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Neuropsychiatric symptoms and Apolipoprotein E: Associations with eventual Alzheimer's disease development

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Abstract

Objective—Alzheimer's disease (AD) is the result of neurodegeneration, which manifests clinically as deficits in memory, thinking, and behavior. It was hypothesized that neuropsychiatric symptoms and the apolipoprotein E genotype increase the likelihood of Alzheimer's disease development.

Methods—Utilizing data from the National Alzheimer's Coordinating Center, information from evaluations of 11,453 cognitively intact participants was analyzed. Survival analysis was used to explore relationships between individual neuropsychiatric symptoms as determined by the Neuropsychiatric Inventory Questionnaire, apolipoprotein E, and eventual AD diagnosis. Cox proportional hazard models were utilized to explore the main effects and synergistic (additive and multiplicative) interactions.

Results—This study provided evidence for an increased hazard of developing AD among participants with any of the symptoms assessed by the NPI-Q. The hazard of developing AD was almost thirteen times higher for $_{\varepsilon}4$ carriers with delusions and eleven times greater for those with apathy and disinhibition. Statistically significant hazards ($p > 0.001$) were also realized by $_{\varepsilon}4$ carriers with hallucinations; agitation; depression; anxiety; elation; apathy; irritability; and motor, sleep, and appetite disturbances.

Conclusions—Findings suggest that neuropsychiatric symptoms are associated with eventual AD diagnosis among a group of cognitively asymptomatic participants at baseline. Many studies begin with a group of participants already impacted by AD diagnosis. The longitudinal analysis of

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Conflict of interest

All authors have stated that they have no conflicts of interest to report.

a group of participants who, at baseline, demonstrated no observable signs of AD was a strength of this study. This investigation contributes to the literature exploring an increased hazard of AD due to potential modifiable risk factors and genetic biomarkers such as apolipoprotein E.

Keywords

Alzheimer's disease; Apolipropotein e; Apoe ε4; Neuropsychiatric symptoms; Delusions; Apathy; Disinhibition; Agitation; Hallucinations; Anxiety; Elation; Irritability; Motor disturbance; Sleep disturbance; Appetite disturbance

Alzheimer's disease due to dementia (AD) is a fatal condition caused by cerebral matter neurodegeneration. Diagnosis of AD is often clinical in nature, as observable symptoms pertaining to memory, cognition, and attention most often inform the diagnosis (Meng & D'Arcy, 2013). Cognitive degeneration and accumulation of plaques and tangles may begin more than 25 years earlier than any observable clinical signs of AD (Bateman et al., 2012). It is well accepted that AD dementia arises from a complex pathophysiological process, and many diagnosed with AD dementia passed through a stage of mild cognitive impairment first (McKhann, Knopman, Chertkow, Hyman, & Kawas, 2011).

The current study examined the occurrence of behavioral symptoms contained within the Neuropsychiatric Inventory Questionnaire) (Cummings, 1997) among cognitively asymptomatic subjects and the effect on the hazard of AD dementia diagnosis among apolipoprotein (APOE) $_{\varepsilon}$4 carriers. These symptoms include delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, sleep disturbance, motor disturbance, appetite fluctuations, and irritability.

Inherited genes create a predisposition for AD dementia increasing susceptibility, though do not ensure development. APOE has been associated with increased susceptibility in sporadic late-onset AD cases (Bennett et al., 1995). Compared to non-APOE $_{\varepsilon}$4 carriers, the risk is two to four times greater in those with one $_{\varepsilon}$4 allele. The risk is 12 times greater in those with two $_{\varepsilon}$4 alleles (Hollingworth, Harold, Jones, Owen, & Williams, 2011). AD onset may occur seven to nine years earlier for each additional $_{\varepsilon}$4 allele compared to non- $_{\varepsilon}$4 carriers (Ashford, 2004). The presence of $_{\varepsilon}$2 is considered to be neuroprotective (Talbot et al., 1994). The presence of $_{\varepsilon}$3 and $_{\varepsilon}$4 confer greater risks (Schipper, 2011). However, the presence of $_{\varepsilon}$3, may confer protective benefits relative to $_{\varepsilon}$4 (Aboud, Mrak, Boop, & Griffin, 2012). The mechanism behind APOE risk is not fully understood; nevertheless, APOE $_{\varepsilon}$3 may decrease the rate at which β-amyloid protein, the precursor to plaques, is cleared from the brain. The APOE $_{\varepsilon}$4 allele appears to slow this process more than other alleles. One study found that decreasing APOE $_{\varepsilon}$3 and $_{\varepsilon}$4 by half in mice led to an increase in β-amyloid clearance in the brain (Jiang et al., 2008).

Gene-environment interaction (Belsky, Moffitt, & Caspi, 2013) offers a framework to consider the differential effects of susceptibility genes in concert with variable environmental influences. This hypothesis suggests that different genotype combinations respond to the environment and psychosocial factors in a varied manner, but that select interactions may serve to increase or decrease risk of particular conditions.

Several studies have examined neuropsychiatric symptoms relative to AD development. Okura et al. (2010) utilized data from the Aging, Demographics, and Memory Study to examine neuropsychiatric symptoms (NPS) such as “agitation, depression, apathy, delusions and hallucinations” relative to AD development. Depression was the most commonly occurring neuropsychiatric symptom for those with cognitive impairment without dementia, as well as mild, moderate, and severe dementias in respondents 71 years of age and older. Many studies previously examining neuropsychiatric symptoms used regional data and focused on groups with mild cognitive impairment or dementia. Okura et al. were among the first to include a clinically asymptomatic (n = 303) nationally representative sample with regard to the prevalence of these symptoms while taking into account the degree of cognitive impairment.

Applying a similar approach, Peters et al. (2013) examined subjects with cognitive impairment without dementia (CIND) (n = 230). The researchers observed the conversion rate from CIND to AD. Their findings indicated that APOE $_{\varepsilon}4$ was a risk factor, as were nighttime behaviors and the presence of even one neuropsychiatric symptom. The findings indicate that even mild neuropsychiatric symptoms create a risk for dementia.

As D’Onofrio, Panza, Seripa, Sancarlo, and Paris (2011) found in their study of the presence and absence of neuropsychiatric symptoms in those with AD (n = 322), there was not a significant association between APOE and NPS. For carriers of APOE $_{\varepsilon}4$ and those diagnosed with AD, there was an increased risk of certain affective syndromes. Results of the aforementioned study contribute to the unresolved debate around the role of APOE $_{\varepsilon}4$ and depression, and identify the need for larger samples and longitudinal designs to enhance the literature. This recommendation was supported by van der Linde, Stephan, Sawa, Dening, and Brayne (2012), who, following their systematic review of the literature, expressed the need for longitudinal studies, larger sample sizes, and the inclusion of commonly cited behavioral and psychological instruments to better understand risk and the course of illness for those with behavioral and psychological risk factors.

This study had three hypotheses. First, it was hypothesized that the main effects of individual neuropsychiatric symptoms and positive ε4 carrier status will increase the hazard of eventual AD diagnosis. Second, it was hypothesized that the additive effects of individual NPS in combination with positive ε4 carrier status will results in statistically significant hazards of eventual AD diagnosis. Last, it was hypothesized that the multiplicative interaction effects of individual NPS in combination with positive ε4 carrier status will result in statistical significant hazards of eventual AD diagnosis.

1. Methods

Data from the National Alzheimer’s Coordinating Center (NACC) Uniform Data Set (UDS) were examined. The information in the UDS is collected during yearly meetings with subjects (or provided by a chosen close friend, family member, neighbor, or caregiver) and trained clinicians. These interviews acquire demographic information; family history; health history; medications used; and a physical is conducted including imaging and labs. Participants are assessed using rating scales concerning cognitive, physical, psychological,

and neuropsychological domains. These rating instruments include: the Clinical Dementia rating (CDR) (sum of boxes and global) (Morris, 1993), the Geriatric Depression Scale (Yesavage et al., 1983), the Functional Activities Questionnaire (Pfeffer, Kurosaki, Chance, & Filos, 1982), and a clinician judgement of symptoms. Neuropsychological testing includes the Montreal Cognitive Assessment (Nasreddine et al., 2005), the Mini Mental State Examination (Folstein, Folstein, & McHugh, 1975), Logical Memory Immediate, Logical Memory Delayed, Digit Span Forward, Digit Span Backward, Category Fluency (Animals and Vegetables), Trail Making Test, WAIS-R Digit Symbol, and the Boston Naming Test (National Alzheimer's Coordinating Center, 2005). A diagnosis regarding dementia status is often determined by a group of two or more clinicians, neuropsychologists, or the examining physician (National Alzheimer's Coordinating Center, 2010).

The variables utilized for this study included normal cognition, probable AD, the symptoms listed in the neuropsychiatric inventory questionnaire (NPI-Q) (Cummings, 1997), and APOE genotype. Normal cognition is defined as a CDR global score of zero and/or neuropsychological testing within the normal range. Sporadic late-onset AD was the outcome of interest and is referred to as probable AD throughout this study. This variable was formed through a combination of cognitive status and etiologic diagnosis (dementia and probable AD) in order to rule-out dementia due to other causes. Probable AD is diagnosed within the UDS using criteria set forth by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA). Those meeting the original 1984 NINCDS-ADRDA criteria also met the 2011 criteria (McKhann et al., 2011). The criteria is a composite and requires that a patient or subject meet the criteria for all-cause dementia. This requires an interference with usual work and activities, a decline in functioning, a rule-out of delirium and other psychiatric explanations for the cognitive presentation, and cognitive and/or behavioral impairment in at least two additional domains. Probable AD is diagnosed as the criteria for dementia is met, and the participant meets additional criterion. This criterion includes a gradual onset, demonstrable decline in cognitive presentation, and determination of amnestic, non-amnestic, or executive functioning impairment (McKhann et al., 1984).

The current study focused on behavioral symptoms on the NPI-Q (Cummings, 1997), an assessment tool, which is completed by trained health professionals. These professionals are certified as interviewers through a training mechanism administered by the University of California, Los Angeles and the NACC. Variables included in this study are the presence and absence of delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, motor disturbance, nighttime behaviors, and appetite disturbance.

APOE is measured by the presence or absence of $_{\varepsilon}4$, denoted by the terms $_{\varepsilon}4$ *carrier* and *non-carrier*. An $_{\varepsilon}4$ carrier has the potential to possess one or two $_{\varepsilon}4$ alleles, while a non-carrier possess other combinations of APOE, none of which contain $_{\varepsilon}4$.

The hypothesis of this study was examined using survival analysis. Survival analysis is used when researchers are concerned with the time until a specific event, and is frequently used to examine longitudinal data (Kleinbaum & Klein, 2012). An event (outcome variable) was defined as a diagnosis of probable Alzheimer's disease by a subject's last visit. Outcomes

will be described as hazard ratios. Right censoring will be utilized to account for the fact that a subject may not develop AD prior to their last observation, or may leave before the study's conclusion. True survival time is unknown unless a participant develops clinically observable AD by their last observation. The statistical program STATA (StataCorp, Release 13, 2013) was utilized for the analyses, and a p value < 0.05 was considered statistically significant.

Out of the 29,765 possible participants, those with normal cognition in their first visit (n = 11,453) were the sample selected for all three analyses. Time zero was equal to the subject's first observation (visit number 1), and time was measured in days.

Univariate analysis was conducted to determine frequencies and distributions of predictor variables and covariates. Baseline survival function was determined using log-rank tests. The relationship of certain predictor variables were examined relative to the outcome variable using the Cox proportional hazards model (Cox, 1972). Additional demographic covariates were added to each model and controlled for appropriately. The hazard ratio is an estimate of the instantaneous probability of developing AD at some point between visit one and another point as observed at a follow-up visit, divided by the probability that the individual would not develop AD beyond the initial visit. Regression modeling included simultaneous control of multiple predictors. The main effects were examined and covariates such as age, sex, race, Hispanic origin, and parental dementia status were controlled. Primary predictors were also stratified by APOE genotype to further examine the role of the biomarker. The additive effects of primary predictors were tested using pairwise comparisons. The assumption of proportionality was examined through inspection of Schoenfeld residuals in order to determine whether the Cox proportional hazards assumption had been met.

2. Results

The minimum amount of time under observation for all included subjects was 208 days until the first occasion that the AD diagnosis occurred, and the maximum was 3229 days (M = 1469.37; Mdn: 1350.5). The mean number of visits for those with normal cognition was three, with a range of one to ten visits. There were 330 diagnoses of AD dementia (failures) by the end of the observation period among older adults who had at least an initial visit as well as a follow-up visit. The mean age of subjects with normal cognition at visit one was 71.2 (SD: 10.89; Mdn: 72). At visit one, 80.7% of the sample were Caucasian, 13.2% were African American, and 5.9% were from other ethnic groups. Six percent of the sample reported Hispanic origin. Almost 35% of subjects reported that their mother had been diagnosed with dementia, while 16.3% reported that their father had been diagnosed with depression. Percentages, means, and standard deviations (where applicable) are displayed in Table 1. Demographic information by converter or non-converter status as well as bivariate analysis of the two groups are displayed in Table 2.

Preliminary univariate analysis using the log-rank test for equality of survivor functions revealed statistically significant differences (p < 0.001) in the survival curves of those who did and did not experience delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, and sleep disturbance.

Three models were developed for exploration of the main effects of the predictor variables. In the first model, unadjusted main effects were examined. In the second model, covariates such as sex, age, race, Hispanic origin, and dementia status of parents were controlled. In the third model, the primary predictor of interest was examined in relation to the previous confounders and with the addition of APOE $_{\varepsilon}4$ carrier status. A similar structure was applied to exploration of additive and interaction effects. The additive and interaction effects of primary predictors by APOE $_{\varepsilon}4$ carrier status were tested in the first model and were adjusted by sex, age, and race in the second model. Dementia status of parents was dropped as a confounder in the interaction models due to a diminished sample size.

The main effects of all NPS present on the NPI-Q were statistically significant ($p < 0.001$). The presence of delusions produced the highest effect, denoting over ten times the hazard of eventual AD diagnosis within the observation period. Apathy, disinhibition, and the presence of hallucinations produced statistically significant ($p < 0.001$) results, indicating more than five times the hazard of subsequent AD development as compared to those not reporting such symptoms. Agitation, elation and appetite disturbances also produced statistically significant outcomes ($p < 0.001$). Anxiety, irritability, and depression produced statistically significant ($p < 0.001$) hazards at least two times more than those who did not experience such symptoms. Statistically significant hazards were experienced by those reporting sleep disturbance as compared to those without such symptoms. Finally, $_{\varepsilon}4$ carrier status also produced statistically significant hazards compared to non-carriers. When these symptoms were adjusted for the effect of sex, age, race, Hispanic origin, dementia status of parents, and APOE, almost all of the hazards increased slightly, while a markedly higher hazard occurred for participants reporting delusions, elation, apathy, and disinhibition. All NPI-Q symptoms remained statistically significant to varying degrees when stratified by $_{\varepsilon}4$ carrier status, except for elation, which was no longer statistically significant for $_{\varepsilon}4$ non-carriers. In most cases, the hazard for $_{\varepsilon}4$ carriers was higher than that of non-carriers, with exceptions in the case of disinhibition and motor disturbance. In these two instances, the hazard among $_{\varepsilon}4$ non-carriers was greater than that for carriers. Main effects for all primary predictors are displayed in Table 2.

Additive effects were examined for each of the NPS of the NPI-Q, with respect to their combination with $_{\varepsilon}4$ carrier status (displayed in Table 3). The additive effects in all cases were statistically significant at $p < 0.001$, with the exception of elation, which was significant at $p < 0.05$. The additive effects remained statistically significant ($p < 0.001$) when sex, age, race, and Hispanic origin were controlled.

Interaction effects were also examined for each of the individual NPI-Q symptoms in concert with $_{\varepsilon}4$ carrier status (displayed in Table 4). Statistically significant effects were demonstrated by $_{\varepsilon}4$ carriers experiencing delusions (HR = 0.585 (0.363–0.945, $p < 0.05$, adjusted) and motor disturbance (HR = 539 (0.323–0.899, $p < 0.05$, adjusted). Interestingly, the majority of interactions in the multiplicative models were non-significant even though the main effects of each independent variable and additive effects of the factors combined demonstrated statistically significant hazards of eventual AD development ($p < 0.001$ in most cases). Furthermore, where significant interactions did occur, they were often demonstrating a reductive factor, such that $_{\varepsilon}4$ carriers with delusions showed a 41.6%

reduction in risk of probable AD as an outcome. $_{\varepsilon}4$ carriers with motor disturbance similar exhibited a 46.1% reduction in risk of progression to AD (Table 5).

3. Conclusions

This study builds upon empirical investigations examining the NPI-Q as a tool to predict AD risk. Findings indicate that the additive effect of behavioral and psychological factors on the NPI-Q and a positive $_{\varepsilon}4$ carrier status increased the hazard significantly for all $_{\varepsilon}4$ allele combinations. It is important to note that an additive interaction model is preferred by many epidemiologists with regard to public health risk analysis (VanderWeele & Knol, 2014).

Using the NACC UDS, DeMichele-Sweet, Lopez, and Sweet (2011) investigated psychotic symptoms, which included delusions and hallucinations, among UDS subjects with possible or primary AD (DeMichele-Sweet et al., 2011). The researchers cited the late development of psychosis among those with AD as a reason for utilizing a group of participants who had already developed AD. In addition, this psychotic phenotype occurs in up to 50% of late-onset AD patients. No association was found between APOE $_{\varepsilon}4$ carrier status and psychotic symptoms in this population (National Alzheimer's Coordinating Center, 2010).

Reports of no association between NPI-Q symptoms and AD from several researchers can be contrasted with positive associations in other studies (D'Onofrio et al., 2011). Prete, Spaccavento, Craca, Fiore, and Angelelli (2009) found $_{\varepsilon}4$ carriers to be afflicted with 75% of the symptoms on the NPI-Q, while non-carriers experienced just 50% of the symptoms when using the NPI-Q as a measurement index. Findings in the current study indicate statistically significant ($p < 0.001$) hazards for those with hallucinations in both the main effect and in the additive model. Small sample size prohibited further adjustment.

This study examined hazards relative to the progression from baseline normal cognition to a diagnosis of AD when NPS and $_{\varepsilon}4$ carrier status were taken into account. Studies examining items on the NPI-Q in the published literature investigate the progression from an impaired status to AD and regularly focus on psychotic or depressive phenotypes (Christie et al., 2012). In the current study, all individual items evaluated on the NPI-Q were included as distinct factors. Empirical research seeking to identify relationships between NPS and AD often cluster symptoms together in an effort to identify phenotypes. Given that the goal of this study was to examine the presence of NPS items individually in relation to AD over the course of several observation intervals, these items were examined discretely. Interestingly, in the current study, statistical significance was found among the components of the psychotic phenotypes (delusions, hallucinations) in main effects models. When analyzed in additive models, taking into account the effect of positive $_{\varepsilon}4$ carrier status, the hazards far exceeded the sum of the predictor variables on their own. In fact, positive and significant associations were revealed among main effects and additive models exploring associations between all NPS factors and eventual AD diagnosis. These findings indicate that the hazard of all NPS are significant at $p < 0.001$, with the exception of elation at $p < 0.05$ in a cognitively asymptomatic population with respect to AD. Interesting findings in the additive models were not echoed by outcomes in the multiplicative models, which demonstrated a

reduction in risk of progression to AD for ε4 carriers with delusions or motor disturbance. This unique variation merits further analysis.

A strength of this study is the longitudinal analysis of a group of participants who, at baseline, demonstrated no observable signs of AD. Many studies begin with a group of participants already impacted by AD diagnosis. Utilization of a clinically cognitively intact population is supported by the work of Lyketsos and Olin (2002), who noted that NPS may precede or develop early in AD development. A strength can also be found in the sample size as the NACC UDS is the largest and most inclusive relational database pertaining to AD in the United States.

Several theoretical frameworks attempt to explicate the relationship between NPS and AD. A professional interest group arising out of the International Society to Advance Alzheimer's Research and Treatment has proposed four explanatory mechanisms (Geda, Schneider, Gitlin, Miller, & Smith, 2013). These models include (a) genetic or otherwise organic etiology, (b) NPS as a shared or confounding risk factor connected by a yet to be confirmed and/or discovered third factor, (c) psychological reactions to an apparent cognitive decline leading to NPS, and (d) an interaction effect between NPS and a genetic influence leading to an increased risk for AD. Synergistic interaction was the focus of this study. The associations found within this group of NACC participants provide support for the four models advanced by VanderWeele and Knol (2014); specifically the hypothesis that a synergistic effect a mechanism increasing risk of AD. Though the exact role of APOE $_{\varepsilon}4$ remains under debate, this study provides evidence that APOE $_{\varepsilon}4$, independently and in interaction with psychiatric symptoms, increases the hazard of all NPS variables, not just those of the psychotic phenotype. Without detailed exposure histories and further understanding in the scientific community regarding the exact causal pathways associated with NPS, APOE, and AD, it is difficult to rule-out any of the proposed hypothetical models. The NPS factors examined here were described by the participants at baseline and at a stage when they were showing no signs of cognitive impairment. Without complete exposure histories, researchers at this time are unable to determine whether a predictor is an early symptom of AD or an actual risk factor. Future research should investigate whether these symptoms are independent risk factors for AD.

This study sought to examine the role of NPS and its progression to AD in a sample not otherwise affected by clinically observable cognitive degeneration. Triangulation of observable asymptomatic status with diagnostic imaging may better ensure that the mental health risk factors are in fact preceding development of AD, as opposed to prodromal symptoms of the disease itself. A focus on imaging at the preclinical stage and emphasizing complete exposure histories may allow for forward causal inferences to be made. In addition, such detailed historical data may solve the longstanding limitation of reverse causation.

Future research should focus on the efficacy of NPS intervention in a baseline cognitively intact sample to examine the relationship to eventual AD diagnosis. Specific attention to samples at-risk for AD development due to family history should be included at cognitively normal stages. Exploration may include whether self-reported or clinician judged

improvement in neuropsychiatric symptomology alters or delays the pathophysiological neurodegeneration process or simply provides self-reported psychosocial relief to the participant. Despite self-reported relief from symptoms, pathophysiological neurodegeneration may be underway in participants with NPS, and treatment may be beneficial solely in a palliative sense. Public health campaigns and the social work community are poised to bring attention to the increased risk posed by neuropsychiatric symptoms on long-term neurodegeneration. Research confirming the association between NPS and AD, as well as an increasing hazard of AD development due to these symptoms, suggests that intervention in NPS symptom presence, intensity, and severity may serve as an intervention site for counseling professionals. Effective treatment of NPS symptoms may delay the onset of AD among otherwise cognitively intact individuals.

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Table 1

Demographic overview of sample and predictor Variables.

Predictor	At Visit One – Baseline		Delusions		Hallucinations		Agitation		Depression		Anxiety	
			Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Normal Cognition	11,453		85 (0.80%)	10,491 (99.20%)	30 (0.28%)	10,546 (99.72%)	612 (5.79%)	9964 (94.21%)	1454 (13.75%)	9122 (86.25%)	915 (8.65%)	9661 (91.35%)
Female	7464 (65.2%)		43 (50.59%)	6849 (65.28%)	17 (56.67%)	6875 (65.19%)	304 (49.67%)	6588 (66.19%)	949 (65.27%)	5943 (65.15%)	611 (66.78%)	6281 (65.01%)
Age	X = 71.18 (SD = 10.87)		X = 74.53 (SD = 0.222)		X = 74.88 (SD = 0.235)		X = 73.11 (SD = 0.158)		X = 71.68 (SD = 0.126)		X = 72.08 (SD = 0.145)	
Race	Caucasian	9188 (80.7%)	65 (76.47%)	8428 (80.34%)	24 (80%)	8469 (80.31%)	503 (89.19%)	7990 (80.19%)	1216 (83.63%)	7277 (79.77%)	774 (84.59%)	7719 (79.90%)
	African-American	1504 (13.2%)	11 (12.94%)	1373 (13.09%)	2 (6.66%)	1382 (13.10%)	63 (10.29%)	1321 (13.26%)	126 (8.67%)	1258 (13.79%)	74 (8.09%)	1310 (13.56%)
	Hispanic	695 (6.07%)	13 (15.29%)	608 (5.80%)	5 (16.66%)	616 (5.84%)	52 (8.50%)	569 (5.71%)	149 (10.25%)	472 (5.17%)	106 (11.58%)	515 (5.33%)
	Other	671 (5.9%)	8 (9.41%)	617 (5.88%)	4 (13.33%)	621 (5.89%)	38 (6.21%)	587 (5.89%)	94 (6.46%)	531 (5.82%)	57 (6.23%)	625 (6.47%)
Mother – Dementia	Yes 3748 (34.6%)	No 7090 (65.4%)	23 (27.06%)	3530 (33.65%)	4 (13.33%)	3549 (33.65%)	200 (32.68%)	3353 (33.65%)	527 (36.24%)	3026 (33.17%)	323 (35.30%)	3230 (33.43%)
Father –Dementia	Yes 1722 (16.3%)	No 8850 (83.7%)	12 (14.12%)	1630 (15.54%)	6 (20%)	1636 (15.51%)	104 (16.99%)	1538 (15.44%)	228 (15.68%)	1414 (15.50%)	151 (16.50%)	1491 (15.43%)
No $_e$4	5876 (70.14%)		35 (41.18%)	5382 (51.30%)	11 (3.33%)	5406 (51.26%)	289 (47.22%)	5128 (51.47%)	706 (48.56%)	4711 (51.64%)	420 (45.90%)	4997 (51.72%)
1 $_e$4 Allele	2278 (27.19%)		13 (15.29%)	2102 (20.04%)	5 (16.66%)	2110 (20.01%)	134 (21.90%)	1981 (19.88%)	286 (19.67%)	1829 (20.05%)	175 (19.13%)	1940 (20.08%)
2 $_e$4 Alleles	224 (2.67%)		0	212 (2.02%)	0	212 (2.01%)	11 (1.80%)	201 (2.02%)	31 (2.13%)	181 (1.98%)	21 (2.30%)	191 (1.98%)

Predictor	At Visit One – Baseline	Elation		Apathy		Disinhibition		Irritability		Sleep Disturbance	
		Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Normal Cognition	11,453	88 (0.83%)	10,488 (99.17%)	484 (4.58%)	10,092 (95.42%)	259 (2.45%)	10,317 (97.55%)	1197 (11.32%)	9379 (88.68%)	1120 (10.6%)	9456 (89.4%)
Female	7464 (65.2%)	48 (54.55%)	6844 (65.26%)	259 (53.51%)	6633 (65.73%)	137 (52.90%)	6755 (65.47%)	619 (51.71%)	6273 (66.88%)	699 (62.4%)	6193 (65.5%)

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Age	X = 71.2 (SD = 10.89)		X = 74.19 (SD = 0.231)		X = 73.11 (SD = 0.163)		X = 73.58 (SD = .191)		X = 72.24 (SD = 0.130)		X = 72.13 (SD = 0.138)	
Race	Caucasian	9188 (80.7%)	75 (85.23%)	8418 (80.26%)	390 (80.58%)	8103 (80.29%)	214 (82.63%)	8279 (80.25%)	999 (83.46%)	7494 (79.90%)	941 (84.6%)	7552 (80.4%)
	African-American	1504 (13.2%)	11 (12.5%)	1373 (13.09%)	63 (13.02%)	1321 (13.09%)	27 (10.42%)	1357 (13.15%)	119 (9.94%)	1265 (13.49%)	100 (9%)	1284 (13.7%)
	Hispanic	695 (6.07%)	9 (10.23%)	612 (5.84%)	52 (10.74%)	569 (5.64%)	25 (9.65%)	596 (5.78%)	100 (8.35%)	521 (5.55%)	108 (9.64%)	513 (5.43%)
	Other	671 (5.9%)	2 (2.27%)	623 (5.94%)	25 (5.17%)	600 (5.95%)	16 (6.18%)	609 (5.90%)	68 (5.68%)	557 (5.94%)	71 (6.4%)	554 (5.9%)
Mother – Dementia	Yes 3748 (34.6%)	No 7090 (65.4%)	25 (28.41%)	3528 (33.64%)	162 (33.47%)	3391 (33.60%)	84 (32.43%)	3469 (33.62%)	425 (35.51%)	3128 (33.59%)	367 (34%)	3186 (35%)
Father – Dementia	Yes 1722 (16.3%)	No 8850 (83.7%)	12 (13.64%)	1630 (15.54%)	69 (14.26%)	1573 (15.59%)	50 (19.31%)	1592 (15.43%)	183 (15.29%)	1459 (15.56%)	196 (18.7%)	1446 (16.3%)
No $_{e}$4	5876 (70.14%)		33 (37.5%)	5384 (51.33%)	219 (45.25%)	5198 (51.51%)	121 (46.72%)	5296 (51.33%)	567 (47.37%)	4850 (51.71%)	565 (50.45%)	4852 (51.31%)
1 $_{e}$4 Allele	2278 (27.19%)		20 (22.73%)	2095 (19.98%)	94 (19.42%)	2021 (20.03%)	53 (20.46%)	2062 (19.99%)	262 (21.89%)	1853 (19.76%)	217 (19.38%)	1898 (20.07%)
2 $_{e}$4 Alleles	224 (2.67%)		3 (3.41%)	209 (1.99%)	13 (2.69%)	199 (1.97%)	5 (1.93%)	207 (2.01%)	26 (2.17%)	186 (1.98%)	22 (1.96%)	190 (2.01%)

Table 2

Demographic overview of converters and non-converters.

	Converters to AD	Non-Converters	*t* or χ^2 Statistic[a]
	620	**947**	
Age (yrs)	84.58 (SD:8.65)[b]	81.83 (SD: 9.41)	−5.85, df = 1565, $p = 0.00$
Female	408 (65.81%)[c]	580 (61.25%)	3.34, df = 1, $p = 0.067$
Education (yrs)	16.33 (SD: 9.99)	15.54 (SD: 3.97)	−2.17, df = 1565, $p = 0.03$
Race			1.12, df = 2, $p = 0.572$
White	528 (85.85%)	792 (84.12%)	
African-American	65 (10.57%)	116 (12.33%)	
Other	22 (3.58%)	33 (3.51%)	
Hispanic	33(5.33%)	25 (2.64%)	7.60, df = 1, $p = 0.006$
E4Carrier	241 (44.96%)	258 (31.81%)	23.93, df = 1, $p = 0.00$
Delusions	79 (13.98%)	22 (2.51%)	69.34, df = 1, $p = 0.00$
Hallucinations	30 (5.31%)	7 (.80%)	27.93, df = 1, $p = 0.00$
Agitation	154 (27.26%)	114 (13.01%)	46.02, df = 1, $p = 0.00$
Depression	194 (34.34%)	179 (20.43%)	34.60, df = 1, $p = 0.00$
Anxiety	173 (30.62%)	151 (17.24%)	35.29, df = 1, $p = 0.00$
Elation	17 (3.01%)	11 (1.26%)	5.54, df = 1, $p = 0.02$
Apathy	193 (34.16%)	104 (11.87%)	104.27, df = 1, $p = 0.00$
Disinhibition	96 (16.99%)	42 (4.79%)	59.00, df = 1, $p = 0.00$
Irritability	187 (33.10%)	173 (19.75%)	32.66, df = 1, $p = 0.00$
Motor Disturbance	65 (11.50%)	18 (2.05%)	56.50, df = 1, $p = 0.00$
Appetite Disturbance	147 (26.02%)	114 (13.01%)	39.16, df = 1, $p = 0.00$
Sleep Disturbance	159 (28.14%)	149 (17.01%)	25.33, df = 1, $p = 0.00$

[a] χ^2 test statistics are displayed for categorical variables, *t* test statistics for continuous variables.

[b] Continuous variables are described with mean and standard deviation.

[c] Categorical variables are described with sample size and percentage.

Table 3

Cox proportional hazards – main effects (Alzheimer's disease dementia as outcome variable).

Predictor Variables	Main Effects (Unadjusted) Hazard Ratio (95% CI)	Wald Statistic	Main Effects Adjusted[a] w/o $_{\varepsilon}$4Carrier status Hazard Ratio (95% CI)	Main Effects Adjusted w/$_{\varepsilon}$4Carrier status Hazard Ratio (95% CI)	Main Effects Stratified by $_{\varepsilon}$4Carrier	Main Effects Stratified by Non- $_{\varepsilon}$4Carrier
Delusions	11.37 (8.02–16.14) **	199.9	17.15 (7.32–40.15) **	16.63 (7.11–38.92) **	17.44 (4.51–67.40) **	13.72 (4.29–43.90) **
Hallucinations	6.00 (2.97–12.13) **	27.04	–	–	–	–
Agitation/ Aggression	4.94 (3.82–6.38) **	153.85	5.00 (2.57–9.75) **	4.82 (2.47–9.40) **	6.15 (2.27–16.65) **	4.57 (1.78–11.71) *
Depression/ Dysphoria	3.06 (2.41–3.97) **	88.43	3.11 (1.69–5.71) **	3.05 (1.65–5.61) **	3.21 (1.33–7.74) *	3.02 (1.29–7.09) *
Anxiety	3.52 (2.75–4.52) *	101.27	3.95 (2.04–7.64) **	3.81 (1.97–7.36) **	5.57 (2.20–14.12) **	3.23 (1.20–8.70) *
Elation	4.50 (2.31–8.73) **	20.64	16.75 (4.94–56.84) **	16.18 (4.78–54.74) **	24.31 (5.25–112.61) **	8.02 (0.991–64.88)
Apathy	6.99 (5.51–8.88) **	267.47	10.36 (5.74–18.72) **	9.51 (5.23–17.31) **	14.02 (5.62–34.95) **	9.51 (4.12–21.95) **
Disinhibition	6.03 (4.39–8.27) **	129.4	8.74 (4.16–18.35) **	8.62 (4.08–18.20) **	8.19 (2.68–25.04) **	9.65 (3.51–26.53) **
Irritability	3.49 (2.75–4.43) **	109.33	5.15 (2.81–9.45) **	4.76 (2.58–8.76) **	5.19 (2.11–12.73) **	4.67 (1.99–10.96) **
Motor Disturbance	6.69 (4.41–10.16) **	82.17	18.05 (6.34–51.34) **	15.33 (5.33–44.04) **	10.28 (2.30–45.86) **	29.66 (6.69–131.46) **
Sleep Disturbance	2.72 (2.11–3.50) **	61.51	3.60 (1.94–6.67) **	3.87 (2.08–7.21) **	4.39 (1.75–10.97) **	3.30 (1.40–7.78) *
Appetite Disturbance	4.40 (3.40–5.69) **	131.93	4.03 (1.98–8.20) **	4.00 (1.96–8.18) **	5.39 (1.92–14.82) **	3.70 (1.38–9.99) *
$_{\varepsilon}$4Carrier	1.96 (1.55–2.49) **	31.31	2.85 (1.62–5.02) **	–	–	–

– denotes sample size too small to complete analysis.

* Statistical significance at $p < 0.05$.

** $p < 0.001$.

[a] Adjusted for sex, age, race, Hispanic origin, maternal dementia, and paternal dementia.

Table 4

Cox proportional hazards – additive effects between predictor variables and $_{\varepsilon}$4Carrier status.

	Additive Effect (Unadjusted) Hazard Ratio (95% CI)	***p*-values**	**Wald test**	**Additive Effect (Adjusted)[a] Hazard Ratio (95% CI)**	***p*-values**	**df**
Delusions × $_{\varepsilon}$4Carrier	18.62 (11.06–31.36) **	<0.001	204.44	14.55 (8.58 – 24.69) **	<0.001	1
Hallucinations × $_{\varepsilon}$4Carrier	12.57 (4.00 – 39.51) **	<0.001	49.4	8.43 (2.67 – 26.59) **	<0.001	1
Agitation × $_{\varepsilon}$4Carrier	10.15 (6.91 – 14.93) **	<0.001	175.64	11.07 (7.51 – 16.32) **	<0.001	1
Depression × $_{\varepsilon}$4Carrier	5.60 (3.82 – 8.19) **	<0.001	96.76	6.51 (4.42 – 9.58) **	<0.001	1
Anxiety × $_{\varepsilon}$4Carrier	7.09 (4.92 – 10.22) **	<0.001	122.38	8.53 (5.88 – 12.36) **	<0.001	1
Elation × $_{\varepsilon}$4Carrier	6.92 (1.71 – 27.96) *	<0.05	37.93	11.90 (2.92 – 48.46) **	<0.001	1
Apathy × $_{\varepsilon}$4Carrier	12.61 (8.50 – 18.71) **	<0.001	256.01	12.09 (8.04 – 18.17) **	<0.001	1
Disinhibition × $_{\varepsilon}$4Carrier	13.39 (8.26 – 21.72) **	<0.001	160.44	12.33 (7.58 – 20.05) **	<0.001	1
Irritability × $_{\varepsilon}$4Carrier	6.85 (4.72 – 9.95) **	<0.001	127.35	7.81 (5.35 – 11.4) **	<0.001	1
Motor Disturbance × $_{\varepsilon}$4Carrier	10.67 (5.42 – 21.01) **	<0.001	89.11	15.35 (7.77 – 30.33) **	<0.001	1
Sleep Disturbance × $_{\varepsilon}$4Carrier	4.97 (3.20 – 7.71) **	<0.001	84.96	5.99 (3.84 – 9.32) **	<0.001	1
Appetite × $_{\varepsilon}$4Carrier	8.04 (5.26 – 12.29) **	<0.001	149.76	8.44 (5.46 – 13.05) **	<0.001	1

[a] Adjusted for age, sex, race, and Hispanic origin.

* $p < 0.05$.

** $p < 0.001$.

Table 5

Cox proportional hazards interaction effects among predictor variables and $_{\varepsilon}$4Carrier status.

	Interaction Effect (Unadjusted) Hazard Ratio (95% CI)	Wald Statistic	Interaction Effect (Adjusted)[a] Hazard Ratio (95% CI)	*p*-value	df
Delusions × $_{\varepsilon}$4Carrier	0.652 (0.409–1.04)	204.44	0.585 (0.363–0.945) *	<0.05	1
Hallucinations × $_{\varepsilon}$4Carrier	0.733 (0.337–1.59)	49.40	0.818 (0.366–1.83)	ns	1
Agitation × $_{\varepsilon}$4Carrier	0.982 (0.681–1.41)	175.64	0.923 (0.637–1.34)	ns	1
Depression × $_{\varepsilon}$4Carrier	0.933 (0.658–1.32)	96.76	0.934 (0.656–1.33)	ns	1
Anxiety × $_{\varepsilon}$4Carrier	1.08 (0.753–1.55)	122.38	1.17 (0.812–1.69)	ns	1
Elation × $_{\varepsilon}$4Carrier	1.77 (0.506–6.18)	37.93	1.86 (0.533–6.53)	ns	1
Apathy × $_{\varepsilon}$4Carrier	0.865 (0.611–1.22)	256.01	0.766 (0.538–1.09)	ns	1
Disinhibition × $_{\varepsilon}$4Carrier	0.748 (0.480–1.16)	160.44	0.703 (0.449–1.10)	ns	1
Irritability × $_{\varepsilon}$4Carrier	0.970 (0.686–1.37)	127.35	0.917 (0.645–1.30)		1
Motor Disturbance × $_{\varepsilon}$4Carrier	0.550 (0.332–0.911) *	89.11	0.539 (0.323–0.899) *	<0.05	1
Sleep Disturbance × $_{\varepsilon}$4Carrier	0.695 (0.479–1.01)	84.96	0.817 (0.561–1.19)	ns	1
Appetite × $_{\varepsilon}$4Carrier	0.756 (0.517–1.11)	149.76	0.875 (0.594–1.29)	ns	1

ns = non-significant.

[a] Adjusted for age, sex, race, and Hispanic origin.

* $p < 0.05$.