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Apolipoprotein E ε4 Allele Increases Risk for Psychotic Symptoms in Alzheimer's Disease

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The apolipoprotein E (ApoE) ε4 allele is a well-documented genetic risk factor for sporadic Alzheimer's disease (AD). Its association with psychopathology among AD patients has been the subject of discrepant reports. We aimed to determine whether ApoE ε4+ and ε4– AD patients exhibit a different risk profile for psychotic symptoms and other behavioral disturbances. The Neuropsychiatric Inventory (NPI) was administered to determine the frequency and severity of psychotic and other behavioral symptoms in a sample of $n = 266$ AD patients who had been genotyped for ApoE. Multiple logistic regression models were used to calculate the association between the ApoE ε4 allele and the presence of psychotic symptoms (delusions or hallucinations). Exploratory analyses were also conducted to determine the impact of disease severity on ε4 effects and to examine the association between ε4 and other behavioral symptoms. ApoE ε4 was significantly associated with psychotic symptoms (odds ratio (OR) = 1.87, 95% CI = 1.07–3.29, $P = 0.029$), adjusting for age, sex, education, and MMSE score. More stringent definitions of clinically significant psychosis yielded similar results. Exploratory analyses suggested that this effect accrued specifically from patients with severe-stage AD and primarily from an association between ε4 and delusions. The ε4 allele did not appear to influence the development of most other behavioral symptoms in our sample. In conclusion, AD patients who carry the ApoE ε4 allele are at greater risk than noncarriers for developing psychotic symptoms, particularly as the severity of their dementia progresses.
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INTRODUCTION

The Apolipoprotein E (ApoE) locus on chromosome 19 is the only well-documented genetic risk factor for the development of sporadic AD (Saunders *et al*, 1993). Among the three major isoforms of ApoE (ε2, ε3, and ε4), the ε4 allele has been reported to increase an individual's risk of developing AD, and decrease age of disease onset, in proportion to the number of ε4 alleles present (Corder *et al*, 1993; Farrer *et al*, 1997). The search for phenotypic correlates of ε4 has included neuropathological studies of the rate of β-amyloid (Aβ) deposition (Schmechel *et al*, 1993; Nagy *et al*, 1995; Norrman *et al*, 1995; Gomez-Isla *et al*, 1996), neurofibrillary tangle formation (Schmechel *et al*, 1993; Nagy *et al*, 1995; Norrman *et al*, 1995; Gomez-Isla *et al*, 1996), cholinergic markers (Poirier *et al*, 1995; Soininen *et al*, 1995), and medial temporal lobe atrophy (Lehtovirta *et al*, 1996b; Hashimoto *et al*, 2001; Basso *et al*, in press).

The links between the ApoE ε4 allele and decreased age of AD onset and increased accumulation of pathological features has prompted the hypothesis that ε4 may play a role in accelerating the clinical manifestations of the disease. However, that hypothesis has thus far not been supported by the majority of clinical studies, which have shown no effect of ApoE genotype on rate of cognitive decline in AD (eg Farlow *et al*, 1999; eg Aerssens *et al*, 2001; Kleiman *et al*, 2006). However, some investigators have reported that the presence of at least one ε4 allele may increase (Craft *et al*, 1998; Hirono *et al*, 2003) or even decrease (Frisoni *et al*, 1995; Stern *et al*, 1997) the rate of cognitive decline.

Investigators have also sought to identify clinical correlates of ApoE genotype by focusing on psychiatric symptoms associated with AD. Behavioral abnormalities contribute to the distress of both AD patients and caregivers (Teri, 1997) and are a significant cause of institutionalization (Bianchetti *et al*, 1995). Previous studies of psychiatric disturbances in AD in relation to ApoE have yielded a wide range of results. However, the most frequent positive

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association has been between ε4 and psychotic symptoms (delusions or hallucinations). Fourteen previous studies have examined psychotic symptoms, and five have reported that ε4 increased the risk for psychosis (Ramachandran *et al*, 1996; Ballard *et al*, 1997; Harwood *et al*, 1999; Weiner *et al*, 1999; Scarmeas *et al*, 2002), whereas nine have found no effect of ε4 (Lehtovirta *et al*, 1996a; Cacabelos *et al*, 1997; Lopez *et al*, 1997; Lyketsos *et al*, 1997; Hirono *et al*, 1998, 1999; Levy *et al*, 1999; Gabryelewicz *et al*, 2002; Sweet *et al*, 2002). Sources of variation among these studies are unclear, but may include differences in patient populations, psychosis criteria, and statistical methods.

The present study was thus designed to clarify the influence of the ApoE ε4 allele on the presence of psychotic symptoms in AD. We hypothesized that ε4+ AD patients would manifest symptoms of psychosis more frequently and severely than ε4– patients. We also conducted an exploratory analysis to examine the association between ε4 and other behavioral symptoms.

MATERIALS AND METHODS

Subjects

The study sample comprised 266 patients who met NINCDS-ADRDA criteria for probable AD (McKhann *et al*, 1984). Five of these patients have subsequently died and had autopsy confirming definite AD (Mirra *et al*, 1991). All patients enrolled in a study of phenotypic correlates of ApoE ε4 in AD and were initially evaluated in the Yale Alzheimer's Disease Research Unit between May 1995 and August 2003. The demographics and clinical characteristics of patients are displayed in Table 1. The racial composition of the sample was: European-American ($n=259$; 97.4%), African-American ($n=3$; 1.1%), and Hispanic ($n=4$; 1.5%).

All patients underwent a comprehensive evaluation by a research physician and ancillary staff, including cognitive assessment, medical history, physical and neurological examinations, serum chemistries, thyroid function studies, complete blood count, B_{12}, folate, VDRL, urinalysis, electrocardiogram, and brain MRI or CT. Subjects were excluded for any neurological or medical disorder (other than AD) that could produce cognitive deterioration or for significant psychiatric illness (prior to the onset of cognitive impairment), alcohol, or substance abuse. Some medications received by subjects at the time of evaluation—in particular, cholinesterase inhibitors, high-dose vitamin E (⩾400 IU daily), and psychotropic drugs—may potentially have impacted behavioral variables analyzed in this study. These treatments were assumed to be independently distributed with regard to ApoE genotype; however, this assumption was also tested statistically (See below).

Table 1 AD Subject Characteristics

Variables	ApoE ε4– ($n=116$) Mean±SD	ApoE ε4+ ($n=150$) Mean±SD	1ε4 ($n=118$) Mean±SD	2ε4 ($n=32$) Mean±SD
Demographics				
Age	75.2±9.2	74.2±7.2	75.1±6.7	71.1±8.0*
Sex (% female)	63%	65%	64%	69%
Education (years)	12.9±3.3	13.6±3.2	13.5±3.4	13.8±2.8
Disease characteristics				
Onset age	71±9.2	69.7±7.1	70.5±6.8	66.7±7.5
Duration (years)	4.6±2.1	4.5±2.1	4.5±2.1	4.4±2.0
Family history (% positive)	41%	53%**	56%	44%
ApoE genotype	$13_{2,3}$ $103_{3,3}$	$4_{2,4}$ $114_{3,4}$ $32_{4,4}$		
Concomitant therapies				
Cholinesterase inhibitors (% use)	51%	49%	49%	47%
Antipsychotics (% use)	4%	5%	6%	0%
Antidepressants (% use)	20%	27%	26%	31%
High-dose Vitamin E (% use)	47%	50%	48%	56%
Neuropsychological data				
MMSE	16.7±6.1	17.2±5.5	17.0±5.8	18.0±4.4
IADL	0.66±0.19	0.65±0.20	0.64±0.20	0.67±0.19
Total NPI score	15.5±14.7	16.0±16.6	16.4±16.8	14.4±15.6

Note: MMSE: mini-mental state examination; IADL: instrumental activities of daily living (IADL); NPI: neuropsychiatric inventory.
*2 ε4 group differs from 1, ε4 and ε4− group, $P<0.05$.
**ε4+ group differs from ε4− group, $P<0.05$.

Family history of AD was assessed using the Alzheimer Dementia Risk Questionnaire (Breitner and Folstein, 1984) and the Dementia Questionnaire (Silverman *et al*, 1986) and was considered to be positive if at least one first-degree relative met criteria for primary degenerative dementia. No cases suggestive of autosomal dominant transmission were identified. Additionally, each subject was evaluated for an approximate date of disease onset, based on careful review of his or her medical records and detailed interviews with one or more primary caregivers. The date of onset was operationally defined as the date at which the 'earliest definite AD symptom' appeared. All subjects (or their responsible next of kin) provided written informed consent and were studied under a protocol approved by the Yale Human Investigation Committee.

Neuropsychiatric Evaluation

All subjects were evaluated for behavioral and psychological symptoms using the Neuropsychiatric Inventory (NPI), a structured interview that assessed the frequency and severity of these symptoms (Cummings *et al*, 1994). Using scripted questions, a caregiver was asked whether the patient's behavior had changed after the onset of dementia and whether the altered behavior had been present during the month preceding the evaluation. This format therefore distinguished between psychiatric symptoms that may have been present before the onset of dementia, and those that emerged during the disease process. The NPI assessed the following behavioral domains: delusions, hallucinations, agitation, depression, anxiety, elation, apathy, disinhibition, irritability, aberrant motor behavior, sleep disturbances and eating disturbances. Specific follow-up questions were used to confirm the presence of symptoms that were reported positive. For each domain in which symptoms were confirmed, the caregiver was asked to score the frequency with which symptoms occurred as: occasionally (1), often (2), frequently (3) or very frequently (4). The caregiver was asked also to score the severity of disturbances as: mild (1), moderate (2) or marked (3). Domains absent of disturbances were scored as 0. The product of the frequency and severity score was determined for each positive item (range = 1–12), and the sum of all item scores yielded the total NPI score. Possible scores ranged from 0 (no behavioral disturbances) to 144 (all behavioral disturbances maximally present).

Cognitive performance was assessed by the Mini Mental State Examination (MMSE) (Folstein *et al*, 1975). The functional capacity of subjects in ADLs was assessed using the Instrumental Activities of Daily Living (IADL) questionnaire (Lawton and Brody, 1969). The IADL questionnaire evaluated everyday functioning along eight domains, such as driving and using the telephone (Lawton and Brody, 1969). A score of 1 for a given domain indicated no impairment, with higher scores denoting greater degrees of impairment. As not all domains were valid for all subjects (eg men who never did laundry before AD onset), the IADL score was calculated as the sum of individual activity scores divided by the total possible number of points valid for that subject. The range of scores was therefore 0.27 (no impairment) to 1.00 (maximal impairment). All subject data were obtained by trained raters who were unaware of the subjects' ApoE genotypes.

Determination of ApoE Genotype

DNA was prepared from whole blood in the laboratory of JG by standard procedures. Genotypes were obtained by the polymerase chain reaction (PCR)—restriction fragment length polymorphism method (Hixson and Vernier, 1990) using a PCR procedure slightly modified from Tsai *et al* (1994). The PCR product was digested by *Hha*I (New England Biolabs) and subjected to electrophoresis in 5% MetaPhor agarose (FMC Corp., Rochland, ME). Gels were stained with ethidium bromide and DNA visualized by UV transillumination. The three alleles were scored as described by Hixson and Vernier (1990). Genotypes (8%) were repeated as a quality check, with complete concordance.

Statistical Analysis

Subject characteristics (including demographics, disease characteristics, and concomitant therapies) were compared between ApoE $\varepsilon 4+$ and $\varepsilon 4-$ patients using Student's *t*-test for continuous variables or χ^2 analysis for dichotomous variables. We hypothesized that $\varepsilon 4+$ patients would manifest symptoms of psychosis more frequently and more severely than $\varepsilon 4-$ patients. We therefore calculated a psychosis rating for each subject by summing the Hallucinations and Delusions items on the NPI. The range of possible NPI-derived psychosis (NPI-Psychosis) scores was 0 to 24. As a result of the skewed distribution of NPI-Psychosis scores, these were dichotomized with scores $\geqslant 1$ indicating the presence of psychosis. The association between $\varepsilon 4$ and psychosis was analyzed using a multiple logistic regression model, with psychosis as dependent variable and the following independent variables (in addition to $\varepsilon 4$ allele carrier status): age, sex, educational attainment, and MMSE as a measure of disease severity.

We performed a number of *post hoc* exploratory analyses. To ascertain whether our results were dependent on a particular definition of psychosis, we repeated the multiple logistic regression analysis using two progressively more restrictive criteria that have been utilized for entry into trials of antipsychotic drug for patients with dementia: (1) score $\geqslant 3$ on either the Delusions or Hallucinations item of the NPI, corresponding with moderate severity or frequency (Street *et al*, 2000); (2) NPI-Psychosis $\geqslant 6$ (Deberdt *et al*, 2005). We also examined the effect of four concomitant medication classes on psychotic symptoms by simultaneously adding them as independent variables to the primary logistic regression analysis. Furthermore, to determine whether the effect of $\varepsilon 4$ on psychosis related to a particular stage of disease, we repeated the multiple logistic regression analyses separately for the same three severity strata (mild: MMSE $\geqslant 20$, moderate: MMSE 12–19, severe: MMSE < 12) analyzed by Harwood *et al* (1999).

Finally, we conducted an exploratory analysis of the possible role of ApoE $\varepsilon 4$ in promoting other behavioral disturbances in AD as measured by total NPI score and all 12 subscores. The distribution of total NPI scores in our sample showed a strong positive skew, so a Mann–Whitney *U*-test was employed to determine if $\varepsilon 4+$ and $\varepsilon 4-$ groups

differed in total NPI score. Potential associations between the presence of ε4 and the presence of symptoms in each individual NPI domain were examined by logistic regression analyses, using the same independent variables as described for NPI-Psychosis. No correction for multiple comparisons was used in this exploratory analysis.

RESULTS

Subject Characteristics

Table 1 summarizes AD subject characteristics as a function of ApoE ε4 status with regard to demographics, disease characteristics, concomitant treatments, and neuropsychological data. ApoE ε4+ and ε4− patients did not differ significantly in age ($t_{264} = 0.94$, $P = 0.35$), sex distribution ($\chi^2 = 0.16$, df = 1, $P = 0.69$), or educational attainment ($t_{264} = -1.73$, $P = 0.085$). With regard to disease characteristics, they also did not differ in age of onset ($t_{264} = 0.82$, $P = 0.41$) or duration of symptoms ($t_{264} = 0.48$, $P = 0.63$). However, ε4+ patients had a higher frequency of positive family history of AD ($\chi^2 = 4.31$, df = 1, $P = 0.038$). Finally, ε4+ and ε4− patients did not differ in terms of current use of cholinesterase inhibitors ($\chi^2 = 0.13$, df = 1, $P = 0.72$), antipsychotics ($\chi^2 = 0.019$, df = 1, $P = 0.89$), antidepressants ($\chi^2 = 2.02$, df = 1, $P = 0.16$), and high-dose Vitamin E ($\chi^2 = 0.18$, df = 1, $P = 0.68$).

Effect of ApoE ε4 Allele on Psychotic Symptoms

Table 2 displays the frequency of psychotic symptoms (according to different criteria) in the AD patients according to ApoE ε4 status. When psychosis was defined by an NPI-Psychosis score ⩾1, the presence of ε4 was significantly associated with psychosis (odds ratio (OR) = 1.87, 95% CI = 1.07–3.29, $P = 0.029$) in a multiple logistic regression model, adjusting for the following variables: age (OR = 1.05, 95% CI = 1.01–1.09, $P = 0.008$), educational attainment (OR = 0.94, 95% CI = 0.86–1.03, $P = 0.17$), sex (OR = 1.37, 95% CI = 0.75–2.49, $P = 0.31$), and MMSE score (OR = 0.92, 95% CI = 0.88–0.97, $P = 0.001$).

Post hoc analyses were conducted to examine more restrictive definitions of psychosis, using the same independent variables in the logistic regression model (Table 2). When psychosis was alternatively defined by a score ⩾3 on either the Delusions or Hallucinations item of the NPI (Street *et al*, 2000), the presence of ε4 was still associated with psychosis (OR = 2.10, 95% CI = 1.11–3.99, $P = 0.020$). When psychosis was instead defined by NPI-Psychosis score ⩾6 (Deberdt *et al*, 2005), the presence of ε4 was significantly associated with psychosis (OR = 2.45, 95% CI = 1.21–4.98, $P = 0.013$).

Although the four aforementioned classes of concomitant medications appeared randomly distributed with regard to ApoE ε4 status, we also conducted a *post hoc* exploratory analysis of the effect of these drug classes on psychotic symptoms by simultaneously adding them as independent variables to the logistic regression analysis. Not surprisingly, current antipsychotic use was positively associated with presence of psychotic symptoms (OR = 4.47, 95% CI = 1.00–19.92, $P = 0.049$), but antidepressant and Vitamin E use were not (data not shown). Interestingly, current cholinesterase inhibitor use was negatively associated with the presence of psychotic symptoms in the logistic regression model (OR = 0.51, 95% CI = 0.28–0.95, $P = 0.03$). Although this effect is best studied in randomized trials of cholinesterase inhibitors (Wynn and Cummings, 2004), our data lend further support to the notion that these drugs may favorably impact psychotic symptoms (Cummings and Kaufer, 1996; Wynn and Cummings, 2004).

To determine whether the effect of ε4 status on psychosis was specific to a particular stage of disease, we performed an additional *post hoc* analysis in which we repeated the multiple logistic regression analyses separately for the same three severity strata (mild: MMSE ⩾ 20, $n = 103$; moderate: MMSE 12–19, $n = 121$; severe: MMSE < 12, $n = 42$) analyzed by Harwood *et al* (1999). The results of that analysis are displayed in Figure 1. Only at the severe stage was the presence of ε4 significantly associated with psychosis (OR = 16.61, 95% CI = 2.11–130.51, $P = 0.008$), but not at the mild (OR = 1.03, 95% CI = 0.39–2.76, $P = 0.95$) or moderate (OR = 1.65, 95% CI = 0.74–3.68, $P = 0.22$) stages.

Effect of ApoE ε4 Allele on Other Behavioral Disturbances

Exploratory analyses were also conducted for the effect of ApoE ε4 on other behavioral disturbances. No differences were found between ε4+ and ε4– AD patients in total NPI score ($Z = -0.302$, $P = 0.76$, Mann–Whitney *U*-test). With regard to individual NPI symptom subscores (Table 3),

Table 2 Frequency of Psychosis in AD Patients According to ApoE ε4 Status

	ApoE ε4– ($n = 116$) frequency		ApoE ε4+ ($n = 150$) frequency					1ε4 ($n = 118$) frequency		2ε4 ($n = 32$) frequency	
Criterion	***n***	**%**	***n***	**%**	**OR**	**95% CI**	***P***	***n***	**%**	***n***	**%**
NPI-Psychosis ⩾1	32	27.6	56	37.3	1.87	1.07–3.29	0.029	44	37.3	12	37.5
NPI Delusions ⩾3 or Hallucinations ⩾3	23	19.8	44	29.3	2.10	1.13–3.94	0.020	35	29.7	9	28.1
NPI-Psychosis ⩾6	15	12.9	34	22.7	2.45	1.21–4.98	0.013	26	22.0	8	25.0

Note: NPI, neuropsychiatric inventory; NPI, psychosis score was defined as the sum of scores on the 'Delusions' and 'Hallucinations' items on the NPI. OR (odds ratio) and 95% CI are for the effect of ε4 carrier status in a multiple logistic regression model, with psychosis as dependent variable and the following additional independent variables: age, sex, education, and MMSE.

ε4 was significantly associated with the presence of delusions (OR = 2.26, 95% CI = 1.24–4.13, $P = 0.008$) and irritability (OR = 1.75, 95% CI = 1.02–3.00, $P = 0.041$). In addition, nonsignificant trends were observed for associations with the presence of hallucinations ($P = 0.100$), aberrant motor behaviors ($P = 0.100$) and sleep disturbances ($P = 0.076$).

DISCUSSION

We investigated the effect of the ApoE ε4 allele on the development of psychotic manifestations in AD. Using multiple logistic regression analyses, we found that the presence of ε4 was associated with psychotic symptoms, adjusting for age, sex, education, and MMSE score. Exploratory analyses suggested that this effect accrued specifically from patients with severe-stage AD and primarily from an association between ε4 and delusions. The ε4 allele did not appear to influence the development of most other behavioral symptoms in our sample.

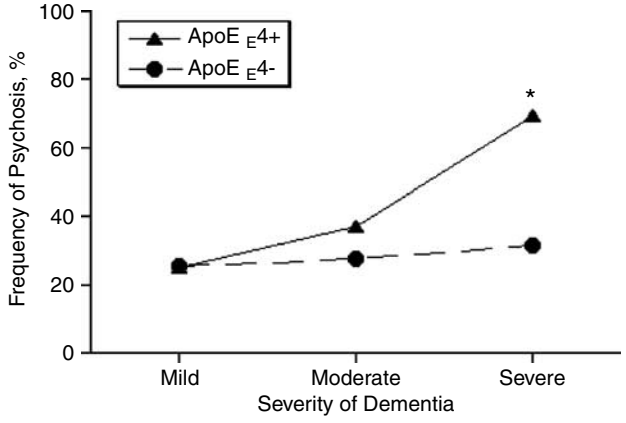

Figure 1 Frequency of psychosis by ApoE ε4 carrier status and dementia severity. Mini Mental State Examination (MMSE) score was used to classify AD patients as mild (MMSE ⩾ 20, $n = 103$), moderate (MMSE = 12–19, $n = 121$), or severe (MMSE < 12, $n = 42$). Separate multiple logistic regression analyses were performed for each severity category, with presence of psychosis as dependent variable and the following independent variables (in addition to ε4 carrier status): age, sex, educational attainment, and MMSE. *Only at the severe stage was the presence of ε4 significantly associated with psychosis (odds ratio (OR) = 16.61, 95% CI = 2.11–130.51, $P = 0.008$).

Comparison to Other ApoE ε4 AD Psychosis Studies

As displayed in Table 4, previous studies of psychosis in AD in relation to ApoE have yielded a wide range of results. However, the most frequent positive association has been between ε4 and psychotic symptoms. Fifteen studies (including the present one) have examined psychotic symptoms, and six (including the present one) have reported that ε4 increased the risk for psychosis (Ramachandran *et al*, 1996; Ballard *et al*, 1997; Harwood *et al*, 1999; Weiner *et al*, 1999; Scarmeas *et al*, 2002), whereas nine have found no effect of ε4 (Lehtovirta *et al*, 1996a; Cacabelos *et al*, 1997; Lopez *et al*, 1997; Lyketsos *et al*, 1997; Hirono *et al*, 1998, 1999; Levy *et al*, 1999; Gabryelewicz *et al*, 2002; Sweet *et al*, 2002). Among the six positive studies only two others (Weiner *et al*, 1999; Scarmeas *et al*, 2002) have considered delusions and hallucinations separately. Our exploratory finding that ε4 was preferentially associated with delusions was shared by Scarmeas *et al* (2002) who observed that ε4 was associated specifically with an increased risk for delusions in a dose dependent manner, whereas ε4 homozygotes actually had a reduced risk for hallucinations. By contrast, Weiner *et al* (1999) reported marginal ($P = 0.05$) positive associations between ApoE ε4 and both delusions and hallucinations. This may reflect a statistical power issue, since delusions are more prevalent among AD patients than hallucinations (Hirono *et al*, 1998; Bassiony and Lyketsos, 2003), including in our present sample

Table 3 Frequency of Neuropsychiatric Symptoms in AD Patients According to ApoE ε4 Status

	ApoE ε4– ($n = 116$) frequency		ApoE ε4+ ($n = 150$) frequency					1ε4 ($n = 118$) frequency		2ε4 ($n = 32$) frequency	
NPI subscore	***n***	**%**	***n***	**%**	**OR**	**95%CI**	***P***	***n***	**%**	***n***	**%**
Delusions	26	22.4	51	34.0	2.26	1.24–4.13	0.008	41	34.7	10	31.3
Hallucinations	14	12.1	27	18.0	1.84	0.89–3.80	0.100	22	18.6	5	15.6
Agitation	36	31.0	52	34.7	1.31	0.76–2.26	0.327	43	36.4	9	28.1
Anxiety	35	30.2	43	28.7	0.94	0.55–1.61	0.825	34	28.8	9	28.1
Depression	41	35.3	48	32.0	0.87	0.52–1.46	0.596	36	30.5	12	37.5
Elation	11	9.5	8	5.3	0.60	0.23–1.55	0.289	6	5.1	2	6.3
Apathy	50	43.1	58	38.7	0.87	0.52–1.43	0.576	48	40.7	10	31.3
Disinhibition	29	25.0	26	17.3	0.69	0.38–1.26	0.226	23	19.5	3	9.4
Irritability	31	26.7	56	37.3	1.75	1.02–3.00	0.041	49	41.5	7	21.9
Aberrant motor behavior	40	34.5	63	42.0	1.57	0.92–2.67	0.100	48	40.7	15	46.9
Sleep disturbances	21	18.1	39	26.0	1.76	0.94–3.27	0.076	34	28.8	5	15.6
Eating disturbances	27	23.3	27	18.0	0.73	0.40–1.33	0.304	21	17.8	6	18.8

Note: NPI, neuropsychiatric inventory. OR (odds ratio) and 95% CI are for the effect of ε4 carrier status in multiple logistic regression models, with NPI subscores as dependent variables and the following additional independent variables: age, sex, education, and MMSE.

Table 4 Studies of Psychotic Symptoms in AD in Relation to ApoE ε4 Status

Study	Sample (*n*)	Measures	Effect of ApoE genotype on psychosis and other behavior
Lehtovirta *et al* (1996a)	58	CI, Ham-D	No effect of genotype on psychosis or depression
Ramachandran *et al* (1996)	46	CI, Ham-D	ε4 increases risk for psychosis and depression
Ballard *et al* (1997)	51[a]	CDS, BSC	ε4 elevates risk for psychosis, lowers risk for depression
Cacabelos *et al* (1997)	207[a]	BPAD, Ham-A/D, SDASDS	No effect of genotype on behavioral disturbances
Lopez *et al* (1997)	194	CI, NE, BRS	No effect of genotype on psychotic symptoms
Lyketsos *et al* (1997)	120	NE	No effect of genotype on psychosis or depression
Hirono *et al* (1998)	228	BPAD, NPI	No effect of genotype on psychotic symptoms
Weiner *et al* (1999)	97[b]	BDRS	ε4 marginally associated with delusions and hallucinations
Harwood *et al* (1999)	501[b]	CI, Ham-D	ε4 increases risk for psychosis
Hirono *et al* (1999)	175	NPI	No effect of genotype on behavioral disturbances
Levy *et al* (1999)	605[b]	NPI	No effect of genotype on behavioral disturbances
Gabryelewicz *et al* (2002)	139	BPAD	No effect of genotype on behavioral disturbances
Scarmeas *et al* (2002)	87	CUSPAD	ε4 increases risk for delusions
Sweet *et al* (2000)	316	BRSD	Genotype does not predict time to onset of psychosis
Zdanys *et al*	266	NPI	ε4 increases risk for psychosis

Studies in bold report a positive association between ApoE ε4 and psychotic symptoms in AD.
Abbreviations: Clinical interview with primary caregiver (CI), Hamilton Depression Rating Scale (Ham-D), Cornell Depression Scale (CDS), Burns symptom checklist for psychosis (BSC), Behavioral Pathology in Alzheimer's Disease Rating Scale (BPAD), Hamilton Anxiety Rating Scale (Ham-A), Senile Dementia-Associated Sleep Disorders Scale (SDASDS), Neuropsychiatric examination of patient (NE), Behavior Rating Scale (BRS), Neuropsychiatric Inventory (NPI), Blessed Dementia Rating Scale (BDRS), Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD), Consortium to Establish a Registry for AD Behavioral Rating Scale for Dementia (BRSD).
[a]Sample included subjects with dementia other than AD.
[b]Sample included subjects with possible and probable AD diagnoses.

(delusions 29%, hallucinations 15%). Two recent studies have used Cox proportional hazards analysis to determine whether ApoE ε4 influences time to onset of psychosis in patients followed longitudinally, but have reported discrepant results (Scarmeas *et al*, 2002; Sweet *et al*, 2002). Sources of variation among these fifteen studies are several, but particularly include differences in psychosis criteria, subject severity, and method of analyzing ApoE ε4 status.

Psychosis criteria. Previous studies have used a variety of methods to identify psychotic symptoms in their subjects, including general clinical examination (Lehtovirta *et al*, 1996a; Lyketsos *et al*, 1997; Hirono *et al*, 1999), rating scales (Ballard *et al*, 1997; Cacabelos *et al*, 1997; Hirono *et al*, 1998; Levy *et al*, 1999; Weiner *et al*, 1999; Gabryelewicz *et al*, 2002; Scarmeas *et al*, 2002), or a combination (Ramachandran *et al*, 1996; Lopez *et al*, 1997; Sweet *et al*, 2002). Those studies that have employed research rating scales have used a wide range of scales (see Table 4), making it difficult to reconcile discrepant reports. Our choice of the NPI has a number of advantages and limitations, some of which derive from its reliance on caregiver interview (Cummings *et al*, 1994). One advantage of the NPI is that it yields a quantitative measure of psychosis based on frequency and severity of symptoms. Although our quantitative NPI scores exhibited too much skew to analyze as continuous variables with parametric statistics, they nonetheless permitted us to consider different thresholds of severity. Virtually all studies to date have considered only presence or absence of psychosis. However, when we alternatively considered two more restrictive thresholds of clinically significant psychosis from the NPI—that have been used as criteria for entry into clinical trials of antipsychotic drugs (Street *et al*, 2000; Deberdt *et al*, 2005) — we found essentially the same results. These analyses suggest that our findings did not depend heavily on the criterion employed to classify AD subjects as psychotic.

Subject severity. Given the well-documented increase in psychotic symptoms with AD severity (Lopez *et al*, 1997; Hirono *et al*, 1998; Harwood *et al*, 1999; Gabryelewicz *et al*, 2002), variations in subject disease stage may represent an important difference among studies. Harwood *et al* (1999), observed that the elevated risk for psychosis was present specifically at the severe stage (MMSE <12) of cognitive impairment among AD patients carrying the ε4 allele. When we stratified our sample using the same cutpoints as Harwood *et al*, we also found that the ε4 effect was statistically significant only for the severe-stage patients (Figure 1). Consequently an association between ApoE ε4 and psychotic symptoms may not be detected by studies that include only (eg Levy *et al*, 1999) or predominantly (eg Hirono *et al*, 1999) mild-to-moderate stage patients. Although several studies do not provide clear description of the severity range of their subject samples, two other positive studies either included severe-stage patients (Weiner *et al*, 1999) or followed patients longitudinally into the severe stage (Scarmeas *et al*, 2002). Discrepant results are not accounted for entirely by differences in patient severity, however, as one positive study was restricted to mild-to-moderate stage patients (Ramachandran *et al*, 1996), and two negative studies enrolled large numbers of severe-stage patients (Cacabelos *et al*, 1997; Gabryelewicz *et al*, 2002).

ApoE ε4 carrier status vs *dose.* Although we chose to evaluate ApoE ε4 carrier status dichotomously, several other studies have examined the number or 'dose' of ε4 alleles in association with psychotic symptoms, including two of the positive studies (Weiner *et al*, 1999; Scarmeas *et al*, 2002). Among the six positive studies only Scarmeas *et al*, 2002 reported a full dose effect of ε4 ($2\varepsilon4 > 1\varepsilon4 > 0\varepsilon4$) on psychotic symptoms in AD. If we alternatively entered ε4 allele number (instead of carrier status) in our multiple logistic regression model, we would still find that ε4 number was significantly associated with psychosis (OR = 1.60, 95% CI = 1.07–2.42, $P = 0.024$). However, we would not observe a full dose effect, as the 1ε4 and 2ε4 groups would not differ in the presence of psychotic symptoms (Table 2).

An important additional limitation of the present study—and of ApoE psychosis studies broadly—pertains to selection bias, with regard to ethnicity, disease severity, and particularly, the range of psychotic symptoms included. Our subjects tended to be recruited from those participating in other research protocols, some of which specifically selected against antipsychotic drug use (thus the low rate of antipsychotic drug use = 5%). The overall prevalence of psychosis in our study (33%) is comparable to other similar studies buy likely underestimates the true population prevalence. Population-based studies that include institutionalized patients would be valuable to confirm our results across the full spectrum of dementia severity.

Interpretation of an Increased Risk of Psychosis in ApoE ε4 + AD

The mechanism by which ApoE ε4 may increase the risk for psychotic symptoms in AD is unclear. Although the ε4 allele has been shown to promote the neuropathological features of AD, including β-amyloid (Aβ) deposition (Schmechel *et al*, 1993; Nagy *et al*, 1995; Norrman *et al*, 1995; Gomez-Isla *et al*, 1996) and neurofibrillary tangle formation (Schmechel *et al*, 1993; Nagy *et al*, 1995; Norrman *et al*, 1995; Gomez-Isla *et al*, 1996), attempts to relate these features to psychotic symptoms in AD have yielded conflicting results (Zubenko *et al*, 1991; Förstl *et al*, 1994; Mukaetova-Ladinska *et al*, 1995; Sweet *et al*, 2000). Additionally, ApoE ε4 has been linked with more profound cholinergic loss in the frontal cortex (Soininen *et al*, 1995) and medial temporal lobe (Poirier *et al*, 1995), and acetylcholine levels have in turn been implicated in psychotic disturbances in AD (Cummings and Kaufer, 1996). Neuroimaging studies may shed additional light on the association between ApoE ε4 and psychotic manifestations of AD. One *in vivo* SPECT study has suggested that delusions in AD may be associated with hypoperfusion in the temporal lobes (Starkstein *et al*, 1994), and some (Lee *et al*, 2003) but not all (van Dyck *et al*, 1998) functional imaging studies have shown that AD patients who carry the ε4 allele have reduced temporal lobe function. The structural MRI literature is more unified in showing greater medial temporal lobe atrophy in association with the ε4 allele in AD (Lehtovirta *et al*, 1996b; Hashimoto *et al*, 2001; Basso *et al*, in press).

In conclusion, AD patients who carry the ApoE ε4 allele are at greater risk than noncarriers for developing psychotic symptoms, particularly delusions. This effect appears to be associated specifically with the severe stages of the disease. Although an association has been made between the ApoE ε4 genotype and psychosis in AD, more research must be conducted to examine the pathological links between the gene and the symptom.

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REFERENCES

Aerssens J, Raeymaekers P, Lilienfeld S, Geerts H, Konings F, Parys W (2001). APOE genotype: No influence on galantamine treatment efficacy nor on rate of decline in Alzheimer's Disease. *Dement Geriatr Cogn Disord* **12**: 69–77.

Ballard C, Massey H, Lamb H, Morris C (1997). Apolipoprotein E: non-cognitive symptoms and cognitive decline in late-onset Alzheimer's disease. *J Neurol Neurosurg Psychiatr* **63**: 273–274.

Bassiony MM, Lyketsos CG (2003). Delusions and hallucinations in Alzheimer's disease: review of the brain decade. *Psychosomatics* **44**: 388–401.

Basso M, Gelernter J, Yang J, MacAvoy MG, Varma P, Bronen RA *et al* (in press). Apolipoprotein E epsilon4 is associated with atrophy of the amygdala in Alzheimer's disease. *Neurobiol Aging*.

Bianchetti A, Scuratti A, Zanetti O, Binetti G, Frisoni GB, Magni E *et al* (1995). Predictors of mortality and institutionalization in Alzheimer disease patients 1 year after discharge from an Alzheimer dementia unit. *Dementia* **6**: 108–112.

Breitner JCS, Folstein MF (1984). Familial Alzheimer's disease: a prevalent disorder with specific clinical features. *Psychol Med* **14**: 63–80.

Cacabelos R, Rodriguez B, Carrera C, Beyer K, Lao JI, Sellers MA (1997). Behavioral changes associated with different apolipoprotein E genotypes in dementia. *Alzheimer Dis Assoc Disord* **11**: S27–S34.

Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW *et al* (1993). Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science* **261**: 921–923.

Craft S, Teri L, Edland SD, Kukull WA, Schellenberg G, McCormick WC *et al* (1998). Accelerated decline in apolipoprotein E-e4 homozygotes with Alzheimer's disease. *Neurology* **51**: 149–153.

Cummings JL, Kaufer DI (1996). Neuropsychiatric aspects of Alzheimer's disease: the cholinergic hypothesis revisited. *Neurology* **47**: 876–883.

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J (1994). The neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology* **44**: 2308–2314.

Deberdt WG, Dysken MW, Rappaport SA, Feldman PD, Young CA, Hay DP *et al* (2005). Comparison of olanzapine and risperidone in the treatment of psychosis and associated behavioral disturbances in patients with dementia. *Am J Geriatr Psychiatr* **13**: 722–730.

Farlow MR, Cyrus PA, Nadel A, Lahiri DK, Brashear A, Gulanski B (1999). Metrifonate treatment of AD—Influence of APOE genotype. *Neurology* **53**: 2010–2016.

Farrer LA, Cupples LA, Haines JL, Hyman BT, Kukull WA, Mayeux R *et al* (1997). Effects of age, sex and ethnicity on the association

between apolipoprotein E genotype and Alzheimer disease—A meta-analysis. *JAMA* **278**: 1349–1356.

Folstein MF, Folstein SE, McHugh PR (1975). Mini-mental state': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**: 189–198.

Förstl H, Burns A, Levy R, Cairns N (1994). Neuropathological correlates of psychotic phenomena in confirmed Alzheimer's disease. *Br J Psychiatr* **165**: 53–59.

Frisoni GB, Govoni S, Geroldi C, Bianchetti A, Calabresi L, Franceschini G *et al* (1995). Gene dose of the e4 allele of apolipoprotein E and disease progression in sporadic late-onset Alzheimer's disease. *Ann Neurol* **37**: 596–604.

Gabryelewicz T, Religa D, Styczynska M, Peplonska B, Pfeffer A, Wasiak B *et al* (2002). Behavioural pathology in Alzheimer's disease with special reference to apolipoprotein E genotype. *Dement Geriatr Cogn Disord* **14**: 208–212.

Gomez-Isla T, West HL, Rebeck GW, Harr SD, Growdon JH, Locascio JJ *et al* (1996). Clinical and pathological correlates of apolipoprotein E e4 in Alzheimer's disease. *Ann Neurol* **39**: 62–70.

Harwood DG, Barker WW, Ownby RL, St. George-Hyslop PH, Duara R (1999). Apolipoprotein-E (APO-E) genotype and symptoms of psychosis in Alzheimer's disease. *Am J Geriatr Psychiatr* **7**: 119–123.

Hashimoto M, Yasuda M, Tanimukai S, Matsui M, Hirono N, Kazui H *et al* (2001). Apolipoprotein E epsilon 4 and the pattern of regional brain atrophy in Alzheimer's disease. *Neurology* **57**: 1461–1466.

Hirono N, Hashimoto M, Yasuda M, Kazui H, Mori E (2003). Accelerated memory decline in Alzheimer's disease With Apolipoprotein epsilon4 allele. *J Neuropsychiatry Clin Neurosci* **15**: 354–358.

Hirono N, Mori E, Yasuda M, Ikejiri Y, Imamura T, Shimomura T *et al* (1998). Factors associated with psychotic symptoms in Alzheimer's disease. *J Neurol Neurosurg Psychiatr* **64**: 648–652.

Hirono N, Mori E, Yasuda M, Imamura T, Shimomura T, Hashimoto M *et al* (1999). Lack of effect of apolipoprotein E E4 allele on neuropsychiatric manifestations in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci* **11**: 66–70.

Hixson JE, Vernier DT (1990). Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res* **31**: 545–548.

Kleiman T, Zdanys K, Black B, Rightmer T, Grey M, Garman K *et al* (2006). Apolipoprotein E e4 is unrelated to cognitive or functional decline in Alzheimer's Disease: Retrospective and prospective analysis. *Dement Geriatr Cogn Disord* **22**: 73–82.

Lawton MP, Brody EM (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist* **9**: 179–186.

Lee KU, Lee JS, Kim KW, Jhoo JH, Lee DY, Yoon JC *et al* (2003). Influence of the apolipoprotein E type 4 allele on cerebral glucose metabolism in Alzheimer's disease patients. *J Neuropsychiatry Clin Neurosci* **15**: 78–83.

Lehtovirta M, Soininen H, Helisalmi S, Mannermaa A, Helkala E-L, Hartikainen P *et al* (1996a). Clinical and neuropsychological characteristics in familial and sporadic Alzheimer's disease: Relation to apolipoprotein E polymorphism. *Neurology* **46**: 413–419.

Lehtovirta M, Soininen H, Laakso MP, Partanen K, Helisalmi S, Mannermaa A *et al* (1996b). SPECT and MRI analysis in Alzheimer's disease: relation to apolipoprotein E e4 allele. *J Neurol Neurosurg Psychiatr* **60**: 644–649.

Levy ML, Cummings JL, Fairbanks LA, Sultzer DL, Small GW (1999). Apolipoprotein E genotype and noncognitive symptoms in Alzheimer's disease. *Biol Psychiatr* **45**: 422–425.

Lopez OL, Kamboh MI, Becker JT, Kaufer DI, DeKosky ST (1997). The apolipoprotein E e4 allele is not associated with psychiatric symptoms or extrapyramidal signs in probable Alzheimer's disease. *Neurology* **49**: 794–797.

Lyketsos CG, Baker L, Warren A, Steele C, Brandt J, Steinberg M *et al* (1997). Depression, delusions and hallucinations in Alzheimer's Disease: No relationship to apolipoprotein E genotype. *J Neuropsychiatr Clin Neurosci* **9**: 64–67.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984). Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* **34**: 939–944.

Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM *et al* (1991). The consortium to establish a registry for Alzheimer's disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology* **41**: 479–486.

Mukaetova-Ladinska EB, Harrington CR, Xuereb J, Roth M, Wischik CM (1995). Biochemical, neuropathological, and clinical correlations of neurofibrillary degenration in Alzheimer's disease. In: Bergener M, Finkel SI (eds). *Biochemical, neuropathological, and clinical correlations of neurofibrillary degenration in Alzheimer's disease*. Springer Publishing: New York. pp 57–80.

Nagy NS, Esiri MM, Jobst KA, Johnston C, Litchfield S, Sim E *et al* (1995). Influence of the apolipoprotein E genotype on amyloid deposition and neurofibrillary tangle formation in Alzheimer's disease. *Neuroscience* **69**: 757–761.

Norrman J, Brookes AJ, Yates C, St. Clair D (1995). Apolipoprotein E genotype and its effect on duration and severity of early and late onset Alzheimer's disease. *Br J Psychiatr* **167**: 533–536.

Poirier J, Delisle M-C, Quirion R, Aubert I, Farlow M, Lahiri D *et al* (1995). Apolipoprotein E4 allele as a predictor of cholinergic deficits and treatment outcome in Alzheimer's disease. *Proc Natl Acad Sci* **92**: 12260–12264.

Ramachandran G, Marder K, Tang M, Schofield PW, Chun MR, Devanand DP *et al* (1996). A preliminary study of apolipoprotein E genotype and psychiatric manifestations of Alzheimer's disease. *Neurology* **47**: 256–259.

Saunders AM, Strittmatter WJ, Schmechel DE, St. George-Hyslop PH, Pericak-Vance MA, Joo BS *et al* (1993). Association of apolipoprotein E allele e4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* **43**: 1467–1472.

Scarmeas N, Brandt J, Albert M, Devanand DP, Marder K, Bell K *et al* (2002). Association between the APOE genotype and psychopathologic symptoms in Alzheimer's disease. *Neurology* **58**: 1182–1188.

Schmechel DE, Saunders AM, Strittmatter WJ, Crain B, Hulette C, Joo SH *et al* (1993). Increased amyloid ß-peptide deposition as a consequence of apolipoprotein E genotype in late-onset Alzheimer's disease. *Proc Natl Acad Sci* **90**: 9649–9653.

Silverman JM, Breitner JCS, Mohs RC, Davis KL (1986). Reliability of the family history method in genetic studies of Alzheimer's disease and related dementias. *Am J Psychiatr* **143**: 1279–1282.

Soininen H, Kosunen O, Helisalmi S, Mannernaa A, Paljärvi L, Talasniemi S *et al* (1995). A severe loss of choline acetyltransferase in the frontal cortex of Alzheimer patients carrying the apolipoprotein e4 allele. *Neurosci Lett* **187**: 79–82.

Starkstein SE, Vazquez S, Petracca G, Sabe L, Migliorelli R, Teson A *et al* (1994). A SPECT study of delusions in Alzheimer's disease. *Neurology* **44**: 2055–2059.

Stern Y, Brandt J, Albert M, Jacobs DM, Liu X, Bell K *et al* (1997). The absence of an apolipoprotein e4 allele is associated with a more aggressive form of Alzheimer's disease. *Ann Neurol* **41**: 615–620.

Street JS, Clark WS, Gannon KS, Cummings JL, Bymaster FP, Tamura RN *et al* (2000). Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. *Arch Gen Psychiatr* **57**: 968–976.

Sweet R, Kamboh MI, Wisniewski SR, Lopez OL, Klunk WE, Kaufer DI *et al* (2002). Apolipoprotein E and alpha-1-antichymotrypsin genotypes do not predict time to psychosis in Alzheimer's disease. *J Geriatr Psychiatr Neurol* **15**: 24–30.

Sweet RA, Hamilton RL, Lopez OL, Klunk WE, Wisniewski SR, Kaufer DI *et al* (2000). Psychotic symptoms in Alzheimer's disease are not associated with more severe neuropathologic features. *Int Psychogeriatr* **12**: 547–558.

Teri L (1997). Behavior and caregiver burden: Behavioral problems in patients with Alzheimer disease and its association with caregiver distress. *Alzheimer Dis Assoc Disord* **11**: S35–S38.

Tsai M-S, Tangalos EG, Petersen RC, Smith GE, Schaid DJ, Kokmen E *et al* (1994). Apolipoprotein E: risk factor for Alzheimer disease. *Am J Hum Genet* **54**: 643–649.

van Dyck CH, Gelernter J, MacAvoy MG, Avery RA, Criden M, Okereke O *et al* (1998). The absence of an apolipoprotein E e4 allele is associated with increased parietal rCBF asymmetry in Alzheimer's disease. *Arch Neurology* **55**: 1460–1466.

Weiner MF, Vega G, Risser RC, Honig LS, Cullum CM, Crumpacker D *et al* (1999). Apolipoprotein E epsilon 4, other risk factors, and course of Alzheimer's disease. *Biol Psychiatr* **45**: 633–638.

Wynn ZJ, Cummings JL (2004). Cholinesterase inhibitor therapies and neuropsychiatric manifestations of Alzheimer's disease. *Dement Geriatr Cogn Disord* **17**: 100–108.

Zubenko GS, Moossy J, Martinez AJ, Rao G, Claassen D, Rosen J *et al* (1991). Neuropathologic and neurochemical correlates of psychosis in primary dementia. *Arch Neurol* **48**: 619–624.