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Neuropsychiatric symptoms as risk factors for progression from CIND to dementia: The Cache County Study

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Abstract

Objectives—To examine the association of neuropsychiatric symptom (NPS) severity with risk of transition to all-cause dementia, Alzheimer's disease (AD), and vascular dementia (VaD).

Design—Survival analysis of time to dementia, AD, or VaD onset.

Setting—Population-based study.

Participants—230 participants diagnosed with cognitive impairment, no dementia (CIND) from the Cache County Study of Memory Health and Aging were followed for a mean of 3.3 years.

Measurements—The Neuropsychiatric Inventory (NPI) was used to quantify the presence, frequency, and severity of NPS. Chi-square statistics, t-tests, and Cox proportional hazard ratios were used to assess associations.

Results—The conversion rate from CIND to all-cause dementia was 12% per year, with risk factors including an *APOE* 4 allele, lower MMSE, lower 3MS, and higher CDR sum-of-boxes. The presence of at least one NPS was a risk factor for all-cause dementia, as was the presence of NPS with mild severity. Nighttime behaviors were a risk factor for all-cause dementia and of AD, while hallucinations were a risk factor for VaD.

Conclusions—These data confirm that NPS are risk factors for conversion from CIND to dementia. Of special interest is that even NPS of mild severity are a risk for all-cause dementia or AD.

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Keywords

CIND; MCI; NPS; NPI; Cache County; dementia; depression; agitation; anxiety

Objective

There has been a notable increase in dementia prevalence driven by an aging population and an increased public awareness of its signs and symptoms¹. This increase has been accompanied by the appreciation that there are individuals with cognitive impairment at a severity level insufficient for a diagnosis of dementia. The terms “Cognitive Impairment, No Dementia” (CIND) and “Mild Cognitive Impairment” (MCI)² have been used to describe these individuals, many of whom are in the prodromal stages of dementia. Specifically, the amnesic form of MCI (aMCI) has been documented as a prodrome of Alzheimer's dementia (AD)³.

In community samples, transition from CIND/MCI to dementia occurs (on average) in 12-15% per year, although these rates vary⁴. Proposed risk factors for transition to dementia include cardiovascular variables⁵, stroke⁶, and *APOE* 4 status⁷. There is a growing interest in identifying indicators that predict a greater likelihood of transition to dementia from CIND or MCI. The hope is to define objective ways to identify patients most likely to transition to dementia as well as clues on how to target specific treatments earlier.

Neuropsychiatric symptoms (NPS) are nearly universal in dementia through the course of illness⁸. As a result, and because NPS are associated with a worse prognosis in dementia⁹, the occurrence of NPS in MCI/CIND has become of interest to clinicians and researchers. In a recent population-based study using data from the Cache County Study of Memory Health and Aging (CCSMHA), we estimated the prevalence of NPS in individuals with CIND and MCI¹⁰. Thirty-one percent of participants with CIND had at least one NPS, a rate halfway between that in the cognitively normal (15%) and those with dementia (60%). These rates are comparable to those reported in the Cardiovascular Health Study¹¹ and by Geda et al¹². A subgroup analysis comparing participants with aMCI to those with other types of CIND showed no significant differences. Using data from the National Alzheimer Coordinating Center (NACC), the largest MCI cohort to date, Rosenberg et al. (2010) similarly found relatively few differences in NPS between aMCI and non-amnesic MCI (non-aMCI) but executive dysfunction was associated with depression, anxiety, agitation, disinhibition, irritability, and sleep problems.

In addition to being highly prevalent in MCI/CIND, several studies have linked NPS in CIND/MCI to dementia conversion^{7, 13-15}. Modrego et al¹⁶ reported that major depression doubled the risk of transition from MCI to dementia, while a report from the Kungsholmen project suggested a doubling of transition risk with increasing levels of anxiety¹⁷.

In this follow-up to our original study of NPS in CIND/MCI using the CCSMHA, we estimate hazard of transition to all-cause dementia by overall total NPS severity, for individual NPS, and for NPS in the mood or psychosis domains. We repeat the above for AD or vascular dementia (VaD), and again for the subgroup of patients diagnosed with aMCI.

Methods

Sampling, Screening, and Procedure

The present study utilized data from the third and fourth triennial waves of dementia ascertainment in Cache County, Utah (Figure 1). The methods of the CCSMHA have been detailed extensively elsewhere^{18, 19}. Briefly, all permanent residents of the county who were 65 years or older in January 1995 (n=5677) were invited into the study. We enrolled 5092 (90%) in Wave 1, all of whom were screened for dementia in a multi-staged assessment protocol. The first stage of screening involved either a revised version of the Modified Mini-Mental State Exam (3MS)^{20, 21} or, for those unable to complete testing, the Informant Questionnaire of Cognitive Status in the Elderly²². Those scoring below the pre-determined education and sensory-adjusted score were selected for an informant-based interview which assessed clinical symptoms consistent with dementia²³. Informed consent was obtained at each interview, directly from the participant for cognitively capable individuals (as determined by score on 3MS and clinical judgment), or from a knowledgeable informant otherwise, typically the next-of-kin. Institutional review boards at Utah State University, Duke University, and The Johns Hopkins University approved and oversaw all study procedures.

Participants whose informant interviews were suggestive of dementia or a prodrome, were selected to undergo a clinical assessment with a trained research nurse and a neuropsychological technician. A designated subsample was created at Wave 1 to match each identified case of AD at a 2:1 ratio, matched on age, gender and *APOE* 4 genotype group, except for participants aged 65-74, whom were matched at a 4:1 ratio¹⁸. Due to attrition, additional individuals were selected in Wave 3 to “replenish” the designated subsample. Given the expanded focus of the study in Waves 3 and 4 on mild cognitive impairment as well as dementia, additional designated subsample members were randomly selected to yield a 2:1 ratio of controls to cases, defined as all-cause dementia, “mild/ambiguous/prodromal AD,” or MCI-Peterson diagnoses, with 100% sampling of all persons aged 85 or older.

The clinical assessment consisted of neuropsychological assessment²⁴, brief physical exam, and informant interview of the development and course of any clinical symptoms. A geropsychiatrist and neuropsychologist, with members of the examination team, reviewed results and assigned preliminary diagnoses of dementia or CIND. The diagnostic panel members were sensitive to the overlapping nature of dementia/CIND and depression, differentiating the two based on the different syndromes found in each.

Dating of age at dementia onset was based on review of the chronology of symptoms and dementia severity using the Clinical Dementia Rating²⁵ (CDR) as a guide. Participants who met *DSM-III-R* criteria for dementia²⁶ or prodromal AD were selected to undergo an MRI scan and laboratory studies to rule out non-degenerative pathology that could explain the present cognitive symptoms. Furthermore, those carrying a dementia diagnosis were invited to complete an exam by a geriatric psychiatrist. Diagnoses of AD, VaD, CIND, aMCI, and other forms of dementia were made by an interdisciplinary geropsychiatric team as previously described²⁷. Diagnosis of AD was made according to NINCDS-ADRDA criteria²⁸. Vascular dementia diagnoses followed the NINDS-AIREN criteria²⁹. Other dementia diagnoses included: diffuse Lewy body dementia, Parkinson's Disease, frontotemporal dementia, traumatic brain injury, alcoholic dementia, and dementia of undetermined etiology. These were rarely the primary diagnosis and are hence not assessed as a subgroup in the current analysis. Participants with dementia at baseline were excluded prior to application of the diagnostic algorithm for CIND/MCI.

CIND diagnosis was assigned according to the criteria used in the Canadian Study of Health and Aging³⁰. Diagnosis required either self report or an informant report of cognitive decline from a previous level of function and objective documentation of decline in a minimum of one of the following domains: memory, executive function, language, or visuospatial function. Operationally, decline was classified as 1.5 standard deviations below normative mean values corrected for age and education. Level of impairment could not rise to the level of dementia, operationalized as significant functional change exceeding a CDR level of 0.5. aMCI participants met the published criteria for at least one of: mild ambiguous/prodromal AD⁷, MCI by Petersen³¹, and/or MCI by CDR criteria¹³. The categories were not mutually exclusive. These subtypes were grouped together due to their use as the CIND types most predictive of conversion to AD. We did not have adequate sample sizes to evaluate each CIND subtype separately. By definition, participants that did not qualify for a diagnosis of CIND or dementia were assigned a CDR rating of 0.

Individuals with a designation of dementia or mild ambiguous prodromal AD were invited to complete an 18-month follow-up clinical assessment and expert panel review to confirm diagnoses ("conversion" from CIND to dementia could thus have occurred between the Wave 3 and 18-month follow-up clinical assessment, or between the latter and the Wave 4 clinical assessment). Participants without dementia at the end of each wave were eligible for participation in the subsequent wave. Mean time of follow-up was 3.3 years. In both Waves 3 and 4, the 3MS cut score was raised (to increase the sensitivity for identification of mild cognitive syndromes), the second screening stage of informant interview was eliminated (as this information was gathered at the third stage, or clinical assessment), and the designated subsample was replenished as discussed above. (Wave 2 3MS cut score: 86/87 for subjects aged <80 and 83/84 for subjects aged 80+; Wave 3 and Wave 4 3MS cut score: 90/91 for all ages).

Because the detailed neuropsychiatric Inventory (NPI)³² and detailed diagnoses of CIND were not rendered until the third study wave, the final sample for the present investigation included only those study participants who completed the NPI at the clinical assessment in wave 3 (considered "baseline" here) and wave 4 (see Figure 1 flow chart).

Assessment of Neuropsychiatric Symptoms

Neuropsychiatric symptoms were evaluated at the clinical assessment using the NPI. No other measures of NPS were used as the NPI is a systematic way to measure multiple NPS domains. The research nurse interviewed a knowledgeable informant about the presence of 12 specific domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, disturbances of sleep, and disturbances of appetite/eating. The presence of symptoms in each domain during the past 30 days was queried with a screening question. If this was endorsed, specific follow up questions were asked to clarify the nature of the symptoms, and their frequency, severity, degree of change from premorbid, and treatment. As in previous studies^{11, 12}, the NPS outcome variable was defined as either the presence or absence of a given NPS domain. The NPI was also analyzed by dividing into absence of any NPS versus 1 NPS (NPI Total). NPI severity was calculated at three levels: no NPS, at least one NPS but no NPS at a severity level 4, at least one NPS at a severity level 4 (NPI Severity). Lastly, the NPI mood domains (depression, anxiety, apathy, and irritability) and NPI psychosis (delusions and hallucinations) domains were analyzed as separate groups.

Analysis

The present analyses were carried out using STATA(SE) Version 10.1. T-test and ² analyses, as appropriate, were used to compare baseline demographics in CIND patients

from Wave 3 who had follow-up to those who did not, as described above, at Wave 4. Significance was set at a p-value <0.05. Given the multiple comparisons performed, a p-value of 0.005 was considered significant for the individual NPS contrasts. Bivariate Cox proportional hazards ratio (HR) analyses were estimated for baseline characteristics, with the time variable defined as time from CIND diagnosis to dementia onset, and the failure variable being onset of all-cause dementia, or in other analyses AD or VaD. Years at risk were calculated from baseline to last follow-up or a diagnosis of dementia, AD, or VaD. The analyses of AD and VaD excluded other forms of dementia and compared participants who developed AD or VaD with those who did not develop any dementia over the follow-up period.

Multi-variable models (adjusted for age, education, *ApoE* status, and 3MS) were used to analyze each of the NPS (same time variable and failures as above). Multi-variable models (same adjustments as above) were calculated for presence/absence of any single NPS, total NPI severity, and the mood/psychosis domains of the NPI.

In addition, we used t-tests and χ^2 to compare the 230 cases of CIND that made up the final sample with the 249 participants who did not have complete follow-up at wave 3 and wave 4 and were excluded in the final sample. There were no baseline differences between the two groups (results not shown).

Results

Table 1 displays demographic data for those who converted to all-cause dementia from CIND, and those who did not convert. Those who converted had lower scores on the MMSE or 3MS and higher scores on the CDR sum-of-boxes (CDR-SB).

Table 2 displays the past 30-day prevalence of NPS by NPI domain in individuals with CIND who did not convert to dementia, compared to those who converted to all-cause dementia, AD, and/or VaD. Statistical comparisons of converters to non-converters were non-significant unless noted below. Among those converting to all-cause dementia, only appetite/eating disturbances were significantly more common at baseline than in non-converters ($\chi^2=5.86$ p=0.016, df=1). In participants who converted to VaD, hallucinations were significantly more common at baseline ($\chi^2=4.68$, p=0.031, df=1).

Table 3 displays HRs for conversion. For all-cause dementia, significant HRs were observed for increasing age, presence of at least one *APOE* 4 allele, lower MMSE or 3MS scores, and higher CDR-SB scores. For AD, significant HRs were observed for increasing age, the presence of at least one *APOE* 4 allele, lower 3MS scores, and higher CDR-SB. For VaD, significant HRs were observed for lower MMSE scores and higher CDR-SB.

Table 4 displays HRs for individual NPS. For all-cause dementia and AD, a significant HR was observed only for nighttime behaviors. The nighttime behaviors included difficulty falling asleep, early morning awakening, and wandering during the night. For VaD, a significant HR was observed only for hallucinations. The hallucinations assessed by NPI include experiencing sensations in the auditory, visual, olfactory and tactile modalities or other unusual sensory experiences from things that are not present or experienced by others. After adjustment, nighttime behaviors were significant predictors (p<0.005), whereas hallucinations were not.

Table 5 displays HRs for the presence/absence of at least one NPS, NPI severity, and the subgroup of NPS related to mood. The sum of psychosis domains of the NPI were also analyzed, but prevalence was rare and comparisons were non-significant (data not shown). Significant HRs for all-cause dementia were seen for the presence of at least one NPS and

for the presence of overall NPI domain severities. No significant HRs were observed for AD or VaD only, although this was likely due to low power.

Restricting the analyses to participants with aMCI (n=104), significantly lower MMSE (t -test stat=3.21, $p=0.001$, $df=102$) and 3MS (t -test stat=2.04, $p=0.02$, $df=102$) scores were seen in converters. χ^2 for the individual NPS were limited by the small number of individuals with aMCI who displayed each NPS. Significant χ^2 were seen for increased prevalence of: nighttime behavior ($\chi^2=3.86$, $p<0.05$, $df=1$) in those converting to all-cause dementia, nighttime behaviors in those converting to AD ($\chi^2=4.45$, $p=0.035$, $df=1$), and for hallucinations in those converting to VaD ($\chi^2=5.82$, $p=0.016$, $df=1$).

The baseline demographic comparisons for the aMCI subgroup showed similar results to those for all CIND. Significant predictors of all-cause dementia were age (HR=1.06, 95% CI 1.01-1.12, $\chi^2=5.76$, $p=0.016$, $df=1$), MMSE (HR=0.86, 95% CI 0.79-0.95, $\chi^2=9.05$, $p=0.003$, $df=1$), 3MS (HR=0.96, 95% CI 0.94-0.99, $\chi^2=5.30$, $p=0.02$, $df=1$), and CDR sum-of-boxes (CDR-SB) (HR=1.14, 95% CI 1.00-1.29, $\chi^2=2.94$, $p=0.049$, $df=1$). Significant predictors for AD were age (HR=1.08, 95% CI 1.02-1.15, $\chi^2=7.19$, $p=0.007$, $df=1$) and the presence of at least one *APOE* 4 allele (HR=2.09, 95% CI 1.12-3.88, $\chi^2=5.21$, $p=0.02$, $df=1$). Significant HRs were seen in those converting to VaD for MMSE (HR=0.78, 95% CI 0.62-0.98, $\chi^2=3.94$, $p=0.047$, $df=1$).

Among aMCI participants, individual NPS, presence/absence of single NPS, NPI severity, or the sum of the NPI mood or NPI psychosis domains were not risk factors for dementia or AD.

Discussion

We report that NPS even at low severity increase risk of transition from CIND to dementia. We observed a conversion rate from CIND to dementia of 12% per year, similar to the rates observed in prior studies¹⁴. We did not observe similar associations for conversion from aMCI to dementia. We recently reported that the prevalence of NPS in aMCI is comparable to CIND¹⁰, so the lack of significant results for the aMCI subgroup analysis is likely a result of inadequate sample size.

The characteristics associated with an increased risk of transition from CIND to all-cause dementia are not new, including known clinical risk factors for dementia incidence (older age, presence of an *APOE* 4 allele) and evidence of greater cognitive and functional impairment (lower MMSE, lower 3MS, and higher CDR-SB). The presence of at least one *APOE* 4 allele was also a risk factor for conversion to AD, but not to VaD, supporting its specificity to AD. The higher conversion risk associated with a higher CDR-SB was significant for all three dementia incidences analyzed: all-cause, AD, and VaD. It was the only of the baseline clinical measures to have this predictive power (i.e. MMSE, 3MS, and raw CDR score did not).

It is noteworthy that mild NPS severity had a HR for transition from MCI to dementia that was larger than for greater severity. The predictive value of individual NPS was limited to the novel finding that nighttime behaviors were a risk factor for all-cause dementia. Hallucinations were a risk factor for VaD, but given the small number of individuals experiencing hallucinations, this finding warrants replication. Given the prominence of NPS in both CIND and dementia, we were surprised that the predictive nature of individual NPS was poor.

Strengths / Limitations

The strengths of this study include its sample size, state of the art (for population studies) measurement of neuropsychiatric symptoms, and the carefully determined diagnoses of CIND/MCI. In addition, this is a study with a high participation rate among those with CIND. In terms of limitations, is the fact that NPI utilizes data provided by the caregiver, not the patient. In addition, the NPI has not been validated for use in MCI patients. Also, the Cache County population is predominantly Caucasian, possibly limiting generalizability to other populations. One limitation of the analyses is that although our assignment of age of onset for CIND and dementia was based on a review of the chronology of symptoms, it is still approximately +/- 1 year.

Conclusions/Implications

Previous studies report that NPS are prevalent in all types of CIND, including aMCI, and predict dementia conversion. We confirm this in another population study. Specific individual NPS were risk factors for progression to dementia, in particular nighttime behaviors. As with other studies of CIND/MCI patients, the ultimate hope is that identification of those individuals most at risk for dementia conversion can improve prognosis and may suggest new therapeutic avenues.

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Abbreviations

3MS	modified mini-mental state exam
AD	Alzheimer's dementia
aMCI	amnesic mild cognitive impairment
CCSMHA	Cache County Study of Memory Health and Aging
CIND	cognitive impairment, no dementia
CDR	clinical dementia rating
CDR-SB	clinical dementia rating sum-of-boxes
CI	confidence interval
HR	hazard ratio
MCI	mild cognitive impairment
MMSE	mini-mental state exam
NACC	National Alzheimer's Coordinating Center
Non-aMCI	non-amnesic mild cognitive impairment
NPI	neuropsychiatric inventory
NPS	neuropsychiatric symptoms
NS	non-significant
VaD	vascular dementia

Figure 1. Cache County and Current Study Design

1. CIND: cognitive impairment, no dementia; 2. aMCI: amnesic cognitive impairment.

Table 1
Baseline Demographic and Population Descriptors of Participants

Characteristic	MEAN (SD) / NO. (%)			T-Test or Chi2*			MEAN (SD) / No. (%)			T-Test or Chi2*		
	All CIND ¹	Converters	Non-Converters	Statistic	P Value	Df [^]	All CIND ¹	Converters	Non-Converters	Statistic	P Value	Df [^]
Age, mean, y	81.9 (5.1)	82.7 (5.1)	81.4 (5.1)	-1.89	0.060	228	26.3 (2.6)	25.6 (2.9)	26.7 (2.4)	3.11	0.002	227
Gender, no.				0.47	0.495	1	87.4 (6.9)	85.4 (7.3)	88.5 (6.4)	3.39	<0.001	228
Male	115 (50.0)	45 (52.9)	70 (48.3)				CDR ⁵ , no.					
Female	115 (50.0)	40 (47.1)	75 (51.7)				0	3 (3.5)	17 (11.7)			
Education, mean, y	13.4 (3.1)	13.6 (3.3)	13.3 (3.1)	-0.758	0.4494	228	0.5	80 (94.1)	126 (86.9)			
GMHR ² , no.				1.556	0.459	2	1	2 (2.4)	2 (1.4)			
Poor/Fair	68 (29.6)	26 (30.6)	42 (29.0)				2+	0 (0.0)	0 (0.0)			
Good	129 (56.1)	50 (58.8)	79 (54.5)				CDR-SB ⁶ , mean					
Excellent	33 (14.3)	9 (10.6)	24 (16.5)				1.30 (1.3)	1.66 (1.4)	1.08 (1.2)	-3.2986	0.0006	226
ApoE Genotype, % ^{4/x}	82 (35.7)	35 (41.2)	47 (32.4)	1.51	0.2188	1						

¹ CIND: cognitive impairment, no dementia;

² GMHR: General Medical Health Rating scale;

³ MMSE: mini-mental state exam;

⁴ ₃MS: modified mini-mental state exam;

⁵ CDR: clinical dementia rating;

⁶ CDR-SB: CDR sum-of-boxes;

* T-Test if mean and Chi2 if proportion;

[^] .degrees of freedom.

Table 2

Neuropsychiatric Symptoms by NPI² Domain at Baseline

NPI ² Domain	No. (%)				
	All CIND ¹ (n= 228)	Non-Converters (n=145)	Patients w/ CIND ¹ who converted to:		
			All Dementia (n=83)	Alzheimer's Dementia (n=58)	Vascular Dementia (n=13)
Delusions	1 (0.4)	0 (0)	1 (1.2)	1 (1.8)	0 (0)
Hallucinations	2 (0.8)	1 (0.7)	1 (1.2)	0 (0)	1 (7.7)
Agitation/Aggression	7 (3.1)	3 (2.1)	4 (4.8)	3 (5.3)	1 (7.7)
Depression/Dysphoria	40 (17.5)	24 (16.6)	16 (19.3)	8 (14.0)	3 (23.1)
Anxiety	11 (4.8)	9 (6.2)	2 (2.4)	1 (1.8)	0 (0)
Elation/Euphoria	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Apathy/Indifference	21 (9.2)	14 (9.7)	7 (8.4)	3 (5.3)	2 (15.4)
Disinhibition	1 (0.4)	1 (0.7)	0 (0)	0 (0)	0 (0)
Irritability/Lability	23 (10.1)	14 (9.7)	9 (10.8)	3 (5.3)	2 (15.4)
Motor Disturbance	1 (0.4)	0 (0)	1 (1.2)	1 (1.8)	0 (0)
Nighttime Behaviors	19 (8.3)	11 (7.6)	8 (9.6)	6 (10.5)	2 (15.4)
Appetite/Eating	5 (2.2)	1 (0.7)	4 (4.8)	2 (3.5)	0 (0)

¹ CIND: cognitive impairment, no dementia;² NPI: neuropsychiatric inventory.

Table 3
Hazard Ratios (HR) for Demographic and Population Descriptors of Participants (bivariate model)

Characteristic	CIND ¹ participants who progressed to:											
	All Dementia (n=85) [*]				Alzheimer's Dementia (n=58) [*]				Vascular Dementia (n=13) [*]			
	HR	95% CI	2	P Value	HR	95% CI	2	P value	HR	95% CI	2	P Value
Age (yrs)	1.05	1.01-1.10	6.40	0.011	1.08	1.02-1.13	8.69	0.003	1.05	0.94-1.16	0.74	0.389
Gender (male)	1.08	0.71-1.66	0.13	0.718	0.73	0.43-1.22	1.46	0.227	1.49	0.48-4.56	0.49	0.483
Education (yrs)	1.01	0.95-1.09	0.17	0.676	1.00	0.92-1.09	0.00	0.981	0.91	0.75-1.10	1.00	0.317
GMHR ²	0.86	0.62-1.20	0.76	0.386	1.09	0.73-1.62	0.18	0.673	0.54	0.22-1.33	1.87	0.172
APOE Genotype: 4/x vs. other	1.58	1.02-2.44	4.06	0.044	2.09	1.24-3.52	7.47	0.006	1.09	0.34-3.55	0.02	0.885
MMSE ³	0.88	0.82-0.95	9.65	0.002	0.93	0.84-1.02	2.46	0.117	0.79	0.66-0.95	5.74	0.017
3MS ⁴	0.96	0.94-0.98	11.0	<0.001	0.97	0.94-0.99	4.28	0.039	0.98	0.92-1.05	0.20	0.658
CDR ⁵	1.74	0.92-3.28	2.20	0.138	1.69	0.77-3.72	1.32	0.251	2.54	0.73-8.86	1.31	0.253
CDR-SB ⁶	1.17	1.07-1.28	8.54	<0.001	1.14	1.01-1.29	3.54	0.029	1.24	1.03-1.51	2.99	0.027

^{*} For all of the above analyses, degrees of freedom is one.

¹ CIND: cognitive impairment, no dementia;

² GMHR: General Medical Health Rating scale;

³ MMSE: mini-mental state exam;

⁴ 3MS: modified mini-mental state exam;

⁵ CDR: clinical dementia rating;

⁶ CDR-SB: CDR sum-of-boxes.

Table 4

Hazard Ratios (HR) for NPI Domains of CIND Participants who Progressed to Dementia (multivariate model controlled for age, education, *APOE* status, and 3MS).

	CIND ¹ participants who progressed to:													
	All Dementia (n=85) [*]							Alzheimer's Dementia (n=58) [*]						
	HR	95% CI	Z	P Value	HR	95% CI	Z	P value	HR	95% CI	Z	P Value	Vascular Dementia (n=13) [*]	
NPI ² Domain														
Delusions	0.82	0.22-2.99	-0.30	0.761	0.95	0.35-2.63	-0.09	0.928	--	--	--	--	--	--
Hallucinations	1.75	0.24-12.8	0.55	0.583	--	--	--	--	10.1	1.1-91.1	2.05	0.04		
Agitation/Aggression	1.44	0.53-3.95	0.71	0.479	1.53	0.47-4.93	0.71	0.476	2.54	0.32-19.9	0.89	0.374		
Depression/Dysphoria	1.10	0.63-1.92	0.33	0.741	0.77	0.36-1.64	-0.68	0.497	1.76	0.47-6.56	0.85	0.398		
Anxiety	0.55	0.13-2.25	-0.83	0.404	0.43	0.06-3.11	-0.84	0.401	--	--	--	--	--	--
Elation/Euphoria	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Apathy/Indifference	0.93	0.43-2.02	-0.19	0.850	0.58	0.18-1.87	-0.91	0.365	1.76	0.39-8.08	0.73	0.464		
Disinhibition	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Irritability/Lability	0.99	0.49-1.98	-0.04	0.971	0.47	0.15-1.51	-1.27	0.206	1.53	0.34-6.96	0.55	0.581		
Motor Disturbance	3.51	0.45-27.4	1.20	0.231	5.33	0.65-43.7	1.56	0.119	--	--	--	--	--	--
Nighttime Behaviors	1.28	1.08-1.52	2.78	0.005	1.34	1.12-1.60	3.19	0.001	1.17	0.59-2.29	0.45	0.656		
Appetite/Eating	1.25	0.99-1.59	1.89	0.058	1.26	0.98-1.64	1.79	0.074	--	--	--	--	--	--

^{*} For all of the above analyses, degrees of freedom is five.

¹ CIND: cognitive impairment, no dementia;

² NPI: neuropsychiatric inventory;

“--” signifies a HR that could not be calculated due to inadequate sample size.

Table 5

Hazard Ratios (HR) for NPI subsets in CIND Participants who Progressed to Dementia (multivariate model controlled for age, education, *APOE* status, and 3MS).

Mean (SD) / No. (% row)			Hazard Ratios (controlled for age, APOE status, 3MS)															
Non -Converters (NC) (n=145)			Patients w/ CIND ^I who converted to:						Patients w/ CIND ^I who converted to:									
			All Dementia (n=85)			Alzheimer's Dementia (n=58)			Vascular Dementia (n=13)			Dementia – All (n=85) [*]			Alzheimer's Dementia (n=58) [*]			Vascular Dementia (n=13) [*]
Characteristic			HR	95% CI	Z	P Value	HR	95% CI	Z	P Value	HR	95% CI	Z	P Value	HR	95% CI	Z	P Value
NPI ² Total, no.			1.65	1.06-2.56	2.21	0.027	1.39	0.80-2.40	1.16	0.244	1.72	0.56-5.34	0.94	0.347				
	0	107 (68.2)	50 (31.8)	37 (23.5)	8 (8.3)													
	1 Domain	38 (52.1)	35 (47.9)	21 (28.8)	5 (6.8)													
NPI Severity																		
	None = 0	107 (68.2)	50 (31.8)	37 (23.5)	8 (8.3)		**Analyses for NPI, severity: minor vs. none & major vs. none**											
	Minor (no domain 4)	26 (51.0)	25 (49.0)	14 (27.5)	3 (5.9)		1.65	1.01-2.69	1.99	0.047	1.31	0.70-2.46	0.84	0.404	1.41	0.37-5.39	0.50	0.616
	Major (1 domain 4)	12 (60.0)	8 (40.0)	6 (30.0)	2 (10.0)		1.24	0.58-2.66	0.56	0.576	1.27	0.52-3.08	0.53	0.596	3.19	0.63-16.2	1.40	0.162
	NPI, mood domain ³ , mean	0.42 (0.82)	0.41 (0.64)	0.26 (0.48)	0.54 (0.88)		0.98	0.75-1.29	-0.14	0.890	0.75	0.49-1.14	-1.35	0.176	1.22	0.68-2.21	0.67	0.505

^{*} For all of the above analyses, degrees of freedom is five.

¹ CIND: cognitive impairment, no dementia;

² NPI: neuropsychiatric inventory;

³ Based on sum of 4 mood domains of the NPI (depression, anxiety, apathy, irritability).