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Neuropsychiatric symptoms, apolipoprotein E gene, and risk of progression to cognitive impairment, no dementia and dementia: the Aging, Demographics and Memory Study (ADAMS)

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Abstract

Objective—To examine the relationship of neuropsychiatric symptoms and Apolipoprotein E (APOE) ε4 allele status to dementia at baseline and progression to dementia in older adults with and without cognitive impairment, no dementia (CIND).

Methods—Adults (n = 856) aged 71 and older (mean age = 79.15), 12.8% ethnic minority and 60.6% women, completed neuropsychological tests, APOE genotyping, and a proxy informant completed the Neuropsychiatric Inventory (NPI).

Results—After adjusting for age and education, neuropsychiatric symptoms and APOE ε4 were independently associated with CIND and dementia status at baseline (compared with cognitively normal). Further, neuropsychiatric symptoms predicted progression to dementia at 16- to 18-month follow-up among participants with CIND at baseline; the presence of these symptoms decreased the risk of progression from normal to CIND or dementia at 36 to 48 months.

Conclusion—Findings provide cross-sectional and longitudinal support for the role of neuropsychiatric symptoms in the prediction of cognitive impairment, particularly dementia. APOE ε4, while important, may be a less robust predictor. This investigation highlights the importance of behavioral symptoms, such as neuropsychiatric symptom status or frequency/severity, as predictors of future cognitive decline.

Keywords

Neuropsychiatric Inventory; Behavioural psychological symptoms in dementia; Apolipoprotein E 4; Cognitive disorders; Cognitive decline; Cognition

Introduction

Neuropsychiatric symptoms, such as apathy, depression, anxiety, and agitation, are more prevalent among older adults with dementia compared with those with mild or no cognitive

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impairment (Fernández-Martínez *et al.*, 2008). Approximately 25% of older adults with no cognitive impairment exhibit neuropsychiatric symptoms (Geda *et al.*, 2008), whereas 43 to 50% of those with mild cognitive impairment (MCI) or cognitive impairment, no dementia (CIND) (Geda *et al.*, 2008; Lyketsos *et al.*, 2002; Okura *et al.*, 2010), and 58% to 75% of those with dementia, exhibit symptoms (Lyketsos *et al.*, 2002; Okura *et al.*, 2010; Lyketsos *et al.*, 2000).

In recent years, researchers have investigated neuropsychiatric symptoms as predictors of functional and cognitive decline. Studies have found neuropsychiatric symptoms to be associated with greater functional impairment in dementia and in MCI and CIND (Fernández-Martínez *et al.*, 2008; Okura *et al.*, 2010; Di Iulio *et al.*, 2010). With regard to cognitive decline, one study found that neuropsychiatric symptoms increased the risk of conversion from MCI to dementia at 2-year follow-up (Teng *et al.*, 2007). Geda and colleagues (Geda *et al.*, 2006) also found that depressive symptoms interacted with a genetic risk factor for dementia, the Apolipoprotein E epsilon 4 allele (APOE ε4), to increase the risk of developing MCI. This finding was replicated recently in an Asian sample (Kim *et al.*, 2010). Consideration of APOE status may therefore help disambiguate the role of a broader range of neuropsychiatric symptoms in predicting progression to dementia in those with normal cognitive status and those with CIND. What remains unanswered in the current literature is whether APOE interacts with neuropsychiatric symptoms, more broadly defined to encompass multiple neuropsychiatric domains (i.e., depression, anxiety, apathy, agitation), to increase the risk of progression to dementia in individuals with CIND, or to increase the risk of progressing from normal cognitive status to CIND or dementia.

In a previous investigation in the Aging Demographics and Memory Study (ADAMS), APOE ε4 was independently associated with dementia status at the study baseline (Plassman *et al.*, 2007), and predicted conversion to dementia at 16 to 18 months in individuals with CIND (Plassman *et al.*, 2008; see Erratum 2009). In another ADAMS study comparing individuals with no cognitive impairment, CIND and dementia (mild, moderate, severe) at baseline neuropsychiatric symptoms (none, one to two, or three or more) were more prevalent in CIND and dementia compared with no cognitive impairment (Okura *et al.*, 2010). The interaction of the APOE ε4 allele and neuropsychiatric symptoms on progression to CIND or dementia has not been examined in ADAMS. Further, neuropsychiatric symptom presence and total severity among normal, CIND and dementia have not been examined at baseline in ADAMS, nor have baseline neuropsychiatric symptoms as predictors of conversion to cognitive impairment (normal to CIND or dementia and CIND to dementia) in the ADAMS follow-up assessments.

We examined baseline neuropsychiatric symptoms and APOE as risk factors for CIND and dementia at three time points using data from the ADAMS. We hypothesized that neuropsychiatric symptoms and APOE would independently and interactively: (a) be associated with baseline dementia status; (b) predict progression to dementia in those with CIND; and (c) predict progression to CIND or dementia in those with no cognitive impairment.

Methods

Participants

Participants were men and women enrolled in the ADAMS, a supplement to the Health and Retirement Study (HRS), sponsored by the National Institute of Aging (grant number NIA U01AG009740) and conducted jointly by Duke University and the University of Michigan. To be eligible, enrollment was limited to participants enrolled in the HRS who were 70 or older at the time of enrollment in ADAMS (see Langa *et al.*, 2005 for further detail).

regarding HRS/ADAMS sampling criteria). Baseline ADAMS data collection occurred from 2001 through 2003, and enrolled 856 adults, 71 years and older. At baseline sampling was stratified by age, gender, and cognitive testing scores. At the first follow-up, 16 to 18 months later (from 2002 to 2005), a subset of participants was selected for in-depth assessment based on a diagnosis of CIND ($n = 241$), a lack of a clear consensus for a diagnosis of dementia ($n = 24$), or lack of a clear consensus for no impairment ($n = 48$). Participants with a clear consensus diagnosis of dementia ($n = 308$) or cognitively normal ($n = 259$) were not followed up at 16 to 18 months. After excluding inconclusive cases and losing 61 participants to follow-up, the remaining sample consisted of 180 participants with mild functional or cognitive impairment based on a diagnosis of CIND (all subtypes) assessed at 16 to 18 months. A second follow-up assessment was conducted 36 to 48 months after baseline assessment from 2006 to 2008 for 216 participants diagnosed as cognitively normal at baseline and 99 participants diagnosed as CIND at baseline. ADAMS excluded CIND participants at the 36- to 48-month follow-up who converted to dementia at the first follow-up at 16 to 18 months ($n = 39$), or who dropped out from the first to second follow-up due to death or refusal to participate ($n = 42$). We excluded 6 cognitively normal participants who converted to CIND at 16 to 18 months and 3 CIND participants who were missing data at 16 to 18 months but followed up at 36 to 48 months. After excluding participants missing the Neuropsychiatric Inventory or APOE genotyping this left a total of 208 cognitively normal participants and 93 in second at 36- to 48-month follow-up. A flow chart of study enrollment and attrition for the baseline and first follow-up of data collection was published by Plassman *et al.*, 2008.

Procedure and Measures

At baseline and the first follow-up, individuals completed a 3- to 4-hour, in-home diagnostic evaluation consisting of a brief medical examination and a neurological exam conducted by a nurse, and a neuropsychological battery, administered by a supervised psychometrician. General demographic information (e.g., date of birth, years of education) was collected at baseline. Medical records were obtained with participant consent. Cognitive status (normal, CIND, or dementia) was determined by preliminary and final expert consensus panels and medical record review by a geropsychiatrist. Dementia diagnoses were based on criteria from the 3rd and 4th editions of the *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 1987; 1994). Diagnoses of CIND were determined based on functional or cognitive impairment insufficient for a diagnosis of dementia on the Dementia Severity Rating Scale (i.e., DSRS score from 6 to 11; Xie *et al.*, 2009); neuropsychological test performance below expectation of estimated baseline intellectual ability, reading ability, or occupational history; or 1.5 standard deviations below established norms on any of the neuropsychological tests (Plassman *et al.*, 2008). All subtypes of CIND were included in our study. Buccal DNA samples were obtained for APOE genotyping.

Proxy informants were interviewed regarding participants' medical history and current medications and rated participants' psychiatric functioning using the Neuropsychiatric Inventory (NPI) (Cummings, 1997). The NPI is a clinician-administered structured interview that queries about the presence, frequency and severity of symptoms in ten psychiatric and behavioral domains. Absence of a neuropsychiatric symptom on a screening question was coded 0. Following a positive response to a screening question, informants indicated the frequency and severity of that symptom. Total scores were calculated by multiplying frequency and severity of reported symptoms. We also coded NPI symptoms as present (NPI total score ≥ 1) or absent (NPI total score = 0) and conducted separate analyses for both the presence of specific NPI symptoms and for the NPI total scores.

Statistical Analyses

We conducted analyses in PASW Statistics 18, Release Version 18.0.2 (SPSS Inc., Chicago, IL) with the complex sampling weight program. To achieve national representation of the stratified random sample, we applied sampling weights that were recently revised by ADAMS using a corrected population estimate (Plassman *et al.*, 2008; see Erratum, 2009) to both descriptive and inferential analyses. The weights were derived by ADAMS based on representativeness of HRS and population controls in nursing homes, stratified subsampling from HRS, and study attrition among surviving participants (ADAMS Supplement to the Health and Retirement Study, 2007; for technical description of weight derivation, see Heeringa *et al.*, 2009). Because these sampling weights adjust for participant attrition, we did not apply them to our analyses comparing participants on key demographic and independent variables among those followed up vs. those lost to follow-up.

We computed descriptive statistics for demographic variables and compared participants diagnosed as cognitively normal, CIND, or dementia at baseline on demographic variables using ANOVAs for continuous variables and chi-squares for categorical variables.

For our primary analyses, we conducted a series of logistic regression analyses with age, education, NPI symptoms (presence vs. absence, or NPI total score) measured at baseline, APOE $\epsilon 4$ carrier status (yes vs. no), and the interaction between NPI and APOE $\epsilon 4$ carrier status as the predictors of either CIND or dementia at baseline or progression to CIND or dementia at follow-up as the outcome. Specifically, we conducted separate analyses with the following outcomes: presence of CIND (reference = normal) or dementia (reference = normal and reference = CIND) at baseline (cross-sectional); conversion from CIND at baseline to dementia at 16 to 18-month follow-up; conversion from CIND at baseline to dementia at 36 to 48-month follow-up; and progression from normal cognitive status at baseline to cognitively impaired (CIND or dementia) at 36 to 48 months.

We also conducted post-hoc analyses comparing the prevalence of specific neuropsychiatric symptoms (presence or symptom total scores) among cognitively normal, CIND, and dementia groups. Of the ten possible neuropsychiatric symptoms we excluded aberrant motor behavior, disinhibition, elation or hallucinations from our analyses because of uncertain validity of the model matrices or inability for the models to run due to limited endorsement of items within or across the cognitive diagnostic groups. We entered age and education as covariates examining normal and CIND as the reference groups. Due to limited statistical power, only main effects from our original model were included in the post-hoc analyses; the interaction between APOE carrier status and specific neuropsychiatric symptoms were excluded. We also limited these post-hoc analyses to baseline due to insufficient power to examine specific neuropsychiatric symptoms at the two follow-up assessments. To limit the chance of a Type I error, models in which the omnibus test (based on the Wald test) for the overarching model were not statistically significant were treated as not significant regardless of the significance of the simple effects tests (t-tests) comparing the cognitive diagnostic groups.

Results

Analyses revealed that, compared with cognitively normal participants who remained in the study through 36- to 48-month follow-up ($n = 210$), cognitively normal participants who dropped out between baseline and the 36- to 48-month follow-up, but did not convert to CIND or dementia at 16- to 18-month follow-up ($n = 82$) were significantly older (mean age = 79.39 ± 6.21 vs. mean age = 77.36 ± 4.93), $t(122.98) = -2.65$, $p = .009$ (adjusted due to equal variances not assumed based on Levene's test), and had fewer years of education (mean years of education = 10.62 ± 3.81 vs. mean years of education = 11.92 ± 3.64), $t(290)$

= 2.70, $p = .007$. No significant differences were found between normal dropouts vs. non-dropouts on the independent variables (i.e., neuropsychiatric symptoms, APOE carrier status) ($ps > .05$). Compared with CIND participants who remained in the study through the 36- to 48-month follow-up, CIND participants who dropped out between baseline and the 16- to 18-month follow-up ($n = 61$) or 16- to 18-month to 36- to 48-month follow-up ($n = 42$) were not significantly on demographic or on the independent variables ($ps > 0.05$).

Participants from ADAMS represent a broad continuum of age, education, and ethnicity (Plassman *et al.*, 2007). Descriptive statistics on baseline predictor and outcome variables for cognitively normal, CIND, dementia and the total sample are presented in Table 1. Normal participants were significantly younger than participants with CIND, $t(26) = -6.40$, $p < 0.001$ or dementia, $t(26) = -9.82$, $p < 0.001$; CIND participants were significantly younger than those with dementia, $t(25) = -6.15$, $p < 0.001$. Normals had more years of education than those diagnosed as having CIND, $t(26) = 4.79$, $p < 0.001$, or dementia, $t(26) = 4.25$, $p < 0.001$, but CIND and dementia were not significantly different with regard to education, $p > 0.05$. Compared with Caucasians, African American participants were more likely to be diagnosed with CIND, $\chi^2 = 3.54$, $p = 0.018$, or dementia, $\chi^2 = 5.93$, $p = 0.015$, than to be cognitively normal. Compared with Latino Americans, African American participants were more likely to be diagnosed as having dementia than cognitively normal, $\chi^2 = 6.73$, $p = 0.024$. No other significant ethnic differences were found in likelihood of being diagnosed as cognitively normal vs. CIND, cognitively normal vs. dementia, or CIND vs. dementia (all $ps > 0.05$). Further, the proportion of men to women was not significantly different among cognitively normal, CIND, or dementia participants, $p > 0.05$.

Descriptive statistics comparing cognitively normal, CIND, and dementia groups on the presence of neuropsychiatric symptoms, NPI total scores and APOE $\epsilon 4$ carrier status are summarized in Table 1.

As described elsewhere (Langa *et al.*, 2005), among participants with CIND at baseline the most common diagnoses at baseline, accounting for 73.5% of CIND cases in our study, were mild cognitive symptoms of either unknown etiology ($n = 94$; 33.8%), due to other medical conditions ($n = 55$; 23.9%), or secondary to stroke or vascular disease ($n = 54$; 26.0%).¹ The remaining CIND diagnoses included cases due to other neurological conditions, depression, amnesic mild cognitive impairment, other psychiatric conditions, alcohol abuse or mental retardation. Among participants with dementia at baseline, the most common diagnoses (97.2%) were Alzheimer's dementia ($n = 229$; 69.6%), vascular dementia ($n = 48$; 17.4%), or undetermined etiology ($n = 23$; 10.2%). Remaining cases of dementia included those due to normal pressure hydrocephalus, Parkinson's, Lewy Body disease, severe head trauma, alcoholism or Frontal lobe dementia.

In cross-sectional analyses at baseline, compared to cognitively normal participants, participants in whom neuropsychiatric symptoms were present had more than 4 times the odds of CIND (odds ratio (OR) = 4.20, 95% confidence interval (CI) 2.14, 8.23) and more than 7 times the odds of dementia (OR = 7.56, 95% CI 3.85, 14.86) (Table 2, Model 1). These associations decreased in magnitude but were also statistically significant for NPI total score (Model 2). Further, in the model with NPI total score (Model 2), the presence of APOE $\epsilon 4$ was associated with approximately 2 times the odds of CIND (OR = 1.97, 95% CI 1.09, 3.57) and 3 times the odds of dementia (OR = 3.03, 95% CI 1.44, 6.39) at baseline compared to cognitively normal participants, but APOE $\epsilon 4$ status was not associated with the presence of dementia compared with CIND at baseline. The interaction between NPI

¹Percentage for CIND secondary to vascular issues or stroke is slightly higher than CIND due to other medical conditions, despite a smaller n , due to the application of population weights.

total score and APOE $\epsilon 4$ at baseline was significantly associated with an almost 20% increased odds of dementia relative to CIND (OR = 1.19, 95% CI 1.04, 1.35), but was not significant in the comparisons with the normal reference group. Additional analyses with APOE $\epsilon 4$ carriers only vs. with non- $\epsilon 4$ carriers only were conducted to determine the nature of the significant interaction between APOE and NPI total score between the CIND and dementia groups (not shown in Table 2). Among APOE $\epsilon 4$ carriers, higher NPI total scores were associated with a 20% increased odds of dementia relative to CIND (OR = 1.22, 95% CI 1.09, 1.35), $p = .001$; this association was not significant among non- $\epsilon 4$ carriers only, (OR = 1.018, 95% CI 0.98, 1.06), $p = .369$. This increased risk of dementia among $\epsilon 4$ s with higher NPI total scores was due to lower NPI total score means $\pm$ SE among the CIND $\epsilon 4$ s (1.027 ± 0.311) vs. non- $\epsilon 4$ s (5.087 ± 1.727) compared with relatively similar means $\pm$ SE for NPI total scores among $\epsilon 4$ s with dementia (7.065 ± 1.016) or non- $\epsilon 4$ s with dementia (7.933 ± 1.474).

Models predicting conversion to cognitive impairment at follow-up from cognitively normal or CIND are presented in Table 3. After adjusting for age and education, the presence of neuropsychiatric symptoms (Model 1) was associated with an approximately 60% lower odds of conversion from normal at baseline to cognitive impairment (CIND or dementia) at 36 to 48 months (OR = 0.38, 95% CI 0.15, 0.99). Neither APOE status, NPI total score, nor the interaction between APOE and neuropsychiatric symptoms (presence or NPI total score) were associated with CIND or dementia at 36 to 48 months among those who were cognitively normal at baseline ($p > .05$), although risk of conversion to cognitive impairment (CIND or dementia) at 36 to 48 months based on the presence of APOE $\epsilon 4$ carrier status approached significance ($p = .062$).

After adjustment for covariates (age and education) in Model 2, NPI total scores were modestly but significantly associated with conversion from CIND to dementia at 16- to 18-month follow-up. Neither the presence of neuropsychiatric symptoms (Model 1) nor the interaction between APOE and neuropsychiatric symptoms (presence or NPI total) were significant predictors of converting from CIND to dementia at 16- to 18-month; however APOE $\epsilon 4$ carrier status approached significance ($p = 0.064$). None of the variables were significant predictors of conversion from CIND to dementia at 36- to 48-months ($p > 0.05$).

Post-Hoc Analyses

Specific neuropsychiatric symptoms conferred a greater risk of cognitive impairment at baseline (see Table 4). Notably, both presence and total scores for agitation, apathy, delusions, and depression were significantly associated with the odds of dementia (vs. normal cognitive status) at baseline. The odds ratios in these analyses were substantially larger for NPI presence (ORs = 3.02 – 49.66) than NPI total scores (ORs = 1.37 – 1.74). Presence and total scores for both apathy and depression were associated with a significantly greater odds of CIND (vs. normal cognitive status), also with substantially higher greater odds associated with presence (ORs = 6.06 and 3.27) than total score (ORs = 1.39 and 1.34). The presence of agitation, but not the agitation total score, was correlated with a 3.7-fold increase in odds of CIND vs. normal at baseline (OR = 3.71, 95% CI 1.48, 9.31). Only apathy total score, (OR = 1.13, 95% CI 1.01, 1.28) and presence of delusions, (OR = 5.67, 95% CI 1.29, 24.88) were associated with a greater odds of CIND vs. dementia. The other neuropsychiatric symptoms, namely anxiety and irritability, were not significantly associated with baseline cognitive status.

Discussion

The present study investigated the extent to which APOE $\epsilon 4$ status, neuropsychiatric symptoms, and their interaction, were associated with cognitive status and cognitive

trajectories in a representative sample of US adults aged 71 and older. This investigation extends findings from cross-sectional studies by demonstrating that neuropsychiatric symptoms predict conversion to CIND or dementia longitudinally.

In cross-sectional (baseline) analyses, we found that APOE $\epsilon 4$ carrier status and neuropsychiatric symptoms (both presence/absence and total score on the Neuropsychiatric Inventory) were independently associated with a greater odds of dementia and CIND versus normal cognitive status. This is consistent with the larger literature that finds both APOE (Betram *et al.*, 2010) and neuropsychiatric symptoms (Geda *et al.*, 2008; Lyketsos *et al.*, 2002; Okura *et al.*, 2010; Peters *et al.*, 2012) to be more prevalent among persons with dementia and CIND. Although APOE and neuropsychiatric symptoms were not independently associated with an increased odds of dementia vs. CIND in our cross-sectional analyses, the interaction between APOE and neuropsychiatric symptom total was significant. Specifically, we found an increased risk of dementia among $\epsilon 4$ s with higher NPI total scores due to *lower* NPI total scores among CIND $\epsilon 4$ vs. non- $\epsilon 4$ carriers compared with similar NPI total scores among dementia $\epsilon 4$ vs. non- $\epsilon 4$ carriers suggesting the importance of complex interactions among key risk factors for understanding the association of dementia relative to CIND. According to a review of cross-sectional studies of individuals with AD, APOE $\epsilon 4$ is significantly associated with elevated neuropsychiatric symptoms such as agitation or aggression, delusions, hallucinations, and symptoms of anxiety and depression (Panza *et al.*, 2011). Further, a recent investigation found that, among individuals with late-onset AD, carriers of the APOE $\epsilon 4$ allele demonstrated more mood and apathy symptoms but $\epsilon 4$ carrier status was not associated with global neuropsychiatric symptoms (D'Onofrio *et al.*, 2011). Our investigation demonstrates the potential for these two variables to interact in a cross-sectional model, although we found no evidence that their interaction predicts future conversion from normal to CIND or dementia, or from CIND to dementia.

The current investigation also lends support to the proposal that neuropsychiatric symptoms are indicators of cognitive impairment. The direction of the association, however, was not in the expected direction for participants who were cognitively normal at baseline as they had a lower risk of conversion to CIND or dementia at 36- to 48-month follow-up in the presence of one or more neuropsychiatric symptoms (note that participants who were cognitively normal at baseline were not followed up at 16- to 18-month follow-up). As expected, higher NPI total scores predicted progression from CIND at baseline to dementia at 16- to 18-month follow-up, although the magnitude of this association was small. The discrepancy between these two models indicates that, while greater frequency and severity of neuropsychiatric symptoms serves to predict future conversion to dementia among individuals with CIND, the mere presence of these symptoms but not their frequency and severity, predicts a *decreased* odds of conversion to any form of cognitive impairment among those deemed cognitively normal at baseline.

Neither APOE $\epsilon 4$ carrier status nor with its interaction with neuropsychiatric symptoms emerged as a predictor of conversion to cognitive impairment at 16 to 18 months or 36 to 48 months among those normal or with CIND at baseline. This was true after accounting for age, education, and neuropsychiatric symptoms. However, APOE approached significance as a predictor of conversion to cognitive impairment at 16 to 18 months. In a previous investigation with ADAMS, Plassman and colleagues (2008; see 2009 Erratum) reported that APOE was a significant predictor of conversion to dementia at 16 to 18 months (information not provided on adjustment for other variables). Thus, while there may be an effect for APOE $\epsilon 4$ in predicting conversion to cognitive impairment, this effect is likely of a lesser magnitude than that of key demographic variables and neuropsychiatric symptoms.

Further evaluation of specific neuropsychiatric symptoms in cross-sectional analyses revealed that both presence and total scores at baseline for apathy, agitation, depression and delusions were associated with an increased odds of CIND at baseline or dementia at baseline. In particular, these four symptoms were associated with an increased odds of dementia relative to normal in a cross-sectional analysis. Presence and total scores for apathy and depression, and presence only for agitation increased the odds of CIND relative to normal. The presence of delusions and total scores for apathy increased the odds of dementia relative to CIND. Thus, we found a pattern of psychotic symptoms, specifically delusions, more common in dementia than normal or CIND, and mood and apathy symptoms more common in CIND and dementia compared with normal. This is consistent with studies demonstrating that mood and apathy symptoms are more common in mild cognitive impairment compared with normal cognition, supporting the hypothesis that mood symptoms are potentially the first neuropsychiatric symptoms to appear in the transition between normal and MCI (Muangpaisan *et al.*, 2008). Further, these findings are in line with studies from the larger literature demonstrating that both mood and psychotic symptom clusters are common in dementia (for review see Cerejeira *et al.*, 2012).

The current investigation has several limitations. First, results may not generalize to non-U.S. samples or samples comprised of adults aged 70 and younger. In addition, sample sizes were not sufficiently large to examine different patterns of results among different CIND and dementia subtypes. Different patterns of results are possible, particularly in the analysis of specific types of neuropsychiatric symptoms—such as apathy in CIND due to stroke or vascular dementia (Jorge *et al.*, 2010; Withall *et al.*, 2011) and hallucinations and delusions in Alzheimer's dementia (Cerejeira *et al.*, 2012) or older individuals with mild cognitive impairment (Muangpaisan *et al.*, 2008). Further, our posthoc analyses of specific neuropsychiatric symptoms and cognitive status were limited to baseline data due to lack of power to examine these associations at follow-up.

In summary, we observed baseline associations between cognitive impairment (CIND and dementia) and neuropsychiatric symptoms and APOE $\epsilon 4$ allele carrier status, as well as the predictive power of neuropsychiatric symptoms on conversion from normal to cognitive impairment (CIND/dementia) and conversion from CIND to dementia. The APOE gene was not a robust predictor of conversion to cognitive impairment. Although undetermined if neuropsychiatric symptoms are a marker or causally linked to conversion from CIND to dementia, it is possible that treating these symptoms could delay further cognitive impairment. Future investigations should consider a broader age range of patients, CIND and dementia subgroups, and the association between neuropsychiatric symptoms and performance on specific neuropsychological tasks (rather than global diagnostic status). In addition, future research is needed to examine specific neuropsychiatric symptoms as predictors of conversion to cognitive impairment in a study with larger follow-up samples and self-reported psychiatric symptoms in lieu of collateral reported behavioral symptoms of psychiatric distress. Further, studies with comprehensive information about cholinergic and anticholinergic medications, known to influence memory, should adjust for their use.

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Key points

- Neuropsychiatric symptoms and APOE are associated cross-sectionally with an increased odds of cognitive impairment (CIND or dementia).
- Longitudinally, neuropsychiatric symptoms are associated with increased odds of converting from CIND or dementia (16- to 18-month follow-up), and a reduced risk of converting from normal to CIND or dementia (36- to 48-month follow-up).
- This investigation highlights the importance and complexity of behavioral symptoms, such as neuropsychiatric symptom status or frequency/severity, as predictors of future cognitive decline.

Table 1Weighted Sample Characteristics (mean $\pm$ SE or n (%)) at Baseline

Baseline	Normal	CIND	Dementia	Total
	(n = 307)	(n = 241)	(n = 308)	(n = 856)
Age	77.37 $\pm$ 0.28 ^{b,c}	80.92 $\pm$ 0.52 ^{a,c}	84.45 $\pm$ 0.55 ^{a,b}	79.15 $\pm$ 0.29
Years of education	12.36 $\pm$ 0.17 ^{b,c}	10.81 $\pm$ 0.22 ^a	10.33 $\pm$ 0.3 ^a	11.73 $\pm$ 0.11
Gender (male)	141 (39.2)	119 (45.0)	95 (31.1)	355 (39.4)
Ethnicity ^d				
Caucasian	238 (88.9)	157 (84.1)	218 (83.5)	613 (87.1)
African-American	40 (5.7)	52 (10.5)	67 (12.4)	159 (7.6)
Latino-American	29 (5.4)	32 (5.4)	23 (4.1)	84 (5.2)
APOE ϵ 4 Carrier [*]	72 (23.5)	53 (27.2)	110 (39.1)	235 (26.4)
NPI Symptom present ^{**}	45 (17.9)	87 (44.8)	190 (58.3)	322 (29.3)
Mean NPI Total ^{**}	0.94 $\pm$ 0.23	3.94 $\pm$ 1.26	7.48 $\pm$ 0.92	2.49 $\pm$ 0.34

Note. Only frequency counts (ns) are unweighted.

^a $p < 0.05$ when compared with normal.

^b $p < 0.05$ compared with CIND.

^c $p < 0.05$, compared with dementia.

^d $p < 0.05$ African American participants were more likely to be diagnosed as having dementia compared with Caucasian and Latino American participants. Compared with Caucasians, African Americans were also more likely to be diagnosed as having CIND than to be normal.

^{*} $n = 14$ cases missing APOE genotyping.

^{**} $n = 16$ cases missing the NPI.

NPI = Neuropsychiatric Inventory. APOE = Apolipoprotein E gene. CIND = cognitive impairment, no dementia.

Table 2
Cross-sectional results: Association of NPI and APOE with cognitive status at baseline

Baseline predictors	CIND (ref = normal)		Dementia (ref = normal)		Dementia (ref = CIND)	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
<i>Model 1</i>						
Age	1.12 (1.08, 1.17)	<0.001	1.25 (1.19, 1.31)	<0.001	1.11 (1.06, 1.16)	0.001
Education	0.89 (0.83, 0.95)	0.001	0.86 (0.80, 0.91)	<0.001	0.97 (0.92, 1.02)	0.185
NPI presence	4.20 (2.14, 8.23)	<0.001	7.56 (3.85, 14.86)	<0.001	1.80 (0.84, 3.87)	0.124
APOE	1.72 (0.85, 3.47)	0.127	3.29 (1.44, 7.54)	0.007	1.92 (0.76, 4.85)	0.160
NPI × APOE	0.60 (0.16, 2.19)	0.424	0.85 (0.35, 2.07)	0.713	1.42 (0.39, 5.21)	0.581
<i>Model 2</i>						
Age	1.12 (1.08, 1.17)	<0.001	1.25 (1.19, 1.31)	<0.001	1.11 (1.06, 1.16)	0.001
Education	0.87 (0.82, 0.93)	<0.001	0.84 (0.78, 0.90)	<0.001	0.96 (0.90, 1.02)	0.162
NPI total	1.16 (1.06, 1.27)	0.003	1.94 (1.08, 1.31)	0.001	1.03 (0.98, 1.07)	0.201
APOE	1.97 (1.09, 3.57)	0.027	3.03 (1.44, 6.39)	0.005	1.54 (0.69, 3.42)	0.279
NPI × APOE	0.87 (0.73, 1.04)	0.120	1.03 (0.91, 1.17)	0.617	1.19 (1.04, 1.35)	0.011

Note: CIND = cognitive impairment, no dementia; NPI = Neuropsychiatric Inventory; APOE ε4 = ε4 carrier (yes/no); NPI × APOE ε4 = the interaction between NPS (yes/no) and APOE ε4 (yes/no). Statistically significant results are bolded in table. P-values in this table are based on t-tests. Normal, $n = 307$; CIND, $n = 241$; Dementia, $n = 308$.

Table 3

Association of NPI and APOE at baseline with subsequent cognitive status.

Baseline predictors	Odds of dementia (ref = CIND) at 16- to 18-month follow-up <i>n</i> = 180		Odds of CIND or dementia (ref = normal) at 36- to 48-month follow-up <i>n</i> = 208		Odds of dementia (ref = CIND) at 36- to 48-month follow-up <i>n</i> = 93	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
<i>Model 1</i>						
Age	0.93 (0.84,1.03)	0.153	0.89 (0.83,0.96)	0.001	0.97 (0.91, 1.04)	0.452
Education	1.07 (0.95,1.21)	0.234	1.17 (1.07,1.28)	<0.001	0.97 (0.88, 1.07)	0.555
NPI presence	2.62 (0.88,7.81)	0.082	0.38 (0.15,0.99)	0.048	0.78 (0.30,2.07)	0.617
APOE	0.42 (0.10,1.78)	0.226	0.44 (0.19,1.04)	0.062	1.17 (0.36, 3.83)	0.789
NPI × APOE	0.40 (0.03,5.12)	0.465	3.84 (0.56, 26.23)	0.169	1.41 (0.16, 12.70)	0.756
<i>Model 2</i>						
Age	0.93 (0.84,1.03)	0.132	0.90 (0.84,0.96)	0.002	0.97 (0.91, 1.04)	0.429
Education	1.07 (0.95,1.20)	0.264	1.17 (1.07,1.27)	0.001	0.96 (0.86, 1.07)	0.475
NPI total	1.08 (1.00,1.17)	0.040	0.93 (0.82,1.05)	0.211	1.01 (0.97, 1.06)	0.614
APOE	0.33 (0.10,1.08)	0.064	0.48 (0.22,1.08)	0.074	1.92 (0.60, 6.08)	0.266
NPI × APOE	1.10 (0.63,1.93)	0.718	1.22 (0.83,1.78)	0.308	0.82 (0.66, 1.01)	0.059

Note: CIND = cognitive impairment, no dementia; NPI = neuropsychiatric symptoms on the Neuropsychiatric Inventory; APOE ε4 = ε4 carrier (yes/no); NPI × APOE = the interaction between NPI and APOE (yes/no). Significant results are bolded. P-values in this table are based on t-tests.

• CIND participants were followed at 16 to 18 months and 36 to 48 months; Cognitively normal participants were followed only at 36 to 48-months. Conversion analyses with cognitively normal participants includes conversion to CIND or dementia.

Table 4

Association of specific neuropsychiatric symptoms (presence and total) with cognitive status at baseline

Baseline predictors	CIND (ref = normal)		Dementia (ref = normal)		Dementia (ref = CIND)	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
<i>Agitation</i>						
Presence	3.71 (1.48, 9.30)	0.007	6.95 (2.83, 17.07)	<0.001	1.87 (0.81, 4.32)	0.135
Total	1.36 (0.94, 1.96)	0.102	1.53 (1.09, 2.16)	0.017	1.13 (0.93, 1.37)	0.204
<i>Anxiety</i>						
Presence	1.11 (1.07, 1.16)	0.702	1.22 (1.16, 1.28)	0.082	1.75 (0.61, 5.04)	0.287
Total	1.13 (0.90, 1.41)	0.273	1.28 (1.04, 1.57)	0.024 *	1.13 (0.90, 1.42)	0.272
<i>Apathy</i>						
Presence	6.06 (1.87, 19.64)	0.004	11.25 (2.85, 44.46)	0.001	1.86 (0.91, 3.80)	0.088
Total	1.39 (1.11, 1.75)	0.006	1.58 (1.27, 1.97)	<0.001	1.14 (1.01, 1.28)	0.034
<i>Delusions</i>						
Presence	8.75 (0.58, 132.30)	0.113	49.66 (3.85, 641.04)	0.004	5.67 (1.29, 24.88)	0.023
Total	1.39 (0.93, 2.08)	0.101	1.74 (1.64, 2.60)	0.009	1.25 (0.89, 1.76)	0.189
<i>Depression</i>						
Presence	3.27 (1.84, 5.83)	<0.001	3.02 (1.55, 5.90)	0.002	0.92 (0.51, 1.67)	0.777
Total	1.34 (1.12, 1.60)	0.001	1.37 (1.15, 1.63)	0.001	1.02 (0.88, 1.18)	0.787
<i>Irritability</i>						
Presence	3.13 (1.20, 8.13)	0.021 *	2.83 (1.05, 7.64)	0.041 *	0.91 (0.42, 1.97)	0.794
Total	1.31 (0.96, 1.79)	0.089	1.43 (1.04, 1.95)	0.027 *	1.09 (0.94, 1.27)	0.261

Note:

*To minimize Type I errors, models in which the omnibus test (Wald F test) yielded a P-value > 0.05 were not interpreted as significant regardless of the results of significant simple effects tests (t-value). Significant results are bolded. P-values in this table are based on t-tests. CIND = cognitive impairment, no dementia. All models adjusted for age and education (data not shown). Models with symptom presence and symptom total conducted separately.