend on the level of caregiver distress associated with these symptoms. Further studies should assess whether interventions to better target and treat these neuropsychiatric symptoms and caregiver distress in people with CIND and dementia may help delay or prevent these negative clinical outcomes.

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