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Risk factors for behavioral abnormalities in mild cognitive impairment and mild Alzheimer's disease

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Abstract

Background—Behavioral symptoms are common in both MCI and AD.

Methods—We analyzed the Neuropsychiatric Inventory Questionnaire data of 3456 MCI and 2641 mild AD NACC participants. Using factor analysis and logistic regression we estimated the effects of age, sex, race, education, MMSE, functional impairment, marital status and family history on presence of behavioral symptoms. We also compared the observed prevalence of behavioral symptoms between amnestic and nonamnestic MCI.

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Results—Four factors were identified: affective behaviors (depression, apathy and anxiety); distress/tension behaviors (irritability and agitation); impulse control behaviors (disinhibition, elation and aberrant motor behavior), and psychotic behaviors (delusions and hallucinations). Male gender was significantly associated with all factors. Younger age was associated with higher prevalence of distress/tension, impulse control and psychotic behaviors. Being married was protective against psychotic behaviors. Lower education was associated with the presence of distress/tension behaviors. Caucasians showed higher prevalence of affective behaviors. Functional impairment was strongly associated with all behavioral abnormalities. Amnestic MCI had more elation and agitation relative to nonamnestic MCI.

Conclusions—Younger age, male gender and greater functional impairment were associated with higher overall presence of behavioral abnormalities in MCI and mild AD. Marital status, lower education and race had effect on selected behaviors.

Keywords

neuropsychiatric symptoms; behavior; MCI; mild cognitive impairment; Alzheimer's disease; AD

Neuropsychiatric symptoms are exceedingly prevalent in Alzheimer's disease (AD). They affect 42% of those with mild, 80% with moderate, and over 90 % with advanced AD. [1] In the mild cognitive impairment (MCI) stage 35 -75% of patients experience at least one neuropsychiatric symptom. [2] Neuropsychiatric disturbances are major contributors to the emotional, social and economical burden of dementia and are the leading cause for hospitalization, residential placement, and psychopharmacologic therapy.[3-6, 15, 16, 17]

The most established risk factor for behavioral symptoms is disease severity. [2] Older age has been linked to lower prevalence of anxiety [7], increased prevalence of psychosis [8, 9] and aberrant motor behaviors [9]. Some researchers have linked higher education in AD to lower [1011, 12] and others to higher [13] prevalence of depression and psychosis. Other studies have reported lack of associations. [14, 15] Family history of dementia has been linked to the presence of anxiety, irritability [16] and psychosis. [16, 17] Female AD subjects have a higher prevalence of anxiety relative to male AD subjects.[7]

The risk/protective factors for manifestation of behavioral symptoms in MCI and mild AD have not been thoroughly researched to date. Here we report in depth analyses of the risk factors associated with prevalence of neuropsychiatric features among MCI and mild AD National Alzheimer's Coordinating Center database (NACC) participants.

Methods

Subjects

We used demographic, cognitive and neuropsychiatric data of 3456 MCI and 2641 mild AD subjects from the NACC. The NACC resource (NIA U01 AG016976) was established in 1999 and contains data from 34 past and present NIA-funded Alzheimer's Disease Centers across the United States. NACC data are freely available to all researchers. Qualifying subjects were required to be 50-100 years old, have a diagnosis of AD or MCI made according to standard research criteria [18, 19], Neuropsychiatric Inventory Questionnaire

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(NPI-Q) data, Mini-Mental State Examination score (MMSE)>20 and no other neurological or psychiatric diagnoses. We limited our analyses to subjects who provided Alzheimer's Disease Centers' Uniform Data Set (UDS) data between September 2005 and August 2011. AD subjects were additionally required to have global Cognitive Dementia Rating scale score (CDR) <2. As this is a study of preexisting data from a national repository that was provided to the PI without any personal identifying information the analyses reported here are IRB exempt. The exemption status has been confirmed with the UCLA IRB.

Variable construction

NACC variables included clinical diagnosis, age, sex, race, education, MMSE, Functional Activity Questionnaire (FAQ) scores, marital status, parental history of dementia and second-degree relative history of dementia. Age, MMSE and FAQ were used as continuous variables. All FAQ entries “not applicable/never did” were coded as missing data. Education was categorized as <6, 6-12 and >12 years of education except in the multivariable regression analyses where it was used as continuous variable for ease of interpretation of odds ratios. The effects of race were studied by constructing dummy variables of African American and Asian relative to Caucasian race. Gender, marital status (married vs. not married), parental and second-degree relative history of dementia were entered as binary variables. The not married category included “never married”, “widowed”, “divorced” and “separated”.

Statistical Analyses

We used two-tailed T-tests for continuous and Chi-Square statistics for categorical variables to compare the demographic, cognitive and neuropsychiatric characteristics of subjects with MCI vs. mild AD and amnestic MCI vs. nonamnestic MCI.

We used principal component factor analysis with varimax rotation to examine the joint variation and interdependencies among the ten NPI variables in the pooled sample. The factor analysis was conducted using the pooled sample of MCI and mild AD subjects for whom all predictor variables were available (N=4874). Four factors were identified and factor scores were computed for each factor, incorporating the ten NPI variables in all of the factor scores. Linear regression analyses were conducted to assess the association between the four factors scores and the predictor variables age, sex, education, race, marital status, parental and second-degree relative history of dementia, MMSE and FAQ.

The following analyses were conducted separately in the mild AD, MCI and pooled samples. We first studied the univariate associations between the presence or absence of neuropsychiatric behaviors and our predictor variables – age, sex, education, race, marital status, parental and second-degree relative history of dementia, MMSE and FAQ, using Chi-Square statistics for categorical variables and univariate logistic regression for continuous variables. Next we conducted multivariable logistic regression to study the adjusted effects of all predictor variables on each neuropsychiatric feature and behavioral factor, respectively using age, sex, education, race, marital status, parental and second-degree relative history of dementia, MMSE and FAQ as predictor variables.

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We compared the prevalence of neuropsychiatric symptoms between amnestic and nonamnestic MCI using Chi-Square statistics. Univariate Chi-Square and T-test analyses were conducted to compare age, sex, education, race, marital status, parental and second-degree relative history of dementia, MMSE and FAQ between amnestic and nonamnestic MCI subjects. Multivariate logistic models were developed to predict the neuropsychiatric symptoms that were found to be significantly different between the amnestic and nonamnestic MCI subjects. Predictor variables that were significantly different between amnestic and nonamnestic MCI subjects in univariate analyses were included in these multivariate logistic models.

Results

Demographic characteristics of the Study Population

The mild AD group was significantly older, less educated, and more cognitively and functionally impaired relative to the MCI group (Table 1). Mild AD subjects had significantly greater proportion of Caucasians, were less likely to be married or have parental history of dementia relative to MCI (Table 1).

2837 MCI participants met criteria for amnestic and 619 for nonamnestic subtype. Amnestic MCI subjects were significantly older (75.6±8.7 vs. 74.1±8.7 years, $p<0.0001$), more cognitively impaired (MMSE 27±2.3 vs. 27.6±2.1, $p<0.0001$), functionally impaired (FAQ 3.5±4.6 vs. 2.6±4.2, $p<0.0001$) and education ($p=0.001$), but had comparable marital status, parental or second-degree relative history of dementia relative to nonamnestic MCI subjects. There was significantly higher proportion of men among amnestic vs. nonamnestic MCI (47% vs. 41.5%, $p=0.0093$).

All neuropsychiatric behaviors except depression were significantly more common in mild AD vs. MCI. MCI subtypes differed only in the prevalence of agitation and elation – both were more common among amnestic MCI (Table 2).

Factor Analyses

We identified four separate factors both in the full sample and in the sample restricted to only those subjects with all predictor variables available (Table 3). Affective behaviors - depression, anxiety and apathy, had the strongest loadings on factor 1. Distress/tension behaviors such as agitation and irritability strongly loaded on factor 2. Impulse control behaviors such as disinhibition, elation and aberrant motor behavior loaded on factor 3. Psychotic behaviors -delusions and hallucinations, loaded on factor 4. These factor loadings were evaluated and determined to represent four behavior groups: 1) Affective behaviors, 2) Distress/tension behaviors, 3) Impulse control behaviors, and 4) Psychotic behaviors.

Factor linear regression analyses—Factor 1 (affective disorders: depression, anxiety and apathy) was negatively associated with age ($p<0.0001$), Asian ($p<0.0001$) and African American race ($p<0.0001$) and positively associated with FAQ ($p<0.0001$).

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Factor 2 (distress/tension disorders: irritability and agitation) was negatively associated with age ($p<0.0001$) and education ($p=0.0298$), and positively associated with male gender ($p<0.0001$), MMSE ($p<0.0001$) and FAQ ($p<0.0001$).

Factor 3 (impulse control disorders: disinhibition, elation and aberrant motor behaviors) showed negative association with age ($p<0.0001$) and positive association with male gender ($p<0.0001$), MMSE ($p=0.0093$) and FAQ ($p<0.0001$).

Factor 4 (psychotic disorders: delusions and hallucinations) showed negative association with age ($p=0.0018$) and being married ($p=0.0021$) and positive association with male gender ($p=0.0444$) and FAQ ($p<0.0001$).

Univariate Analyses

Significance results from the univariate analyses are presented in Table 4.

Younger age was associated with the presence of depression, anxiety and irritability across all samples, as well as elation in the MCI and pooled samples, delusions in the pooled and apathy in the AD sample only.

Female sex was associated with higher prevalence of depression but lower prevalence of apathy, agitation, irritability and disinhibition in all three samples. Women also showed significantly lower frequency of elation in the pooled and MCI samples and higher prevalence of anxiety in the pooled sample. Women had higher prevalence of delusions in the mild AD and pooled samples.

Lower education was associated with a higher prevalence of delusions and depression in all three samples (pooled, MCI only and AD only), higher prevalence of hallucinations in the MCI and pooled samples, higher prevalence of agitation in the mild AD and pooled samples, and lower prevalence of apathy in the mild AD sample.

Being married was associated with higher prevalence of apathy and irritability and lower prevalence of depression and delusions in all three samples, higher prevalence of agitation in the MCI and pooled sample, anxiety in the pooled sample, and lower prevalence of hallucinations in the mild AD sample.

Parental history of dementia was associated with higher frequency of irritability in the MCI and pooled sample, higher prevalence of delusions and disinhibition in the pooled sample and depression in mild AD.

Second-degree relative history of dementia was associated with greater prevalence of hallucinations, disinhibition and aberrant motor behaviors in mild AD and the pooled sample and greater prevalence of anxiety and apathy in mild AD.

Functional impairment measured with the FAQ showed significant positive associations with the presence of all neuropsychiatric symptoms in all three samples except for depression where a positive association was observed only for MCI.

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The univariate effects of race are best explained by associations with the factor variables. For all factor 1 variables Caucasian race showed the highest, African American race the second highest and Asian race the lowest prevalence. This effect was significant for depression in the MCI and pooled samples, apathy in the pooled sample and anxiety in the MCI sample. Factor 2 distress/tension behaviors were significantly more common among African American compared to Asian subjects in all samples. Caucasians had the highest prevalence of irritability (i.e., higher then both African Americans and Asians) in the MCI and pooled samples and agitation in the MCI sample. Caucasians also showed the lowest prevalence of agitation in the mild AD sample. For Factor 3 impulse control behaviors the only significant associations were seen for disinhibition where we found Caucasians had the highest and Asians the lowest prevalence among MCI while at the same time in the AD sample Asians showed the highest and African Americans the lowest prevalence in the pooled sample. In both the AD and pooled samples Factor 4 psychotic behaviors were significantly more prevalent among African Americans followed by Asians and finally by Caucasians.

Multivariable analyses

Multivariable analyses were restricted to subjects with all predictor data available (2786 MCI and 2075 mild AD). 11 subjects (6 MCI and 5 mild AD) had missing race variable. 1227 subjects (651 MCI and 576 mild AD) had missing parental or second-degree relative history of dementia. Finally 24 subjects (13 MCI and 11 mild AD) had missing FAQ variable.

Multivariable logistic regression analyses—Table 5 lists the odds ratios and confidence intervals for all significant predictors. Younger subjects showed significantly higher odds for having apathy, depression, anxiety, irritability and elation across all three samples, and higher odds for agitation and aberrant motor behavior in the MCI and pooled samples, and disinhibition in the mild AD and pooled samples. The odds ratio for each additional year of age across all behaviors ranged between 0.96-0.99.

Female gender was associated with higher odds for depression in the MCI and pooled sample (OR=1.5 and 1.33, resp.), and anxiety in the MCI (OR=1.28). Women had lower odds for irritability, apathy, disinhibition in all three samples, agitation and elation in the MCI and pooled samples and aberrant motor behavior in the MCI sample with odds ratios ranging from OR=0.3 for elation among MCI to OR=0.69 for apathy in the mild AD sample (Table 4).

Education influenced the odds for agitation in the pooled sample (OR=0.98).

Not being married was associated with higher odds for depression and delusions in all samples, and disinhibition and elation in the MCI sample only. The odds ratios ranged from OR=1.27 for depression to OR=2.6 for elation. Being married translated in greater odds for agitation in the mild AD sample (OR for not being married=0.76) (Table 5).

Parental history of dementia was associated with higher odds for delusions (OR=1.46) in mild AD and lower odds for depression in the mild AD and pooled sample (OR=0.75 and

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0.85, resp). Second-degree relative history of dementia was associated with higher odds for hallucinations in the mild AD and pooled samples (OR=1.86 and 1.62, resp), as well as with decreased odds of elation in the AD sample (OR=0.5) (Table 5).

African American MCI subjects had lower odds of depression (OR=0.51) and disinhibition (OR=0.27) than Caucasians. African American mild AD subjects had greater odds for agitation relative to Caucasians (OR=2.27). Asian MCI subjects showed lower odds for depression (OR=0.36), apathy (OR=0.25) and anxiety (OR=0.21) and higher odds for disinhibition (OR=1.39) relative to Caucasians. Similar associations were seen in the pooled sample (Table 4).

Subjects with greater functional impairment (higher FAQ) showed greater odds for the presence of all neuropsychiatric behaviors with the sole exception of depression in the mild AD and pooled samples (Table 4).

Univariate and multivariable analyses by MCI subtype

The univariate analyses included 2837 amnestic and 619 nonamnestic MCI. Agitation and elation were significantly more common among amnestic MCI (p=0.034 for both, see Table 2).

Twenty MCI subjects were excluded from multivariate analyses due to missing data (N=3436). We ran multivariable logistic regression models with elation and agitation as dependent variables and MCI subtype, age, gender, MMSE, FAQ and education - the five variables that were significantly different between the subtypes - as predictors (see Table 2). Amnestic MCI subjects showed significantly higher odds for the presence of elation (OR=3.03, 95% CI 1.08-8.53; p=0.036) but not agitation after controlling for other variables. In addition to MCI subtype the odds of elation associated with younger age (OR=0.95, 95% CI 0.93-0.98; p=0.0016), male gender (OR=2.7, 95% CI 1.5-4.9; p=0.0007) and higher FAQ (OR=1.1, 95% CI 1.06-1.15; p<0.0001). Higher odds for agitation is associated with younger age (OR=0.99, 95% CI 0.975-0.996; p=0.0094), male gender (OR=1.76, 95% CI 1.5-2.1; p<0.0001) and worse FAQ scores (OR=1.12, 95% CI 1.10-1.14; p<0.0001).

Discussion

This is the largest study of behavioral symptoms in MCI and mild AD to date. The large sample size allowed us to conduct in depth analyses of the risk factors associated with prevalence of neuropsychiatric features among MCI and mild AD NACC participants. In our most conservative analyses after grouping NPI-Q variables in four factors we applied linear regression to investigate which demographic and cognitive variables show significant association with each factor. The four factors identified were affective behaviors – depression, apathy and anxiety, distress/tension behaviors – irritability and agitation, impulse control behaviors – disinhibition, elation and aberrant motor behavior and psychotic behaviors – delusions and hallucinations. We found that male gender was significantly associated with the presence of all four behavioral factors. Younger age was associated with higher prevalence of distress/tension, impulse control and psychotic behaviors, while being

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married seemed protective against psychotic behaviors. Lower education was significantly related to the presence of distress/tension behaviors. Subjects from the Caucasian race were significantly more susceptible to affective behaviors.

Our findings agree with many observations reported in the literature. All analyses consistently demonstrated that disease severity measured by functional decline (FAQ) was the most powerful predictor for the presence of all behavioral abnormalities, which is consistent with previous reports. [2]

The association of younger age with anxiety has been previously reported in AD in one Cache County study. [7] We confirmed this association in the MCI and pooled samples in both the univariate and multivariable logistic regression analyses. While Puccinini et al. [9] previously reported an association of older age and aberrant motor behaviors, we observed the opposite effect in the univariate and multivariable logistic regression analyses of the MCI and pooled samples. We were also unable to confirm the association between older age and psychosis reported by two previous studies [8, 9] and found the opposite association across all three samples in the univariate but not the multivariable analyses.

Our findings in respect to education extend previous reports. Three studies [10-12] reported a negative association between education and prevalence of depression in AD. Others reported lack of association or an association in the opposite direction[13-15]. We observed a negative association between education and prevalence of depression in all samples in the univariate analyses that disappeared once we corrected for multiple comparisons.

In terms of family history of dementia our univariate and multivariable logistic regression findings agree with those of [16, 20] who reported higher prevalence of anxiety, irritability and psychosis among AD subjects with positive family history.

Our findings are also in agreement with the reported association from the Cache County study of females with AD having higher prevalence of anxiety.

In regards to prevalence of neuropsychiatric symptoms among MCI subtypes our findings disagree with previous reports. We failed to see higher prevalence of apathy among amnestic MCI and hallucinations among nonamnestic MCI as previously reported [21, 22]. We somewhat surprisingly uncovered higher prevalence of elation (univariate and multivariable analyses) and agitation (univariate analyses) among amnestic compared to nonamnestic MCI.

In addition our multivariable logistic regression analyses showed many previously unrecognized associations. We found that younger age associates with higher prevalence of depression, elation and irritability in all three samples, agitation, apathy and aberrant motor behavior in MCI and the pooled sample and disinhibition in the pooled sample in the multivariable logistic regression analyses. Female gender was largely protective against NPI symptoms with the exception of depression and anxiety. Married MCI subjects were less likely to have depression, delusions, elation and disinhibition. Married mild AD subjects had less depression and agitation.

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Several strengths and weaknesses of our study need to be recognized. Due to its large sample size our paper is the first one to report several important observations in respect to NPI symptom prevalence. Those that stand out are the overall higher prevalence of behavioral abnormalities in younger subjects, males and those with more significant functional impairment. The weaknesses of our study are the fact that several putative risk factors –especially those associated with cognitive reserve such as occupational attainment, socio-economic status and social and leisure activities were not available in the NACC database and limited out ability to study the presence of behavioral reserve in MCI and mild AD. Given the lack of strong association between education and lower prevalence of NPI symptoms we must conclude that we find no evidence of behavioral reserve in MCI and mild AD although this might very well be a premature conclusion in view of the lacking data points to exhaust this question. Other more thorough datasets might offer a better opportunity to firmly establish the absence or presence of behavioral reserve. Additional limitation of the study is the fact that the data are collected at tertiary health care centers with federally funded Alzheimer's disease research programs. Such environments are well known to attract highly educated, predominantly Caucasian subjects. The fact that we report many associations in non-Caucasian participants is however reassuring that we have at least some statistical power to make such observations. NACC data is being collected at all more than 30 sites – the NIH funded Alzheimer's Disease Research Centers (ADRCs). These Centers are spread across the United States. As such NACC data doesn't suffer from a significant geographical bias. It does however suffer from a sampling bias as it represents a collection of multiple convenience samples. Patients seen at ADRCs are typically highly educated, predominantly white and many have a positive family history of AD (see Table 1). Hence the NACC cohort is not an accurate representation of the elderly population in the US. Despite the fact that we have in our multivariable analyses adjusted for age, race and dementia family history, our study findings should be generalized with caution.

In summary our comprehensive analysis of the social and demographic factors that influence behavioral symptom prevalence revealed that younger subjects, Caucasian subjects, men, subjects with lower education and subjects with greater functional impairment have higher overall presence of behavioral abnormalities in MCI and mild AD. Marital status, lower education and race had effect on the prevalence of selected behaviors only. Following this comprehensive investigation our next step will be to study the risk factors associated with emergence (i.e., incidence) of neuropsychiatric behaviors across the spectrum from normal aging to AD.

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Table 1

Demographic characteristics

Variable	Categories	Pooled Sample N=6097	MCI N=3456	Mild AD N=2641	Mild AD vs. MCI p-value
Age, yr		75.7 (8.7)	75.4 (8.7)	76.0 (8.8)	**.0034**
Gender, N (%)	Male	2784 (46%)	1598 (46%)	1186 (45%)	.30
	Female	3313(54%)	1858 (54%)	1455 (55%)	
Education, yr	<12	561(9%)	327 (9%)	234(9%)	**<.0009**
	12-16	3834 (63%)	2105 (61%)	1729 (65%)	
	>16	1702 (28%)	1024 (30%)	678 (26%)	
Race	White	4960(81%)	2706(78%)	2254(85%)	**<.0001**
	African American	825 (14%)	559 (16%)	266 (10%)	
	Asian	117 (2%)	79 (2%)	38 (1%)	
	Other	195 (3%)	112 (3%)	83 (3%)	
Married	Yes	3876(63%)	2101 (61%)	1775 (66%)	**<.0001**
	No	2221 (37%)	1355 (39%)	866 (34%)	
Parental history of dementia	Yes	2814 (52%)	1555 (45%)	1259 (48%)	**.017**
	No	3165 (46%)	1844 (54%)	1321 (50%)	
	Unknown	91 (2%)	44 (1%)	48 (2%)	
	Missing	27 (<0.5%)	13 (<0.5%)	14 (<0.5%)	
Second-degree relative history of dementia	Yes	1486(24%)	871 (25%)	615 (23%)	.142
	No	3424 (56%)	1936 (56%)	1488 (57%)	
	Unknown	1160 (19%)	636 (19%)	524 (20%)	
	Missing	27 (<0.5%)	13 (<0.5%)	14 (<0.5%)	
MMSE		25.7 (2.9)	27.1 (2.3)	23.9 (2.6)	**<.0001**
FAQ		7.1 (7.2)	3.3 (4.5)	12.0 (7.2)	**<.0001**

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Table 2

Frequency of NPI symptoms

NPI variable	Pooled sample N=6097	MCI N=3456	Mild AD N=2641	Mild AD vs. MCI p-value	Amnestic MCI N=2837	Nonamnestic MCI N=619	Amnestic vs. nonamnestic MCI p=value
Delusions	428 (7%)	122 (4%)	306 (12%)	**<.0001**	97 (3%)	25 (4%)	0.5
Hallucinations	117 (2%)	34 (1%)	83 (3%)	**<.0001**	27 (1%)	7 (1%)	0.7
Depression	1116 (18%)	669 (19%)	447 (17%)	**.015**	553 (20%)	116 (19%)	0.7
Apathy	1624 (27%)	627 (18%)	997 (38%)	**<.0001**	520 (18%)	107 (17%)	0.5
Anxiety	1579 (25%)	705 (20%)	825 (31%)	**<.0001**	585 (21%)	120 (19%)	0.5
Irritability	1891 (31%)	908 (26%)	983 (37%)	**<.0001**	749 (26%)	159 (26%)	0.7
Agitation	1340 (22%)	562 (16%)	778 (30%)	**<.0001**	479 (17%)	83 (13%)	**0.034**
Disinhibition	707 (12%)	274 (8%)	433 (16%)	**<.0001**	218 (8%)	56 (9%)	0.3
Elation	148 (2%)	56 (2%)	92 (3%)	**<.0001**	52 (2%)	4 (1%)	**0.034**
Aberrant motor behavior	482 (8%)	149 (4%)	333 (13%)	**<.0001**	117 (4%)	32 (5%)	0.2

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Table 3

Factor loadings based on a principle components analysis with verimax rotation for ten NPI variables

NPI variables	Affective Behaviors	Distress/Tension Behaviors	Impluse Control Behaviors	Psychotic Behaviors
Depression	**0.47**	0.15	0.05	0.09
Anxiety	**0.43**	0.13	0.14	0.11
Apathy	**0.38**	0.18	0.15	0.10
Agitation	0.24	**0.50**	0.22	0.14
Irritability	0.30	**0.49**	0.17	0.08
Disinhibition	0.17	0.25	**0.34**	0.17
Elation	0.06	0.08	**0.26**	0.10
Aberrant Motor Behavior	0.22	0.10	**0.22**	0.13
Delusions	0.13	0.19	0.19	**0.28**
Hallucinations	0.06	0.03	0.08	**0.25**

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Table 4

Univariate Chi-Square and logistic regression analyses

The values listed are p-values. For direction of the effect please see section Results: Univariate Analyses.

Variable	Sample	DEL	HAL	DEP	APA	ANX	IRR	AGIT	DISN	ELAT	MOT
Age	Pooled	**.02**	.36	**<.0001**	.15	**<.0001**	**<.0001**	.28	.75	**.03**	.31
	MCI	.14	.44	**<.0001**	.43	**<.0001**	**<.0001**	.28	.55	**.0046**	.087
	AD	.16	.19	**.03**	**.03**	**<.0001**	**.0001**	.26	.16	.41	.54
Sex	Pooled	**.0002**	.79	**<.0001**	**<.0001**	**.026**	**<.0001**	**<.0001**	**.0005**	**.0021**	.71
	MCI	.42	.43	**<.0001**	**<.0001**	.076	**<.0001**	**<.0001**	**.0049**	**.0004**	.062
	AD	**.0002**	.46	**.0009**	**.0012**	.22	**<.0001**	**.022**	**.017**	.23	.51
Education	Pooled	**<.0001**	**.0012**	**<.0001**	.21	.31	0.85	**.0061**	.77	.21	.64
	MCI	**.04**	**.003**	**.0091**	.52	.74	.62	.12	.44	.56	.45
	AD	**.0017**	.056	**.0032**	**.03**	.15	.93	**.025**	.51	. 12	.88
Race	Pooled	0.050	**.013**	**<.0001**	**<.0001**	**.0007**	**.0015**	.86	**.0077**	.15	.86
	MCI	.53	.41	**<.0001**	**.0011**	**.0002**	**.0006**	**.003**	**<.0001**	.13	.12
	AD	**<.0001**	**<.0001**	.10	.20	.78	.99	**<.0001**	.12	.94	.13
Married	Pooled	**<.0001**	.10	**<.0001**	**<.0001**	**.047**	**<.0001**	**.0006**	.15	.50	.97
	MCI	**.0075**	.91	**.0088**	**.015**	.42	**<.0001**	**.022**	.85	.77	.94
	AD	**<.0001**	**.010**	**<.0001**	**.0021**	.26	**.0005**	.14	.37	.47	.27
Parental history	Pooled	**.011**	.19	.07	.18	.43	**.0098**	.24	**.033**	.46	.26
	MCI	.45	.64	.8	.98	.99	**.012**	.45	.5	.79	.12
	AD	.045	.36	**.019**	.17	.39	.23	.46	.069	.21	.99
2nd -degree relative history	Pooled	.23	**.04**	.14	.43	.0502	.17	.79	**.0033**	.22	**.0031**
	MCI	.98	.76	.054	.63	.42	.29	.54	.52	.47	.24
	AD	0.23	**.038**	.45	**.02**	**.014**	.44	.51	**.0037**	.10	**.014**
MMSE	Pooled	**<.0001**	**<.0001**	.67	**<.0001**	**<.0001**	**.0019**	**<.0001**	**<.0001**	**.014**	**<.0001**
	MCI	.055	0.29	.28	**.005**	.87	.087	.42	.8	.52	.42
	AD	**<.0001**	**.0041**	.25	.54	.86	.056	.09	.87	.55	**<.0001**
FAQ	Pooled	**<.0001**	**<.0001**	.06	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**
	MCI	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**.0002**	**<.0001**

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Variable	Sample	DEL	HAL	DEP	APA	ANX	IRR	AGIT	DISN	ELAT	MOT
	AD	**<.0001**	**<.0001**	.25	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**	**<.0001**

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Table 5
Logistic regression results – odds ratios of all significant predictors

Neuropsychiatric behavior	MCI N=2779 OR (95% CI)	Mild AD N=2075 OR (95% CI)	Pooled sample N=4854 OR (95% CI)
Delusions	Not married 1.78 (1.1-2.85) FAQ 1.15 (1.11-1.19)	Parent 1.46 (1.09-1.94) FAQ 1.1 (1.08-1.12) Not married 1.41 (1.01 – 1.99)	FAQ 1.12 (1.1-1.14) Not Married 1.5 (1.15-1.99)
Hallucinations	FAQ 1.18 (1.12-1.24)	2nd degree 1.86 (1.05 -3.32) FAQ 1.07 (1.03-1.11)	2nd degree 1.62 (1.01 -2.59) FAQ 1.11 (1.08-1.15)
Depression	Age 0.98 (0.964-0.987) Female 1.5 (1.22-1.85) Asian 0.36 (0.15-0.84) AA 0.51 (0.38-0.69) Other race 1.6 (0.98-2.67) Not married 1.27 (1.03-1.58) FAQ 1.05 (1.03-1.58)	Age 0.98 (0.96-0.99) Other race 1.83 (0.91-3.66) Not married 1.6 (1.2-2.05) Parent 0.73 (0.58-0.92)	Age 0.98 (0.97-0.99) Female 1.33 (1.13-1.56) Asian 0.34 (0.16-0.74) Other race 1.80 (1.21-2.69) Not married 1.40 (1.18-1.65) Parent 0.85 (0.73-0.99)
Apathy	Age 0.98 (0.967-0.992) Female 0.63 (0.51-0.78) Asian 0.25 (0.087-0.71) FAQ 1.15 (1.13-1.17)	Age 0.99 (0.98-0.10) Female 0.69 (0.56-0.85) MMSE 1.05 (1.01-1.09) FAQ 1.07 (1.06-1.09)	Age 0.98 (0.98-0.992) Female 0.64 (0.56-0.75) Asian 0.43 (0.23-0.81) FAQ 1.11 (1.1-1.12)
Anxiety	Age 0.97 (0.959-0.982) Female 1.28 (1.04-1.57) Asian 0.21 (0.075-0.58) FAQ 1.09 (1.07-1.12)	Age 0.97 (0.96-0.98) FAQ 1.05 (1.03-1.07)	Age 0.97 (0.96-0.98) Asian 0.39 (0.21-0.75) FAQ 1.067 (1.057-1.079)
Irritability	Age 0.97 (0.959-0.98) Female 0.65 (0.54-0.79) FAQ 1.11 (1.09-1.13)	Age 0.98 (0.967-0.988) Female 0.67 (0.55-0.83) MMSE 1.06 (1.02-1.10) FAQ 1.04 (1.03-1.06)	Age 0.97 (0.966-0.98) Female 0.65 (0.57-0.75) MMSE 1.05 (1.03-1.08) FAQ 1.07 (1.06-1.08)
Agitation	Age 0.99 (0.972-0.997) Female 0.6 (0.48-0.75) FAQ 1.12 (1.09-1.14) MMSE 1.06 (1.02-1.11)	AA 2.27 (1.64 -3.12) Not married 0.76 (0.6-0.98) MMSE 1.09 (1.05-1.14) FAQ 1.06 (1.04-1.07)	Age 0.99 (0.981-0.997) Female 0.68 (0.59-0.8) Edu 0.98 (0.96-0.1) MMSE 1.05 (1.02-1.08) FAQ 1.09 (1.07-1.1)
Disinhibition	Female 0.59 (0.43-0.81) Asian 1.39 (0.61-3.17) AA 0.27 (0.14-0.52) Not married 1.48 (1.06-2.06) FAQ 1.15 (1.12-1.17)	Age 0.98 (0.97-0.10) Female 0.65 (0.5 -0.86) MMSE 1.06 (1.01-1.11) FAQ 1.08 (1.06-1.1)	Age 0.98 (0.97-0.995) Female 0.61 (0.5-0.75) Asian 1.73 (0.96-3.1) MMSE 1.05 (1.01-1.1) FAQ 1.1 (1.09-1.12)
Elation	Age 0.97 (0.904-0.967) Female 0.3 (0.15-0.61) Not married 2.6 (1.3-5.0) FAQ 1.1 (1.05-1.16)	Age 0.97 (0.94-0.1) FAQ 1.09 (1.05-1.13) 2nd degree 0.50 (0.27-0.92)	Age 0.95 (0.93-0.97) Female 0.48 (0.32-0.74) FAQ 1.1 (1.07-1.13)
Aberrant motor behavior	Age 0.97 (0.949-0.993) Female 0.63 (0.41-0.96) FAQ 1.14 (1.1-1.17)	FAQ 1.1 (1.08-1.13)	Age 0.98 (0.97-0.994) FAQ 1.12 (1.1-1.14)

2nd degree – second-degree relative history of dementia; AA – African American; Edu – education; FAQ – Functional Activity Questionnaire score, Female = female sex; Parent – parental history of dementia; MMSE – Mini-Mental State Examination score