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Research Article

Psychosis in Alzheimer's Disease in the National Alzheimer's Disease Coordinating Center Uniform Data Set: Clinical Correlates and Association with Apolipoprotein E

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Approximately 50% of late-onset Alzheimer's disease (AD) patients develop psychosis (AD+P), a heritable phenotype associated with more rapid cognitive decline. Prior studies conflict regarding whether apolipoprotein E (APOE) $\epsilon 4$ alleles are associated with AD+P, possibly due to small sample sizes, inconsistent diagnostic criteria, and different methodologies to assess psychosis. We used the National Alzheimer's Coordinating Center Uniform Data Set to evaluate the largest uniformly characterized sample of AD+P subjects studied to date for the association of APOE $\epsilon 4$ genotype, along with other demographic and clinical variables. Greater cognitive impairment and depressive symptoms were associated with AD+P, while the Caucasian race was protective. Neither APOE $\epsilon 4$ carrier status nor allele number was associated with psychosis. The AD+P phenotype is not associated with the APOE $\epsilon 4$ genotype. AD+P may represent a useful phenotype for the discovery of non-APOE $\epsilon 4$ genetic variation contributing to the risk of AD.

1. Introduction

Psychotic symptoms, delusions, and hallucinations are common in Alzheimer's disease (AD; AD+P), occurring in approximately 40% of individuals over the course of the illness [1]. AD+P causes significant distress for patients and family members [2]. AD+P is a predictor of worse cognitive and functional outcome, higher likelihood of institutionalization, and higher mortality rate [3]. Importantly, a number of studies indicate that the occurrence of psychosis in AD is familial [4–6], with an estimated heritability of 61% [7], indicating a distinct neurobiology of this phenotype [8].

Recently, Ropacki and Jeste [1] comprehensively reviewed the literature on psychosis in AD. They reviewed 55 studies comprised of 9,749 subjects. The most consistent correlate of AD+P was greater cognitive impairment than is found in AD without psychosis (AD−P). In twenty of thirty studies which assessed this relationship, the prevalence of psychosis increased as cognitive impairment worsened as determined by the Mini Mental State Exam (MMSE). Studies conducted more recently have continued to support the relationship between greater cognitive impairment and AD+P [9, 10]. In contrast, only inconsistent associations have been detected between AD+P and age, age at onset of AD, illness duration, gender, and education. AD+P may be associated with race, though it has only been examined in a limited number of studies to date [1]. It should be noted that the above conclusions are limited by the inconsistencies across the reviewed studies. Few variables are examined in all studies; sample sizes of individual studies were not always sufficient to detect small-to-moderate effects, and approaches to characterization of subjects, including identification of psychosis, also varied considerably.

Apolipoprotein E (APOE) is well documented as being an important genetic determinant for the development of late-onset AD [11]. However, its association with development of psychosis is less clear. We have identified 22 studies that examined the association of the APOE $\epsilon 4$ allele with AD+P, with nine reporting that $\epsilon 4$ increased the risk for AD+P, whereas 13 studies found no effect of $\epsilon 4$ [12]. As in the studies of clinical correlates of AD+P, these reports varied considerably in their subject populations, sample sizes, definitions of AD+P, and analytic approaches, precluding clear interpretation of the conflicting pattern of results. Moreover, as highlighted by recent genome-wide association studies, genes of small, but real, effects (e.g., RR 1.1-1.2) often show inconsistent results in studies with small sample sizes, with the currently recommended sample sizes numbering in the thousands. Although APOE $\epsilon 4$ confers greater relative risk for AD, it may have a smaller, if any, effect on the development of psychosis in AD.

To more reliably determine the correlates of the AD+P syndrome, it would be desirable to analyze a large cohort of individuals with late-onset AD who have been characterized in a standardized manner. To accomplish this goal we utilized the Uniform Data Set (UDS) collected by the National Alzheimer's Coordinating Center (NACC) to characterize the clinical correlates of AD+P. To date, this is the largest data set used to look at the association of APOE $\epsilon 4$ with AD+P. We hypothesized that the APOE $\epsilon 4$ genotype is not associated with the development of AD+P. We also hypothesized that AD+P is associated with greater cognitive impairment.

2. Methods

2.1. NACC Data Center. The NACC was developed in 1999 with the purpose of developing and maintaining a database that included data from NIH-funded Alzheimer's Disease Centers (ADC) across the country. The UDS was developed by NACC to provide the ADCs with standardized assessments thereby allowing uniformity amongst centers when diagnosing these subjects with mild cognitive impairment or Alzheimer's disease [13]. Individual centers may use additional assessments for their particular research protocols, but every center must complete the UDS assessments [14]. Since 2005, these have included ratings of psychosis on the Neuropsychiatric Inventory Questionnaire (NPI-Q) [15].

2.2. Eligibility Criteria. Subjects were selected for analysis on the basis of having a primary diagnosis of possible or probable AD with an age of onset ≥ 60. Subjects with comorbid Parkinson's disease or dementia with Lewy bodies were excluded. Additionally, subjects were required to have available psychosis ratings on the NPI-Q and an APOE genotype. Other variables requested, but not available for all subjects, included demographics (age at first visit, age of onset of dementia, sex, race, ethnicity, primary language, education) and scores on the Mini-Mental State Exam (MMSE) [16], global Clinical Dementia Rating Scale (CDR) [17], Hachinski Ischemic Scale [18], and the Geriatric Depression Scale (GDS) [19]. Because some subjects had multiple visits over time, for these individuals the last available scores for MMSE, CDR (global), Hachinski, and GDS were used for analysis. Regarding race and ethnicity, subjects reported their race to a clinician from the following choices: White, Black, or African-American, American-Indian, or Alaska Native, Native Hawaiian or other Pacific Islander, Asian, other, or Unknown. From this, subjects were grouped as Caucasian, African-American, or other for analysis. Subjects also reported as to whether they had Hispanic/Latino ethnicity. This study had Institutional Review Board approval through the University of Pittsburgh and Universities contributing their data to the NACC.

2.3. Classification of Psychosis. Each subject was assessed for psychosis at each visit using the NPIQ. Informants for the NPIQ ratings were most commonly a subject's spouse (2889, 57.7%) or child (1606, 32.1%) and rarely other informants (515, 10.3%). Subjects were rated positive for psychosis at any visit if they exhibited delusions (question 1) and/or hallucinations (question 2) within a one-month time frame prior to the interview. Subjects with neither item endorsed at any visit were categorized as Never Psychotic. Subjects with one item present at no more than one visit were characterized as having Single Psychosis. Subjects with both items present at any one visit, or one or more items present at multiple visits, were characterized as Multiple/Recurrent Psychosis.

2.4. Statistical Analysis. The association of AD+P with baseline clinical and demographic variables was analyzed using univariate (Chi-square and ANOVA, as appropriate) tests. We tested the associations of AD+P with APOE genotype and $\epsilon 4$ carrier status by Chi-square. Follow-up analyses of association used multinomial logistic regression models, including APOE genotype, and clinical and demographic variables. Because MMSE and CDR score are highly correlated, in these latter analyses we omitted the CDR score. Additional multinomial logistic regression analyses were conducted including a main effect of site (24 ADCs contributed to the data set) but were not reported as they yielded essentially identical results.

3. Results

We identified 2317 subjects in the NACC database who fulfilled all eligibility criteria for analysis. Of these subjects, 777 (33.5%) had one visit, 730 (31.5%) had two visits, 485 (20.9%) had three visits, 307 (13.2%) had 4 visits, and 18 (0.8%) had five visits for a total number of 5010 visits reported to NACC. The majority of subjects were diagnosed with probable AD (2117, 91.4%) and the remaining (200, 8.6%) with possible AD. The sample predominately consisted of Caucasian (1957, 84.5%) and female (1309, 56.5%) subjects (Table 1). The majority of patients were carriers of the APOE $\epsilon 4$ allele (1383, 59.7%) (Table 1).

Table 1: Demographic and clinical characteristics and their association with AD+P.

Variable	Psychosis Status			Total N (%) or mean (SD)	$\chi^{2\dagger}$ or $F^{\ddagger}$	df	P value
	Never N (%) or mean (SD)	Single N (%) or mean (SD)	Multiple/Recurrent N (%) or mean (SD)				
Age	78.2 (6.8)	79.0 (7.1)	78.3 (7.1)	78.4 (6.9)	2.197‡		.111
Age of onset	73.3 (6.9)	73.4 (7.1)	72.3 (6.9)	73.2 (6.9)	2.862‡		.057
Sex							
Male	704 (46.5)	188 (38.1)	116 (37.5)	1008 (43.5)	15.673†	2	<.001
Female	811 (53.5)	305 (61.9)	193 (62.5)	1309 (56.5)			
Race							
Caucasian	1347 (89.0)	394 (80.0)	216 (70.0)	1957 (84.5)	82.409†	4	<.001
African-American	132 (8.7)	76 (15.4)	69 (22.3)	277 (12.0)			
Other	35 (2.3)	23 (4.6)	24 (7.7)	82 (3.5)			
Hispanic							
No	1429 (94.3)	448 (90.9)	270 (87.4)	2147 (92.7)	21.161†	2	<.001
Yes	86 (5.7)	45 (9.1)	39 (12.6)	170 (7.3)			
Primary language							
English	1425 (94.1)	455 (92.3)	273 (88.3)	2153 (92.9)	13.100†	2	.001
Other	90 (5.9)	38 (7.7)	36 (11.7)	164 (7.1)			
Education	14.2 (3.6)	13.4 (3.6)	13.0 (4.2)	13.8 (3.7)	19.138‡		<.001
MMSE	18.7 (6.7)	16.8 (7.0)	14.2 (7.1)	17.7 (7.0)	59.922‡		<.001
CDR (global)							
0.0	12 (0.8)	0 (0.0)	0 (0.0)	12 (0.5)			
0.5	364 (24.0)	52 (10.5)	12 (3.9)	428 (18.5)	177.772†	8	<.001
1.0	583 (38.5)	192 (39.0)	83 (26.9)	858 (37.0)			
2.0	408 (26.9)	182 (36.9)	132 (42.7)	722 (31.2)			
3.0	148 (9.8)	67 (13.6)	82 (26.5)	297 (12.8)			
Hachinski	1.1 (1.4)	1.1 (1.3)	1.3 (1.5)	1.1 (1.4)	2.417‡		.089
GDS	2.2 (2.4)	2.5 (2.8)	2.7 (3.0)	2.3 (2.6)	6.849‡		.001
APOE $\epsilon 4$ allele carrier status					4.008†	2	.135
$-\epsilon 4$	632 (41.7)	190 (38.5)	112 (36.2)	934 (40.3)			
$+\epsilon 4$	883 (58.3)	303 (61.5)	197 (63.8)	1383 (59.7)			
APOE $\epsilon 4$ allele number							
0	632 (41.7)	190 (38.5)	112 (36.3)	934 (40.3)	5.097†	4	.277
1	712 (47.0)	236 (47.9)	158 (51.1)	1106 (47.7)			
2	171 (11.3)	67 (13.6)	39 (12.6)	277 (12.0)			

Abbreviations: AD+P, Alzheimer's disease plus psychosis; MMSE, Mini-mental state exam; CDR, Clinical dementia rating scale; GDS, Geriatric depression scale; APOE, Apolipoprotein E.
†Pearson's Chi-square test: χ^2 values are presented.
‡One-way analysis of variance: F values are presented.

Demographic and clinical variables were analyzed for association with AD+P. Univariate analyses revealed significant associations for psychosis with sex (female), race (non-Caucasian), Hispanic ethnicity, primary language (non-English), lower education, lower MMSE score, higher CDR score, and higher GDS score (Table 1). There were no significant associations of psychosis with age at presentation, age of onset of dementia, Hachinski score, APOE $\epsilon 4$ allele carrier status, or the number of APOE $\epsilon 4$ alleles (Table 1).

Because psychosis does not typically manifest in early stages of AD, classifying someone as a "true AD−P" requires individuals to have reached at least mild to moderate stages of disease [6]. Therefore, we conducted follow-up analyses in which individuals classified as AD−P were restricted to those who had at least reached a CDR score ≥ 1, $N = 1941$. In these univariate analyses, significant associations remained for sex, race, Hispanic ethnicity, primary language, education, MMSE, CDR, and GDS. Psychosis was now also significantly

Table 2: Demographic and clinical characteristics and their association with AD+P with Never Psychotic (AD−P) cases restricted to CDR ≥ 1.

Variable	Psychosis status			Total N (%) or mean (SD)	$\chi^{2\dagger}$ or $F^{\ddagger}$	df	P value
	Never N (%) or mean (SD)	Single N (%) or mean (SD)	Multiple/Recurrent N (%) or mean (SD)				
Age	78.8 (6.8)	79.0 (7.1)	78.3 (7.1)	78.7 (6.9)	0.886‡		.413
Age of onset	73.4 (6.9)	73.4 (7.1)	72.3 (6.9)	73.2 (7.0)	3.094‡		.046
Sex							
Male	529 (46.4)	188 (38.1)	116 (37.5)	833 (42.9)	14.035†	2	.001
Female	610 (53.6)	305 (61.9)	193 (62.5)	1108 (57.1)			
Race							
Caucasian	1024 (90.0)	394 (79.9)	216 (70.0)	1634 (84.2)	83.311†	4	<.001
African-American	87 (7.6)	76 (15.4)	69 (22.3)	232 (12.0)			
Other	27 (2.4)	23 (4.7)	24 (7.7)	74 (3.8)			
Hispanic							
No	1069 (93.9)	448 (90.9)	270 (87.4)	1787 (92.1)	15.243†	2	<.001
Yes	70 (6.1)	45 (9.1)	39 (12.6)	154 (7.9)			
Primary language							
English	1070 (93.9)	455 (92.3)	273 (88.3)	1798 (92.6)	11.252†	2	.004
Other	69 (6.1)	38 (7.7)	36 (11.7)	143 (7.4)			
Education	14.2 (3.6)	13.4 (3.6)	13.0 (4.2)	13.8 (3.7)	16.762‡		<.001
MMSE	16.9 (6.5)	16.8 (7.0)	14.2 (7.1)	16.4 (6.8)	19.386‡		<.001
CDR (global)							
0.0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)			
0.5	0 (0.0)	52 (10.5)	12 (3.9)	64 (3.3)	186.669†	6	<.001
1.0	583 (51.2)	192 (39.0)	83 (26.9)	858 (44.2)			
2.0	408 (35.8)	182 (36.9)	132 (42.7)	722 (37.2)			
3.0	148 (13.0)	67 (13.6)	82 (26.5)	297 (15.3)			
Hachinski	1.1 (1.4)	1.1 (1.3)	1.3 (1.5)	1.1 (1.4)	1.864‡		.155
GDS	2.1 (2.3)	2.5 (2.9)	2.7 (3.0)	2.3 (2.6)	6.947‡		.001
APOE $\epsilon 4$ allele carrier status					3.100†	2	.212
$-\epsilon 4$	471 (41.4)	190 (38.5)	112 (36.2)	773 (39.8)			
$+\epsilon 4$	668 (58.6)	303 (61.5)	197 (63.8)	1168 (60.2)			
APOE $\epsilon 4$ allele number							
0	471 (41.3)	190 (38.5)	112 (36.3)	773 (39.8)	3.502†	4	.478
1	527 (46.3)	236 (47.9)	158 (51.1)	921 (47.5)			
2	141 (12.4)	67 (13.6)	39 (12.6)	247 (12.7)			

Abbreviations: AD+P, Alzheimer's disease plus psychosis; AD−P, Alzheimer's disease minus psychosis; MMSE, Mini-mental state exam; CDR, Clinical dementia rating scale; GDS, Geriatric depression scale; APOE, Apolipoprotein E.
†Pearson's Chi-square test: χ^2 values are presented.
‡One-way analysis of variance: F values are presented.

associated with age of onset (younger). Age at presentation, Hachinski score, APOE $\epsilon 4$ allele carrier status, and APOE $\epsilon 4$ allele number remained insignificant for association with psychosis (Table 2).

Using multinomial regression, increased age at presentation, lower age of onset of dementia, being non-Caucasian, lower MMSE, and increased GDS were significantly associated with both Single and Multiple/Recurrent Psychosis (Table 3). Lower education was significantly associated with Single, but not Multiple/Recurrent Psychosis. When AD−P status was restricted to patients with a CDR ≥ 1, race and GDS remained significant predictors of both Single and Multiple/Recurrent Psychosis (Table 4). Age, age of onset, and MMSE were significantly associated with only Multiple/Recurrent Psychosis, while education was significantly associated with Single Psychosis. Sex, Hispanic origin,

Table 3: Multinomial logistic regression analysis of Single and Multiple/Recurrent Psychosis.

Psychosis category	Variable	OR	95% CI	Wald χ^2 (df = 1)	P value
Single	Age	1.053	(1.016, 1.092)	8.083	.004
	Age of onset	0.960	(0.926, 0.995)	5.047	.025
	Sex	0.799	(0.633, 1.010)	3.515	.061
	Race				
	Caucasian	0.457	(0.233, 0.898)	5.168	.023
	African-American	0.834	(0.398, 1.750)	0.230	.632
	Other[a]				
	Hispanic origin	0.520	(0.263, 1.029)	3.524	.061
	Primary language	1.925	(0.901, 4.110)	2.862	.091
	Education	0.965	(0.932, 0.999)	4.181	.041
	MMSE	0.969	(0.951, 0.987)	10.924	.001
	Hachinski	0.972	(0.895, 1.056)	0.437	.508
	GDS	1.051	(1.007, 1.096)	5.179	.023
	APOE ϵ4 allele number				
	0	0.778	(0.542, 1.115)	1.867	.172
	1	0.815	(0.575, 1.154)	1.329	.249
	2[a]				
Multiple/Recurrent	Age	1.078	(1.034, 1.123)	12.485	<.001
	Age of onset	0.914	(0.876, 0.953)	17.716	<.001
	Sex	0.847	(0.631, 1.136)	1.233	.267
	Race				
	Caucasian	0.311	(0.151, 0.642)	9.977	.002
	African-American	1.008	(0.455, 2.232)	0.000	.985
	Other[a]				
	Hispanic origin	0.457	(0.207, 1.007)	3.774	.052
	Primary language	1.157	(0.495, 2.703)	0.113	.736
	Education	0.974	(0.935, 1.014)	1.654	.198
	MMSE	0.911	(0.892, 0.931)	71.322	<.001
	Hachinski	1.039	(0.948, 1.140)	0.673	.412
	GDS	1.077	(1.025, 1.132)	8.489	.004
	APOE ϵ4 allele number				
	0	0.817	(0.518, 1.290)	0.751	.386
	1	0.999	(0.647, 1.541)	0.000	.996
	2[a]				

Abbreviations: MMSE, Mini-mental state exam; GDS, Geriatric depression scale; APOE, Apolipoprotein E.
[a]Reference group.

primary language, Hachinski score, and APOE ϵ4 allele number were not significantly associated with psychosis in either analysis.

The UDS also requires reporting on several vascular burden and comorbidity variables, such as hypertension. We did univariate analyses of 12 such variables (see Supplementary Table 1 in Supplementary Material available online at doi:10.4061/2011/926597). Only hypertension and diabetes were significantly associated with psychosis. When the analyses were restricted to patients who has at least reached a CDR score $\geq$1, significance for diabetes remained, but significance for hypertension was lost (Supplementary Table 2). In multinomial regression analyses in which hypertension and diabetes were entered as covariates, along with age, age of onset, sex, race, ethnicity, primary language, education, MMSE, GDS, Hachinski, and APOE, neither was significantly associated with any psychosis measure. The association of all other variables with psychosis remained unchanged (data not shown).

4. Discussion

This is the largest study to date to look at the association between APOE ϵ4 and AD+P. We were able to examine the associations of APOE and other variables with both any occurrence of psychotic symptoms and with progressively more heritable (and therefore perhaps more biologically relevant) psychotic phenotypes defined by the presence of multiple and/or recurrent psychotic symptoms and with a more stringently restrictive definition of nonpsychotic AD cases. Neither APOE ϵ4 carrier status nor APOE ϵ4 allele number was associated with psychosis in any analysis.

Table 4: Multinomial logistic regression analysis of Single and Multiple/Recurrent Psychosis when Never Psychotic (AD−P) cases were restricted to CDR ≥ 1.

Psychosis category	Variable	OR	95% CI	Wald χ^2 (df = 1)	*P* value
Single	Age	1.022	(0.985, 1.061)	1.326	.250
	Age of onset	0.980	(0.944, 1.017)	1.178	.278
	Sex	0.833	(0.653, 1.063)	2.151	.143
	Race				
	Caucasian	0.482	(0.236, 0.983)	4.028	.045
	African-American	1.046	(0.476, 2.297)	0.013	.911
	Other[a]				
	Hispanic origin	0.590	(0.295, 1.178)	2.234	.135
	Primary language	1.699	(0.787, 3.670)	1.822	.177
	Education	0.958	(0.924, 0.993)	5.583	.018
	MMSE	1.016	(0.995, 1.036)	2.221	.136
	Hachinski	0.966	(0.886, 1.053)	0.605	.437
	GDS	1.053	(1.007, 1.101)	5.160	.023
	APOE ϵ4 allele number				
	0	0.858	(0.592, 1.243)	0.655	.418
	1	0.917	(0.641, 1.313)	0.223	.637
	2[a]				
Multiple/Recurrent	Age	1.052	(1.009, 1.098)	5.543	.019
	Age of onset	0.929	(0.889, 0.969)	11.458	.001
	Sex	0.876	(0.649, 1.182)	0.750	.387
	Race				
	Caucasian	0.326	(0.153, 0.695)	8.438	.004
	African-American	1.204	(0.523, 2.769)	0.190	.663
	Other[a]				
	Hispanic origin	0.522	(0.237, 1.151)	2.597	.107
	Primary language	1.030	(0.440, 2.408)	0.005	.946
	Education	0.969	(0.930, 1.010)	2.274	.132
	MMSE	0.947	(0.925, 0.968)	22.376	<.001
	Hachinski	1.034	(0.942, 1.136)	0.499	.480
	GDS	1.080	(1.026, 1.137)	8.692	.003
	APOE ϵ4 allele number				
	0	0.883	(0.557, 1.398)	0.283	.595
	1	1.087	(0.702, 1.685)	0.140	.709
	2[a]				

Abbreviations: AD−P, Alzheimer's disease minus psychosis; MMSE, Mini-mental state exam; GDS, Geriatric depression scale; APOE, Apolipoprotein E.
[a]Reference group.

Similarly, the degree of vascular disease as rated on the Hachinski scale was not associated with AD+P in any analysis. Our analysis of these multiple definitions of AD+P also revealed other patterns. Greater cognitive impairment and greater depressive symptoms were associated with increased incidence of psychosis across multiple analyses, with the strongest associations observed with Multiple/Recurrent Psychosis. A similar pattern of association was seen for Caucasian race, although it was protective against AD+P. Other variables demonstrated less consistent associations, emerging (e.g., age and age of onset of AD), or disappearing (sex, Hispanic ethnicity, primary language), after controlling for the effects of other variables in multivariate analyses. Finally, years of education showed associations with AD+P in both univariate and multivariate analyses, but not in the latter with the Multiple/Recurrent phenotype.

Many studies have looked at the association of APOE ϵ4 with AD+P, with conflicting, albeit largely negative, results [12]. A number of possible reasons might have contributed to these contradictory findings, including the variability in sample size across studies, heterogeneity of AD subjects (with regard to early versus late stages of AD and early- or late-onset AD), and different methods of psychosis assessment and classification. Adding to the inconsistencies across studies, prior studies varied regarding whether they analyzed APOE genotype, ϵ4 allele number, or ϵ4 carrier

status and the extent to which they included relevant clinical and demographic information in multivariate models.

We were able to overcome many of these problems by utilizing the NACC UDS to evaluate the largest sample of subjects studied for the association of APOE with AD+P to date. Subjects from 24 ADCs across the country were assessed using a standardized battery allowing for multivariate analyses including a number of potentially relevant clinical and demographic measures in essentially all subjects. Further, guided by data indicating the stage-dependent emergence of psychotic symptoms during AD [6, 20] and the increased heritability of an AD+P phenotype defined by the presence of multiple and/or recurrent symptoms [6, 7], we were able to assess the association of APOE with a restrictive definition of AD+P likely to be enriched for association with causal genetic variants.

Using these approaches we found no evidence that APOE $\epsilon 4$ is associated with AD+P. It is possible from the small magnitude of the odds ratios observed in our study that a significant association would be observed in a much larger sample. However, the current results are consistent with the majority of the prior evidence, in which only nine of 22 prior studies, comprising more than 5,200 subjects with AD, found any evidence of significant association [12]. Furthermore, we showed previously that the time from entry into our clinic to the onset of psychosis was not associated with APOE genotypes, lending additional support to the current findings [21]. Thus, the most likely conclusion is that APOE $\epsilon 4$ carrier status and allele number are not associated with psychosis in a population of patients with late-onset Alzheimer's disease.

As with APOE, the current data set and analytic approach can also shed some light on the conflicting results of prior studies which have examined the association of AD+P with other clinical and demographic variables. As summarized in a recent review by Ropacki and Jeste [1], AD+P was significantly associated with older age in 12/25 studies, with age of onset in 5/12 studies (older in 4/5, younger in 1/5), with gender in 7/24 studies (male in 3/7, female in 4/7), with African-American race in 5/7 studies, and with lower education in 4/17 studies. More recent studies have found a significant association between AD+P and the severity of depressive symptoms [6, 22–24]. Our findings would suggest that the associations with AD+P of age, age of onset of dementia, non-Caucasian race, and depressive symptom severity represent "true positives" while those for sex, ethnicity, and primary language are explained by confounding with other variables.

One of the most consistent correlates of AD+P in prior studies is greater burden of cognitive impairment, whether measured as degree of cognitive impairment at time of psychosis or as more rapid cognitive decline [1, 10, 25]. Our current findings are congruent with the former of these prior observations; however, we did not measure the rate of cognitive decline in this study because of the limited number of subjects who have had follow-up assessments entered to date. The mechanisms underlying the association between greater cognitive impairment and AD+P are not known, but the current analysis suggests that one potential mediator, increased vascular burden [26], as measured by a global summary, the Hachinski, does not explain the association., We followed this up by analysis of direct measures of vascular risk factors and cerebrovascular disease. Of the 12 UDS variables, only history of hypertension and diabetes achieved marginal significant associations with AD+P in univariate analyses, In multivariate analysis the significance for both was lost. Therefore, the most conservative interpretation is that increased vascular burden is not associated with AD+P.

Amongst the other demographic variables that we tested, the finding that non-Caucasian (predominantly African-American) subjects are more likely to develop psychosis during the progression of AD deserves some comment. It is not clear if this association is due to differences between ethnic groups in allele frequencies of potential AD+P risk genes [27] or if being rated as positive for psychotic symptoms, such as persecutory delusions, represents culturally or socioeconomically biased measures of psychosis or referral bias within minority communities. Without having a representative sample of minorities from all socioeconomic backgrounds, it will be impossible to make this distinction. Regardless, the implication for studies of genetic association in AD+P is that non-Caucasian subjects should be evaluated separately from Caucasian populations and combined in analyses only if heterogeneity is not observed.

The presence of $\epsilon 4$ alleles of APOE is currently the strongest genetic determinant for late-onset AD, a fact underlined by the findings in most genome-wide association studies of late-onset AD, which have "rediscovered" the association with APOE (http://www.alzgene.org/). We provide evidence that a heritable subtype of AD, defined by the presence of multiple or recurrent psychotic symptoms, is not associated with APOE $\epsilon 4$. As the discovery of non-APOE genetic variation contributing to the risk of late-onset AD remains a high priority, one approach to enriching cohorts to enhance successful discovery may be to examine the AD+P phenotype.

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