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Gender and Pathology-Specific Effect of Apolipoprotein E Genotype on Psychosis in Alzheimer's Disease

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Abstract

Background—Symptoms of psychosis is one of the common clinical manifestations of Alzheimer's disease (AD). However, the pathophysiology behind psychosis is unknown.

Objective—The aim of the present study was to explore the relationship between Apolipoprotein E (APOE) genotype, Lewy body pathology, and psychosis in AD.

Methods—The data was obtained from the National Alzheimer's disease Coordinating Centre (NACC), using the Uniform Data Set and the Neuropathology Data Set. Subjects with frequent neuritic plaque on CERAD, and Braak Stage of V or VI, corresponding to high probability of AD based on the NIA-AA Regan criteria were included in the analysis.

Results—Subject with two copies of $\epsilon 4$ alleles were significantly more likely to develop psychosis, both delusions and/or hallucinations, during the course of their illness. This association was gender-specific, only reaching significance in females. Our findings further showed that presence of two copies of $\epsilon 4$ allele was positively associated with the formation of Lewy bodies.

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CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary Table 1 describes the distribution of the number of *APOE* $\epsilon 4$ allele and psychosis.

Only in females with Lewy bodies was the effect of two copies of $\epsilon 4$ allele significant, reaching an odd ratio of 4.5.

Conclusion—The *APOE* $\epsilon 4$ allele has a female-specific effect in inducing psychosis in AD through the formation of Lewy bodies.

Keywords

Alzheimer's disease (AD); Apolipoprotein E; Neuropathology; Lewy Bodies; Neuropsychiatric symptoms; Delusions; Hallucinations

INTRODUCTION

Psychotic symptoms such as delusions and hallucinations are one of the common and persistent clinical manifestations of Alzheimer's disease (AD). It has been estimated that nearly half of the patients with AD experience psychosis during the course of their illness (1). Psychosis has been associated with greater cognitive and functional impairments (2, 3), behavior disturbances such as agitation and aggression (4, 5), and worse overall health (6), diminishing the quality of life of the patients and their caregivers (7).

One of the strongest genetic determinants of AD is the Apolipoprotein E (APOE) gene (8). The APOE gene has three common polymorphic forms, $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$; the $\epsilon 4$ allele is associated with the risk of developing AD. It has been estimated that approximately 40% of subjects with AD have the $\epsilon 4$ allele compared to 15% in healthy older subjects (9). This effect of *APOE* is codominant, with $\epsilon 4$ allele acting in a dose-related manner, increasing the likelihood of AD by 3 times in heterozygotes and 15 times in homozygotes (9). From a neuropathological perspective, $\epsilon 4$ allele acts by increasing AD pathology, including neurofibrillary tangles and senile plaques (8, 10, 11). Recently, $\epsilon 4$ allele has also been found to be associated with the development of Lewy bodies (12), which are frequently found comorbid with AD pathology, occurring in approximately 50% of subjects with AD (13). Unlike the overt phenotype of Lewy body dementia (DLB) (14–16), the clinical manifestations of Lewy body pathology in AD are muted, just resulting in higher scores on Neuropsychiatric Inventory Questionnaire and Unified Parkinson Disease Rating Scale motor subscale [12].

The present study seeks to investigate the relationship between the APOE genotype and psychosis in subjects with neuropathologically confirmed diagnosis of AD, and the role of Lewy body pathology in this manifestation. Furthermore, given that gender-specific effects of $\epsilon 4$ allele in AD have been commonly reported, males and females are analyzed separately (17).

METHODS

Data Source

The database was obtained from the National Alzheimer's Coordinating Centre (NACC). The NACC encompasses records from 34 past and present Alzheimer's Disease Centres in the United States collected between September 2005 and December 2015.

The Uniform Data Set (UDS), which include demographic and clinical information and the Neuropathology (NP) Data Set, which include autopsy records were used for analysis. Demographics included age, sex, ethnicity, and education. The presence of psychotic symptoms was evaluated based on the Neuropsychiatric Inventory Questionnaire quick version, assessing delusions or hallucinations in the month prior to clinical visit.

Only subjects in the NP Data Set were assessed. The severity of AD pathology was assessed based on the density of neocortical neuritic plaques (CERAD) and the Braak Stage for neurofibrillary degeneration on the NP Data Set. Lewy body pathology as determined by alpha-synuclein immunohistochemistry was categorized into either absence (if no Lewy body pathology) or presence (if Lewy body pathology was observed in the brainstem, limbic region or amygdala, neocortical, olfactory bulb, or regions unspecified). The severity of Lewy body pathology was assessed as low (if brainstem predominant), moderate (if limbic or amygdala predominant), and severe (if neocortical predominant), following the recommendations of the Third report of the DLB consortium (18). The presence of Lewy bodies in the olfactory bulb or regions unspecified were excluded from the severity analysis. The *APOE* genotypes were reported by individual centres where the autopsy was performed, and further confirmed by reports from the Alzheimer's Disease Genetic Consortium (ADCG).

Subject Criteria

Subjects with other primary diagnosis of brain injury, CNS neoplasm, Down's syndrome, and Huntington's disease were excluded. Subjects with frequent neuritic plaque on CERAD, and Braak Stage of V or VI, corresponding to NIA-AA Reagan of high probability of AD were selected (19). A total of 575 subjects with discrepant CERAD and Braak Stage were excluded, thus ensuring that only subjects with severe AD were included in the analysis. With respect to the *APOE* genotype, subjects were categorized into corresponding number of *APOE* $\epsilon 4$ alleles: no $\epsilon 4$ alleles, 1 copy of $\epsilon 4$ allele, and 2 copies of $\epsilon 4$ allele. Subjects with delusions or hallucinations at any clinical visit during the course of their illness were considered psychotic. The severity of delusions and hallucinations were not analyzed due to small sample size. Subjects were categorized based on the NPI-Q scores as never psychotic (AD-P), or any history of psychosis (AD+P), and the latter further classified into two overlapping groups of delusions with and without hallucinations (AD+D), and hallucinations with or without delusions (AD+H).

Statistical Analyses

Subjects with psychosis (AD+P), and each of the sub-groups (AD+D and AD+H) were independently compared to subjects without psychosis (AD-P). For categorical data, the Pearson's chi-square test was employed. For continuous data with normal distribution, the independent t-test was used. For continuous data with non-normal distribution (if statistically significant using Kolmogorov-Smirnov test), the Mann-Whitney test was employed. For ordinal data, the ordinal logistics regression analysis was performed. The statistical analysis performed in this study did not correct for multiple testing. All the statistical analysis was done using statistical software SPSS Statistics 23.0. The statistical significance was established at $p = 0.05$.

RESULTS

Subject Demographics

On the NACC database, 1509 subjects were identified as having high probability of AD based on the NIA-AA Reagan criteria on post-mortem neuropathological evaluation. Of these subjects, 1284 subjects had their APOE gene status evaluated, and 1236 of those had NPI-Q scores. In this cohort, 503 subjects had comorbid Lewy bodies, and 733 subjects did not; there were 625 AD+P and 611 AD+H, further classified into 475 AD+D, 331 AD+H; 195 subjects had both delusions and hallucinations and thus were included in both groups (Figure 1). Of the 558 females identified, 79 had two copies, 267 had one copy, 212 had no copies of $\epsilon 4$ allele. Of the 678 males identified, 114 had two copies, 337 had one copy, and 227 had no copies of $\epsilon 4$ allele. The demographic and clinical correlations of the NACC database pertaining to psychosis has already been investigated in a previous study by our group (20). With respect to *APOE* status, subjects with one (78.55 ± 10.07 , $N=624$) or two (77.27 ± 8.34 , $N=202$) copies of $\epsilon 4$ allele were significantly younger at death compared to subjects with no $\epsilon 4$ allele (79.67 ± 11.93 , $N=463$). There was no association between *APOE* status and the average time between last clinical visit and death. All analysis performed in this study were corrected for age.

Gender-Specific Effect of $\epsilon 4$ Allele on Psychosis

In the group of subjects with severe AD, the presence of two copies of $\epsilon 4$ allele was positively associated with AD+P (OR = 1.53, 95% CI: 1.08–2.15, $p = 0.010$), including both AD+D (OR = 1.57, 95% CI: 1.09–2.25, $p = 0.010$) and AD+H (OR = 1.54, 95% CI: 1.03–2.31, $p = 0.020$). A minimal trend was observed in subjects with one copy of $\epsilon 4$ allele and AD+P (OR = 1.22, 95% CI: 0.95–1.56), but did not reach significance ($p = 0.110$).

When the analysis was repeated stratified by gender, a gender-specific effect was observed. In females, carrying two copies of the $\epsilon 4$ allele was significantly associated with AD+P (OR = 2.00, 95% CI: 1.17–3.41, $p = 0.008$), and both AD+D (OR = 1.86, 95% CI: 1.06–3.26, $p = 0.025$) and AD+H (OR = 1.98, 95% CI: 1.07–3.69, $p = 0.025$). There was no significant association between one copy of the $\epsilon 4$ allele and psychosis. In males, a positive, but not significant trend between $\epsilon 4$ allele and psychosis was observed (Figure 2).

APOE $\epsilon 4$ Allele and Lewy Bodies

To investigate the role of $\epsilon 4$ allele and Lewy body pathology on psychosis, the relationship between $\epsilon 4$ allele and Lewy body pathology was analyzed first. A significant association was found between two copies of $\epsilon 4$ allele and Lewy bodies. The likelihood of having Lewy bodies increased from 36% in subjects with no $\epsilon 4$ allele to 50% in subjects with two copies of $\epsilon 4$ allele ($p = 0.001$). A positive trend was observed in subjects with one copy of $\epsilon 4$ allele, with 40% likelihood of having Lewy bodies, but did not reach significance. A double dose of the $\epsilon 4$ allele was also associated with the severity of Lewy bodies ($p = 0.008$) (Table 1).

The association between $\epsilon 4$ allele and Lewy bodies were also gender-specific. In females, two copies of $\epsilon 4$ allele was associated with the both the presence and severity of Lewy bodies. In males, a positive trend was observed, but did not reach significance. Specifically,

two copies of $\epsilon 4$ allele in females resulted in a 51% likelihood of developing Lewy bodies compared to 32% in subjects with no $\epsilon 4$ alleles ($p = 0.002$). In subjects with one copy of $\epsilon 4$ allele, no gender specific differences were found (Table 1).

Gender-Specific Effect of $\epsilon 4$ Allele on Psychosis Is Mediated Through Lewy Bodies

Given that $\epsilon 4$ allele is associated with Lewy body pathology, we then investigated the role of $\epsilon 4$ allele on psychosis in subjects in the absence and presence of Lewy bodies. In subjects with comorbid Lewy bodies, a significant association was found between carriers of two copies of $\epsilon 4$ allele and AD+P (OR = 1.86, 95% CI: 1.11–3.12, $p = 0.018$), including both AD+D (OR = 1.92, 95% CI: 1.10–3.33, $p = 0.020$) and AD+H (OR = 1.83, 95% CI: 1.01–3.33, $p = 0.046$). A positive trend was observed in subjects with one copy and AD+P (OR = 1.36, 95% CI: 0.92–2.04), but did not reach significance ($p = 0.123$). However, in subjects without Lewy bodies, there was minimal association between one or two copies of $\epsilon 4$ allele and AD+P.

The associations became more apparent when the analysis was separated by gender. In females, the likelihood of having two copies of $\epsilon 4$ allele in the presence of Lewy bodies was increased in AD+P (OR = 4.5, 95% CI: 1.83–11.10, $p = 0.001$), including both AD+D (OR = 4.5, 95% CI: 1.75–11.51, $p = 0.001$), and AD+H (OR = 3.6, 95% CI: 1.31–9.88, $p = 0.011$). There was no significant association between one copy of $\epsilon 4$ allele and psychosis. The same analyses in males also showed no associations. In females without Lewy bodies, having one or two copies of $\epsilon 4$ allele was not associated with psychosis, even showing negative trends. In males without Lewy bodies, having one or two copies of $\epsilon 4$ allele resulted in an increase in the likelihood of psychosis, but did not reach significance (Figure 2).

DISCUSSION

Our study on a large neuropathologically confirmed series of AD cases show that presence of two copies of *APOE* $\epsilon 4$ induces psychosis, both delusions and hallucinations. It should be noted that the criteria for delusions on the NPI-Q is mainly persecutory delusions. Therefore, the extent to which $\epsilon 4$ allele affects other types of delusions will need to be further investigated. Previous studies investigating the relationship between *APOE* $\epsilon 4$ and psychosis have produced mixed results. A comprehensive review by Panza and colleagues summarize the contradictory findings (21). Several studies have reported no association between $\epsilon 4$ allele and psychosis. Studies that have shown positive associations are inconsistent as to whether $\epsilon 4$ allele influences the onset of delusions or hallucinations (21). A study by Chang and colleagues show a strong association between $\epsilon 4$ allele and hallucinations (22). On the other hand, other studies reported a protective effect of $\epsilon 4$ allele on hallucinations (23, 24). With respect to delusions, a longitudinal study by Scarmeas and colleagues found that subjects with one copy of the $\epsilon 4$ allele were at 2.5-fold risk, and two $\epsilon 4$ alleles are at 5.6-fold risk of developing delusions (24). However, several crosssectional and longitudinal studies did not find any associations (23, 25, 26). A recent study by DeMichele-Sweet and colleagues using the NACC database did not find an association between $\epsilon 4$ allele and psychosis (27).

The inconsistencies in the past findings may be due to differences in sample size, criteria for psychosis, and statistical method. Importantly, these studies have based their results on clinical diagnosis of AD as opposed to neuropathologically confirmed diagnosis. A recent study by Fischer and colleagues showed the importance of differentiating the findings from clinical diagnosis and neuropathological diagnosis of AD, showing that findings from clinical diagnosis can drive false results (20). A study by Weiner and colleagues was the first to investigate the relationship between $\epsilon 4$ allele and psychosis in 61 neuropathologically confirmed cases of AD. They found a marginal association between $\epsilon 4$ allele with both delusions and hallucinations (28).

Gender-specific differences in both neuropathological and clinical manifestation of AD is a common finding (17). A study by Corder and colleagues on more than 5000 autopsy cases showed that $\epsilon 4$ allele imposes a greater risk of developing senile plaque and neurofibrillary tangles in females than in males (10). Clinically, a female-specific effect of $\epsilon 4$ allele has been manifested by faster rate of cognitive decline (29), and other neuropsychiatric symptoms including disinhibition and irritability (30). Several studies have also reported that females are at higher risk of developing psychosis (31, 32). On the other hand, a study by Fischer and colleagues using the NACC database did not find an association between gender and psychosis in neuropathologically confirmed AD (20). Our results indicate that although the males and females have similar likelihood of developing psychosis, the $\epsilon 4$ allele is a much more important determinant of this phenotype in females.

Given that $\epsilon 4$ allele is associated with higher AD load (8, 11), several studies have suggested the role of AD load as mediator of psychosis (33). However, a recent study by Fischer and colleagues found no correlation between AD pathology load and psychosis (20). Furthermore, Sweet and colleagues showed no correlation between psychosis and AD load, controlling for Lewy bodies (34). Recent studies have reported that $\epsilon 4$ allele is also related to increased Lewy body pathology (35, 36). In our study, this association was confirmed to be much more prominent and statistically significant in females. Studies examining the role of Lewy body pathology on psychosis have focused on subjects with dementia with Lewy bodies, where psychosis, particularly visual hallucinations, and to a lesser degree delusions are characteristic (37, 38). A study by Engelborghs and colleagues on 11 subjects with dementia with Lewy bodies showed a relationship between $\epsilon 4$ allele and delusions (39).

Our results indicate that the contribution of *APOE* $\epsilon 4$ to the development of psychosis in AD may be mediated by the formation of Lewy bodies. Furthermore, this association is specific to females. Our study shows that $\epsilon 4$ allele has recessive-like effect in inducing both delusions and hallucinations whereas a single copy of the $\epsilon 4$ allele has minimal effect on this phenotype. While the mechanism is clear cut, it affects a relatively limited subgroup of subjects with psychosis because of the relative rarity of *APOE* $\epsilon 4$ homozygosity, representing 17% of all subjects with psychosis. Females with two copies of $\epsilon 4$ allele and with Lewy bodies represent 5% of all subjects with psychosis, and the males represent 4% of the population. Therefore, it has a minor contribution to the development of psychosis observed in the AD population in general.

CONCLUSION

The *APOE* $\epsilon 4$ has recessive-like effect in inducing delusions and hallucinations, which is femalespecific. Furthermore, the mechanism through which this occurs may be through the formation of Lewy bodies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Ropacki SA, Jeste DV. Epidemiology of and risk factors for psychosis of Alzheimer's disease: a review of 55 studies published from 1990 to 2003. *Am. J. Psychiatry.* 2005; 162(11):2022–30. [PubMed: 16263838]
2. Chui HC, Lyness SA, Sobel E, Schneider LS. Extrapyraxidal signs and psychiatric symptoms predict faster cognitive decline in Alzheimer's disease. *Arch Neurol.* 1994; 51(7):676–81. [PubMed: 8018040]
3. Fischer CE, Ismail Z, Schweizer TA. Delusions increase functional impairment in Alzheimer's disease. *Dement Geriatr Cogn Disord.* 2012; 33(6):393–9. [PubMed: 22814093]
4. Gilley DW, Whalen ME, Wilson RS, Bennett DA. Hallucinations and associated factors in Alzheimer's disease. *J Neuropsychiatry Clin Neurosci.* 1991; 3(4):371–6. [PubMed: 1821255]
5. Kotrla KJ, Chacko RC, Harper RG, Doody R. Clinical variables associated with psychosis in Alzheimer's disease. *Am. J. Psychiatry.* 1995; 152(9):1377–9. [PubMed: 7653698]
6. Bassiony MM, Steinberg MS, Warren A, Rosenblatt A, Baker AS, Lyketsos CG. Delusions and hallucinations in Alzheimer's disease: prevalence and clinical correlates. *Int J Geriatr Psychiatry.* 2000; 15(2):99–107. [PubMed: 10679840]
7. Hopkins MW, Libon DJ. Neuropsychological functioning of dementia patients with psychosis. *Arch Clin Neuropsychol.* 2005; 20(6):771–83. [PubMed: 15936921]
8. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science.* 1993; 261(5123):921–3. [PubMed: 8346443]
9. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. *APOE and Alzheimer Disease Meta Analysis Consortium. JAMA.* 1997; 278(16):1349–56. [PubMed: 9343467]

10. Corder EH, Ghebremedhin E, Taylor MG, Thal DR, Ohm TG, Braak H. The biphasic relationship between regional brain senile plaque and neurofibrillary tangle distributions: modification by age, sex, and APOE polymorphism. *Ann. N. Y. Acad. Sci.* 2004; 1019:24–8. [PubMed: 15246987]
11. Bu G. Apolipoprotein E and its receptors in Alzheimer's disease: pathways, pathogenesis and therapy. *Nat. Rev. Neurosci.* 2009; 10(5):333–44. [PubMed: 19339974]
12. Chung EJ, Babulal GM, Monsell SE, Cairns NJ, Roe CM, Morris JC. Clinical Features of Alzheimer Disease With and Without Lewy Bodies. *JAMA neurology.* 2015; 72(7):789–96. [PubMed: 25985321]
13. Hamilton RL. Lewy bodies in Alzheimer's disease: a neuropathological review of 145 cases using alpha-synuclein immunohistochemistry. *Brain Pathol.* 2000; 10(3):378–84. [PubMed: 10885656]
14. Del Ser T, Hachinski V, Merskey H, Munoz DG. Clinical and pathologic features of two groups of patients with dementia with Lewy bodies: effect of coexisting Alzheimer-type lesion load. *Alzheimer Dis Assoc Disord.* 2001; 15(1):31–44. [PubMed: 11236823]
15. Boot BP, Orr CF, Ahlskog JE, Ferman TJ, Roberts R, Pankratz VS, et al. Risk factors for dementia with Lewy bodies: a case-control study. *Neurol.* 2013; 81(9):833–40.
16. Donaghy PC, McKeith IG. The clinical characteristics of dementia with Lewy bodies and a consideration of prodromal diagnosis. *Alzheimer's Res. Ther.* 2014; 6(4):46. [PubMed: 25484925]
17. Payami H, Zarepari S, Montee KR, Sexton GJ, Kaye JA, Bird TD, et al. Gender difference in apolipoprotein E-associated risk for familial Alzheimer disease: a possible clue to the higher incidence of Alzheimer disease in women. *Am. J. Hum. Genet.* 1996; 58(4):803–11. [PubMed: 8644745]
18. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurol.* 2005; 65(12):1863–72.
19. Hyman BT, Trojanowski JQ. Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. *J Neuropathol Exp Neurol.* 1997; 56(10):1095–7. [PubMed: 9329452]
20. Fischer CE, Qian W, Schweizer TA, Millikin CP, Ismail Z, Smith EE, et al. Lewy Bodies, Vascular Risk Factors, and Subcortical Arteriosclerotic Leukoencephalopathy, but not Alzheimer Pathology, are Associated with Development of Psychosis in Alzheimer's Disease. *Journal of Alzheimer's disease : JAD.* 2015; 50(1):283–95.
21. Panza F, Frisardi V, Seripa D, D'Onofrio G, Santamato A, Masullo C, et al. Apolipoprotein E genotypes and neuropsychiatric symptoms and syndromes in late-onset Alzheimer's disease. *Ageing Res Rev.* 2012; 11(1):87–103. [PubMed: 21763789]
22. Chang JB, Wang PN, Chen WT, Liu CY, Hong CJ, Lin KN, et al. ApoE epsilon4 allele is associated with incidental hallucinations and delusions in patients with AD. *Neurol.* 2004; 63(6):1105.
23. Pritchard AL, Harris J, Pritchard CW, Coates J, Haque S, Holder R, et al. The effect of the apolipoprotein E gene polymorphisms and haplotypes on behavioural and psychological symptoms in probable Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* 2007; 78(2):123–6. [PubMed: 16980336]
24. Scarmeas N, Brandt J, Albert M, Devanand DP, Marder K, Bell K, et al. Association between the APOE genotype and psychopathologic symptoms in Alzheimer's disease. *Neurol.* 2002; 58(8):1182–8.
25. Levy ML, Cummings JL, Fairbanks LA, Sultzer DL, Small GW. Apolipoprotein E genotype and noncognitive symptoms in Alzheimer's disease. *Biol Psychiatry.* 1999; 45(4):422–5. [PubMed: 10071711]
26. Sweet RA, Kamboh MI, Wisniewski SR, Lopez OL, Klunk WE, Kaufer DI, et al. Apolipoprotein E and alpha-1-antichymotrypsin genotypes do not predict time to psychosis in Alzheimer's disease. *J. Geriatr. Psychiatry Neurol.* 2002; 15(1):24–30. [PubMed: 11936240]
27. Demichele-Sweet MA, Lopez OL, Sweet RA. Psychosis in Alzheimer's disease in the national Alzheimer's disease coordinating center uniform data set: clinical correlates and association with apolipoprotein. *Int J Alzheimers Dis.* 2011:926597. [PubMed: 21461363]

28. Weiner MF, Vega G, Risser RC, Honig LS, Cullum CM, Crumpacker D, et al. Apolipoprotein E epsilon 4, other risk factors, and course of Alzheimer's disease. *Biol Psychiatry*. 1999; 45(5):633–8. [PubMed: 10088051]
29. Mortensen EL, Hogh P. A gender difference in the association between APOE genotype and age-related cognitive decline. *Neurol*. 2001; 57(1):89–95.
30. Xing Y, Tang Y, Jia J. Sex Differences in Neuropsychiatric Symptoms of Alzheimer's Disease: The Modifying Effect of Apolipoprotein E epsilon4 Status. *Behav Neurol*. 2015;275256. [PubMed: 26538817]
31. Hirono N, Mori E, Yasuda M, Ikejiri Y, Imamura T, Shimomura T, et al. Factors associated with psychotic symptoms in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 1998; 64(5):648–52. [PubMed: 9598682]
32. Leroy I, Voulgari A, Breitner JC, Lyketsos CG. The epidemiology of psychosis in dementia. *Am. J. Geriatric Psychiatry*. 2003; 11(1):83–91.
33. Farber NB, Rubin EH, Newcomer JW, Kinscherf DA, Miller JP, Morris JC, et al. Increased neocortical neurofibrillary tangle density in subjects with Alzheimer disease and psychosis. *Arch Gen Psychiatry*. 2000; 57(12):1165–73. [PubMed: 11115331]
34. Sweet RA, Hamilton RL, Lopez OL, Klunk WE, Wisniewski SR, Kaufer DI, et al. Psychotic symptoms in Alzheimer's disease are not associated with more severe neuropathologic features. *Int Psychogeriatr*. 2000; 12(4):547–58. [PubMed: 11263720]
35. Tsuang DW, Wilson RK, Lopez OL, Luedeking-Zimmer EK, Leverenz JB, DeKosky ST, et al. Genetic association between the APOE4 allele and Lewy bodies in Alzheimer disease. *Neurol*. 2005; 64(3):509.
36. Harrington CR, Louwagie J, Rossau R, Vanmechelen E, Perry RH, Perry EK, et al. Influence of apolipoprotein E genotype on senile dementia of the Alzheimer and Lewy body types. Significance for etiological theories of Alzheimer's disease. *Am J Pathol*. 1994; 145(6):1472–84. [PubMed: 7992850]
37. Del Ser T, McKeith I, Anand R, Cicin-Sain A, Ferrara R, Spiegel R. Dementia with lewy bodies: findings from an international multicentre study. *Int J Geriatr Psychiatry*. 2000; 15(11):1034–45. [PubMed: 11113984]
38. Jacobson SA, Morshed T, Dugger BN, Beach TG, Hentz JG, Adler CH, et al. Plaques and tangles as well as Lewy-type alpha synucleinopathy are associated with formed visual hallucinations. *Parkinsonism Rel Disord*. 2014; 20(9):1009–14.
39. Engelborghs S, Dermaut B, Marien P, Symons A, Vloeberghs E, Maertens K, et al. Dose dependent effect of APOE epsilon4 on behavioral symptoms in frontal lobe dementia. *Neurobiol Aging*. 2006; 27(2):285–92. [PubMed: 16399213]

Figure 1.
The distribution of neuropathologically confirmed AD subjects into diagnostic groups.

Figure 2.

The proportion of the number of APOE $\epsilon 4$ allele (White Bar: Zero, Grey Bar: One, Black Bar: Two copies) within each diagnostic group (AD-P: Never Psychotic, AD+P: Psychotic, AD+D: Delusions with and without hallucinations, AD+H: Hallucinations with and without delusions). Each diagnostic category (AD+P, AD+D, and AD+H) was independently analyzed against the AD-P group. The first row represents both males and females, second row represent females only, and third row represent males only. The first column represents all cases, second column represent cases with Lewy bodies (+LB), and third column represent cases without Lewy bodies (-LB). The difference in the effect of APOE $\epsilon 4$ on psychosis is best shown in comparing the black bars between AD-P and AD+P in each panel. * indicates $p=0.010$ to 0.050 ; ** indicates $p < 0.010$.

Table 1
The distribution of presence and severity of Lewy bodies and the number of ε4 alleles stratified by gender

	No ε4 allele		1 Copy of ε4 allele		2 Copies of ε4 allele	
	N	%	N	%	N	%
-/+ LB						
<i>All</i>						**
-	297	64%	374	60%	101	51%
+	164	36%	248	40%	99	50%
<i>Females</i>						**
-	153	68%	180	64%	40	49%
+	72	32%	100	36%	42	51%
<i>Males</i>						
-	144	61%	194	57%	61	52%
+	92	39%	148	43%	57	48%
Severity of LB						
<i>All</i>						**
None	297	70%	374	67%	101	59%
Low	13	3%	18	3%	7	4%
Intermediate	61	14%	86	15%	33	19%
Severe	53	13%	79	14%	31	18%
<i>Females</i>						**
None	153	73%	180	71%	40	56%
Low	6	3%	6	2%	5	7%
Intermediate	28	13%	40	16%	11	15%
Severe	24	11%	29	11%	16	22%
<i>Males</i>						
None	144	68%	194	64%	61	61%
Low	7	3%	12	4%	2	2%
Intermediate	33	15%	46	15%	22	22%
Severe	29	14%	50	17%	15	15%

-/+; Absence/Presence; LB: Lewy Bodies.

* indicates p < 0.05;
** indicates p < 0.01;
*** indicates p < 0.001.

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