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APOE Genotype Predicts Depression in Women with Alzheimer's Disease

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Abstract

The association between the epsilon-4 type allele of apolipoprotein E (APOE ε4) and depression was investigated in 323 AD patients. Patients were divided into two groups based on the presence (n=61) or absence (n=262) of depression as assessed by the DSM-based Diagnostic Interview Schedule. Both subgroups were demographically comparable with regard to age, education, gender, and severity of cognitive impairment. Analysis of the frequency of APOE ε4 alleles between the groups revealed a significantly higher prevalence rate of the APOE ε4 genotype in the depressed group (72% of depressed AD patients carried at least one copy of the ε4 allele) compared to the non-depressed AD patients (58%). This effect was primarily accounted for by women. Specifically, an interaction was revealed wherein women who possessed the APOE ε4 allele were almost 4 times more likely to be depressed in comparison to those who did not carry the allele, and APOE ε4 status did not predict depression among men in our sample. These results are consistent with recent suggestions that the APOE ε4 genotype may be over-represented among women with AD and depression and highlight a need for additional research investigating the links between APOE genotype, mood, and gender.

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by progressive neuropsychological, functional, and behavioral decline. Currently, there are 4.5 million people with AD in the United States and the prevalence is expected to increase to 11 – 16 million by 2050 (Alzheimer's Association, 2004). Psychiatric disturbance is frequently seen in AD and, although prevalence rates vary considerably across studies (e.g., 1 – 90%), average rates of coexisting AD and depression appear to hover around 20 to 40% (Wragg & Jeste, 1989; Cummings, Ross, Absher, Gornbein & Hadjiaghai, 1995; Tractenberg, Weiner, Patterson, Teri, & Thal, 2003; Green et al., 2003). Lyketsos and Olin (2002) reported that behavioral disturbances among AD patients are 3 to 4 times higher than that seen in normal aging.

Adverse consequences of depression in patients with AD are numerous, including greater impairment in activities of daily living (Lyketsos et al., 1997b), poorer quality of life (Gonzales-Salvador et al., 2000), earlier institutionalization (Magni, Bionetti, Bianchetti, & Trabucchi, 1996), greater caregiver depression and level of burden (Gonzales-Salvador et al., 1999), more

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rapid declines in cognition (Stern et al., 1997), and higher mortality rates (Ganguli, Hodge, & Mulsant, 2002; Hoch et al., 1993). In addition, neuropsychiatric symptoms significantly increase direct annual costs of care among AD patients, even after adjusting for the severity of cognitive impairment and other medical comorbidities (Murman et al, 2002).

Neuropathologically, depressive symptoms appear to be associated with a selective loss of noradrenergic and serotonergic nuclei in the brainstem (Zubenko, 2000) and these losses may be related to genetic risk factors for AD (Craig, Hart, McIlroy, & Passmore, 2005). Although it is now clear that the ε4 allele of the apolipoprotein E gene (APOE-ε4), a plasma protein involved in the transport of cholesterol and lipids throughout the body, is an important risk factor for AD (Saunders et al., 1993; Corder et al., 1993; Farrer et al.,1997; Aggarwal et al., 2005), inconsistencies exist across studies investigating whether this susceptibility gene modifies the risk for depression in AD. Early studies examining this relationship showed a positive association between depression and the APOE ε4 allele in patients with AD (Murphy, Taylor, Tinklenberg, & Yesavage, 1997; Ramachandran et al., 1996), and other investigators have demonstrated combined risks of developing AD among those with late-onset depression and APOE ε4 genotypes in nondemented geriatric populations (Krishnan et al., 1996; Steffens et al., 1997; Wilson et al., 2002; Rigaud et al., 2001). A recent study suggested that depression and APOE ε4 genotype may be higher in women with AD but not in men (Muller-Thomsen et al., 2002). Despite these findings supporting an association between APOE and depression, several other published studies have not supported the notion that APOE ε4 genotype influences depression in AD (Liu et al., 2002; Scarmeas, et al., 2002; Craig et al., 2005).

Discrepant findings may be due to a number of factors including small sample sizes, differences in sample compositions (e.g., general "dementia" groups versus strictly diagnosed patients with "probable AD"), and the use of very brief, wide-ranging, or unstructured psychopathology inventories. In addition, others have shown trends toward association between APOE genotype and depression but have rendered conclusions of no relationship. For example, Forsell et al. (1997) found that "the odds for depression tended to be elevated in those who carried an ε4 allele (vs. ε3/ε3 allele)" though this did not reach statistical significance. The authors concluded there was no association and did not report any accompanying power or effect size estimates. Moreover, they reported a somewhat low prevalence rate (11%) for depression in their AD sample, causing some speculation about the representativeness of their sample or the diagnostic methodology used to assess depression. Other studies have also used varying schemes for diagnosing depression in AD. For example, Scarmeas et al. (2002) employed a psychiatric inventory that measured only three depression-related symptoms (i.e., depressed mood, change in appetite and sleep problems), two of which are vegetative symptoms and thus problematic for use in older adult samples that frequently have somatic symptoms secondary to physical comorbidity. Similarly, Levy et al. (1999) and Craig et al. (2005) utilized the Neuropsychiatric Inventory (NPI) which contains few items pertaining to depressive symptoms. Thus, the bulk of published studies reporting a lack of association between APOE ε4 genotype and depression in AD have suffered from small sample sizes, low reported prevalence rates for depression, very brief inventories of depressive symptoms, and/or low diagnostic rigor in the determination of the presence or absence of a DSM-based diagnosis of depression.

Given that negative findings in the literature may relate to measurement issues (i.e., insensitive instruments), the current study was designed to address these limitations by employing the Diagnostic Interview Schedule (DIS), a standardized DSM-based interview for depression (i.e., Diagnostic Interview Schedule for the DSM-III-R) in a large sample of AD patients. Thus, the present study examined a sample of well-characterized probable AD patients to investigate whether an association between APOE genotype and depression exists. Although there is considerable debate regarding the relationship between APOE genotype and depression in AD, we hypothesized that the APOE ε4 allele would significantly predict depression in our sample

of rigorously diagnosed AD patients. This relationship was posited given previous findings as well as the observation that the APOE ε4 allele is associated with an increased density of neurotoxic beta-amyloid plaques in brain regions thought to be important in emotion regulation (i.e., limbic structures) (Roses, 1994; Shearman, 1998). Furthermore, a secondary aim of this study was to assess possible gender differences within the sample given recent suggestions that depression may be more prevalent in women with the APOE ε4 genotype (i.e., Muller-Thomsen et al., 2002).

Methods

Participants and Procedure

Data from 323 consecutive patients diagnosed with probable AD were retrospectively drawn from a larger cohort participating at the University of California, San Diego Alzheimer's Disease Research Center (ADRC). All the participants were selected without regard to ethnicity or race. A written informed consent was obtained from all participants (or their caregivers) after full explanation of the study protocol which had been approved by the UCSD Human Research Protection Program.

All participants were independently diagnosed with probable AD by two staff neurologists according to the NINCDS-ADRDA criteria (McKhann et al., 1984) and received (a) annual neurological, medical, and psychiatric examinations; (b) global cognitive screening (i.e., Mattis Dementia Rating Scale; DRS; Mattis, 1988; and the Mini-Mental Status Examination; MMSE; Folstein, Folstein, & McHugh, 1975); (c) a neuropsychological battery of tests that assess basic cognitive domains such as attention, memory, language, visuospatial skill, problem solving and abstraction, and motor coordination. Included in this battery were verbal memory tests consisting of the Wechsler Memory Scale-Revised, Logical Memory subtest (WMS-R; Wechsler, 1987) and the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987). See Salmon and Butters (1992) for a detailed description of all tests that comprise this battery.

Individuals were excluded from this study if an alternate cause of dementia was determined (i.e., hypothyroidism, vitamin B_{12} deficiency, electrolyte imbalance), or if they had a history of severe head injury, recent alcohol dependence or abuse, or serious psychiatric disturbance (i.e., schizophrenia). Finally, to ensure that no participants in the study had a dementia with a significant vascular component, participants with modified Hachinski Ischaemia scores (Hachinski et al., 1975) greater than four were excluded.

Concurrent with the dementia diagnosis, all participants were evaluated for psychopathology according to the DIS, which was administered by trained nurse practitioners, and the diagnosis of depression or other psychiatric disorders was made by two board-certified psychiatrists. For this analysis, patients were divided into two groups on the basis of the presence ($\underline{n}$ = 61) or absence ($\underline{n}$ = 262) of a current diagnosis of co-occurring depression. Specific categories of affective diagnoses included Dementia with Depression (n = 39), Adjustment Disorder with Depressed Mood ($\underline{n}$ = 11), Major Depressive Disorder ($\underline{n}$ = 8), Dysthymic Disorder ($\underline{n}$ = 2), and Atypical Depression ($\underline{n}$ = 2).

Participants were genotyped for APOE using a method based on polymerase chain reaction identical to that of Saunders et al. (1993), and were divided into two groups on the basis of the presence ($\underline{n}$ = 196) or absence ($\underline{n}$ = 127) of the APOE-ε4 allele (overall percentage = 61%). This allelic frequency is highly consistent with prior published percentages (e.g., Corder et al., 1993; Saunders et al., 1993).

Statistical Analyses

Univariate level associations between different demographic and clinical variables and depression status were made with t-tests, Chi-Square tests, or Fisher's Exact test, as appropriate. Logistic regression was used to determine the relationship of APOE ε4 status to depression, while controlling for confounders. Variables significantly related at the $p<0.10$ level to depression status at the univariate level were selected for inclusion into the multivariate model. An interaction term for gender and APOE ε4 status was selected for inclusion in the model, *a priori*, to address differences in the APOE ε4 relationship to depression by gender, and any confounders significantly related at the $p<0.10$ level to gender were selected for inclusion in the model. All analyses were run in SPSS (Version 13.0) and confirmed with STATA (version 8.2; College Station, TX).

Results

The sample included a total of 323 participants who were diagnosed with probable AD. Overall, there were 163 men and 160 women, with a mean age of 73 (SD = 9), and a mean education of 13 years (SD = 4). The proportion of patients diagnosed with a depressive disorder was approximately 19 percent and, as shown in Table 1, there were no statistical differences between the depressed and non-depressed AD groups with respect to demographic variables (i.e., age, education, and gender), cognitive status (i.e., DRS total score, MMSE, and verbal memory on the CVLT), or disease duration. For subjects with verbal memory scores, there was no difference between depressed and non-depressed patients on the delayed portion of the Logical Memory subtest of the WMS-R (LM-II) (mean raw score: 2.7 [SD 5.6] vs. 2.1 [SD 3.3]; $p = 0.44$) or the CVLT (Long Delay Free Recall; LD FR) (mean raw score: 1.2 [SD 1.9] vs. 1.0 [SD 1.8]; $p = 0.63$). However, results are not generalizable to the entire sample as a large portion of all participants were missing these scores ($n = 171$ and $n = 127$, respectively); MMSE values were significantly lower in those subjects who were missing these measures than in those who had them due to the discontinuation rules for administration of these memory tests in severe AD: mean MMSE for those with WMS-R LM II raw = 22.8 (SD 3.6) vs. 16.7 (SD 5.8) for those without, $p < 0.001$; and mean MMSE for those with CVLT LD FR raw 22.6 (SD 5.9) vs. 17.1 (SD = 17.1) for those without, $p < 0.001$. When the demographic measures were also compared by gender, only education differed, with women averaging nearly two years less education than men. There was no difference in APOE ε4 status by gender.

As depicted in Table 1, the frequency of the ε4 allele in depressed patients was approximately 77% (47/61) versus 58% (152/262) in the non-depressed patients. This finding indicates that the depressed AD patients were significantly more likely to possess an APOE ε4 allele than were those without depression (chi-square $_{[df=1, N=323]} = 4.13$, $p = .04$). When stratified by gender, the relationship between APOE genotype and depression was significant: of the 33 women who were depressed, 28 were APOE ε4 positive (85%) versus only 75 of the 127 women who were not depressed (59%) [Fisher's exact chi-square $_{(df=1, N=160)} = 7.60$, $p = .007$]. Among men, there was no relationship between APOE ε4 status and depression, with 16 of the 28 men with depression (57%) and 77 of the 135 men without depression (57%) being APOE ε4 positive [Fisher's exact chi-square $_{(df=1, N=163)} = 0.01$, $p = .99$].

The relationship of APOE ε4 status on depression was further investigated using multivariate regression analyses (Table 2). When controlled for education and years of AD duration (see Methods), there is a significant interaction between APOE ε4 status and gender on depression: women who were APOE ε4 positive had increased odds of being depressed of 1.75 compared to APOE ε4 positive men, and women who are APOE ε4 negative had decreased odds of 0.46 over APOE ε4 negative men. This relates to a 3.83-fold increased risk of depression by APOE status among women. APOE ε4 status did not appear to increase the odds of depression among men (OR 1.00).

Overall, results indicate that the interaction of APOE genotype and gender significantly impacted whether individuals were classified as depressed or not depressed. Figure 1 depicts the APOE by gender interaction in terms of the predicted probability of depression. Results show that the APOE ε4 allele seems to impact the probability of being depressed for women but not for men and that women with AD who are positive for the APOE ε4 allele have nearly a four-fold increase in risk for depression compared to everyone else as a group.

Discussion

Consistent with some of the previous studies demonstrating a relationship between APOE genotype and depression in AD (Murphy et al., 1997; Ramachandran et al., 1996; Muller-Thomsen et al., 2002), we found that depressed AD patients had a significantly higher frequency of APOE ε4 genotype than non-depressed AD patients. This relationship was evident despite the groups' comparability on demographic characteristics and cognitive status. Although the depressed AD group demonstrated a slightly longer duration of dementia (approximately 8 months longer), the difference was not statistically significant. Moreover, when duration of illness was statistically controlled for in the group analysis, the higher frequency of the APOE ε4 allele in the depressed group remained. Thus, it did not appear that the increased likelihood of depression in AD patients with a copy of the APOE ε4 allele was due specifically to disease severity or duration.

Our findings stand in contrast to a number of other studies that demonstrated a lack of association between depression and APOE genotype in AD. One possible explanation for our positive finding and its absence in prior studies may be that we obtained a relatively large sample of depressed AD patients and thus had a greater power to detect group differences. Several recent studies (i.e., Forsell et al., 1997; Liu et al., 2002; Gabryelewicz et al., 2002) included between 21 and 39 depressed individuals, whereas the current study included approximately twice those sample sizes (i.e., 61 depressed AD patients) and many more non-depressed patients. Another factor may be that the use of limited screening measures for determining depression could be leading to poorer diagnostic accuracies and thus different prevalence rates of depression in AD. In contrast to the current study in which 19% of the sample was diagnosed as depressed, Forsell et al. (1997) reported depression rates of 11% and Levy et al. (1999) reported more than double the prevalence we observed (40–50% prevalence of depression in their group of AD patients). These highly variable findings may represent significant heterogeneity within depressed groups. For example, Liu et al. (2002) included a large proportion of patients with Dysthymic Disorder in their sample (52%) whereas our study contained only 3% with Dysthymia. It appears that greater specification of diagnostic categories is clearly needed to inspect for important subgroup differences.

In contrast to standardized psychiatric interviews such as the DIS used in the current study, studies employing the use of very brief inventories for depression or multi-symptom profile inventories add further variability and likely diminish diagnostic accuracy. Determining whether individuals are depressed on the basis of a brief screening measure limited to but a few questions may reduce reliability and diagnostic accuracy rates.

To date, existing studies investigating associations between APOE ε4 genotype and depression in older adults with AD remain mixed and thus the relationship is not well understood. However, recent evidence has been accumulating to suggest that APOE, a low density protein, may be linked to vascular risk factors in late life and, in turn, may be associated with depression (Lavretsky et al., 2000). Indeed, apolipoprotein E is known to play a role in lipid metabolism, cholesterol transport, and neuronal repair (Zubenko et al., 1996), and it has been posited that the ε4 allele may be a predisposing genetic marker for ischemic cerebrovascular disease (Hoffman, Ott, & Breteler et al., 1997; McCarron, Delong, & Alberts, 1999) given its

association with hyperlipidemia (Sawada et al., 2000), atherosclerosis (Davignon, Cohn, Mabile, & Bernier, 1999), myocardial infarction (Brscic, 2000), and subcortical white matter lesion pathology (de Leeuw et al., 2004). Moreover, vascular risk factors have been closely linked with depression in late-life and it has been suggested that they may predispose or give rise to depressive symptoms ("vascular depression hypothesis;" Alexopoulos et al., 1997). Furthermore, the APOE ε4 allele appears to be less efficient than other isoforms at inducing cholesterol transport (Michikawa et al., 2000), which may have an important role in maintaining the integrity of membranes, and in synaptic plasticity. Thus, it appears that the APOE ε4 allele is associated with impaired response to cerebral damage and diminished capacity for neuronal repair (Arendt et al., 1997; Crawford et al., 2002), and that this poorer neuronal reparative capacity may be implicated in the development of cognitive decline and depression in older adults with the APOE ε4 genotype. Finally, it has been proposed that, for those carrying a copy of the allele, the destructive effect of subtle, underlying vascular risk factors may be enhanced (de Leeuw et al., 2004). Our findings were limited to those AD patients without significant cerebrovascular disease risk. However, future studies should examine a broader range of patients to determine the relative contributions of cerebrovascular disease risk to depression in AD.

Our results also demonstrated that the association between APOE genotype and depression in AD was primarily seen in women and not men. These findings are consistent with those of Müller-Thomsen (2002) who indicated that the APOE ε4 genotype may be more highly associated with depression in AD for women but not men. Our finding is also supported by a study showing an increased rate of the APOE ε4 genotype in late-onset depressed women with AD relative to men (Steffens et al., 1997) as well as a finding that family history of depression may be a risk factor for depression in AD, but only in women (Lyketsos, Tune, Pearlson, Steele, 1996). Recent research has shown that women demonstrate higher rates of vascular risk factors (i.e., hyperlipidemia) compared to men (Hippisley-Coz, Pringle, Crown, Meal, & Wynn, 2001; de Leeuw et al., 2004) and depressed women have been shown to be overly represented in diffuse neurological disease such as Alzheimer's disease (Okiishi et al., 2001). Thus, our findings suggest that it may be important to consider potential sex differences in the risk for depression for AD patients possessing the APOE ε4 allele. Indeed, sex effects have not been taken into account in many of the previous studies that have demonstrated negative findings. For example, many studies have not distinguished between men and women across APOE genotypes (Weiner et al., 1998; Cantillon et al., 1997; Harwood, Barker, Ownby, St. George-Hyslop, & Duara, 1999; Scarmeas et al., 2002; Craig et al., 2005), have not directly assessed sex differences within their samples (Levy, Cummings, Fairbanks, Sultzer, & Small, 1999; Harwood et al., 1999; Weiner et al., 1999; Scarmeas et al., 2002; Craig et al., 2005), or have not provided sex distributions for their samples (Cantillon et al., 1997). Thus, it is unclear to what extent the lack of measurement for sex differences may have contributed to a lack of association reported in previous studies.

There has also been an interest in the relationship between the effects of estrogen on mood and cognition in aging women. For example, Steffens et al. (1999) examined postmenopausal estrogen use in a population of 2, 388 nondemented older women aged 65 and older. It was found that depression and the APOE ε4 allele both independently predicted depression and that current and past estrogen users demonstrated significantly higher scores on the Modified Mini-Mental State Examination (3MSE). The effect of estrogen replacement therapy (ERT) on cognitive functioning remained after controlling for age, education, and possession of the APOE ε4 allele. When those study participants were followed longitudinally (Carlson et al., 2001), the effect remained and the oldest-old (aged 75 and older) appeared to benefit the most from lifetime ERT. Finally, in a retrospective study which focused on the effects of estrogen on depression, Morrison and Tweedy (2000) reported that estrogen appeared to improve response to antidepressant treatment in postmenopausal women.

To better understand the relationship between ERT and depression in our sample, we completed a post-hoc analysis using retrospective hormonal self-report data. We found a decreased risk of depression among women who underwent ERT (15%) versus those who did not undergo ERT (28.6%). Although the relationship was not statistically significant (possibly due to the low sample size (n = 59)), the trend that was demonstrated warrants further consideration. Overall, there is a paucity of studies that have concurrently investigated the links between estrogen, mood, and APOE genotype, and increased focus and attention in this area is greatly needed.

There are a few limitations of the current study that should be noted. Specifically, although we assessed a broad range of depressive disorders, it is difficult to ascertain the specific causes of depression within the sample. For example, several factors can contribute to depression in later life (i.e., bereavement, polypharmacy, vascular risk factors) and disentangling the potential etiologies is particularly challenging. In addition, a diagnosis of current depression was necessary for inclusion in the depressed group, and we did not assess the lifetime chronicity or time course of depression for each participant. Such information would be preferable in order to track other potential contributors or predisposing factors. Moreover, it is widely known that depression is often one of the first symptoms of AD, although the natural history of depression in AD is poorly understood (Lyketsos & Olin, 2002). Nevertheless, the results of the current study favor a rigorous diagnostic approach in assessing the impact of genetic and other risk factors on depression in AD.

At present, the effect of APOE ε4 genotype on depression in AD is equivocal and there is a need for additional studies to better elucidate this relationship. Future studies may wish to include examination of the various psychiatric assessment instruments employed for diagnosing depression in older adults given the wide-ranging reported rates of depression reported across studies. Also, close examination of the diagnostic criteria utilized in studies to diagnose participants with depression and with AD is critically needed, given the varying reports of APOE ε4 genotypic influences on depression in AD. Including sufficiently large samples of depressed individuals is crucial because of the possible subtle influence of APOE genotype on psychiatric symptomatology. Finally, in addition to our observed gender differences, future efforts should include greater emphasis on links between the APOE ε4 allele and subtle vascular risk (i.e., hypertension, hyperlipidemia, white matter lesion abnormalities) as well as hormonal factors (i.e., estrogen).

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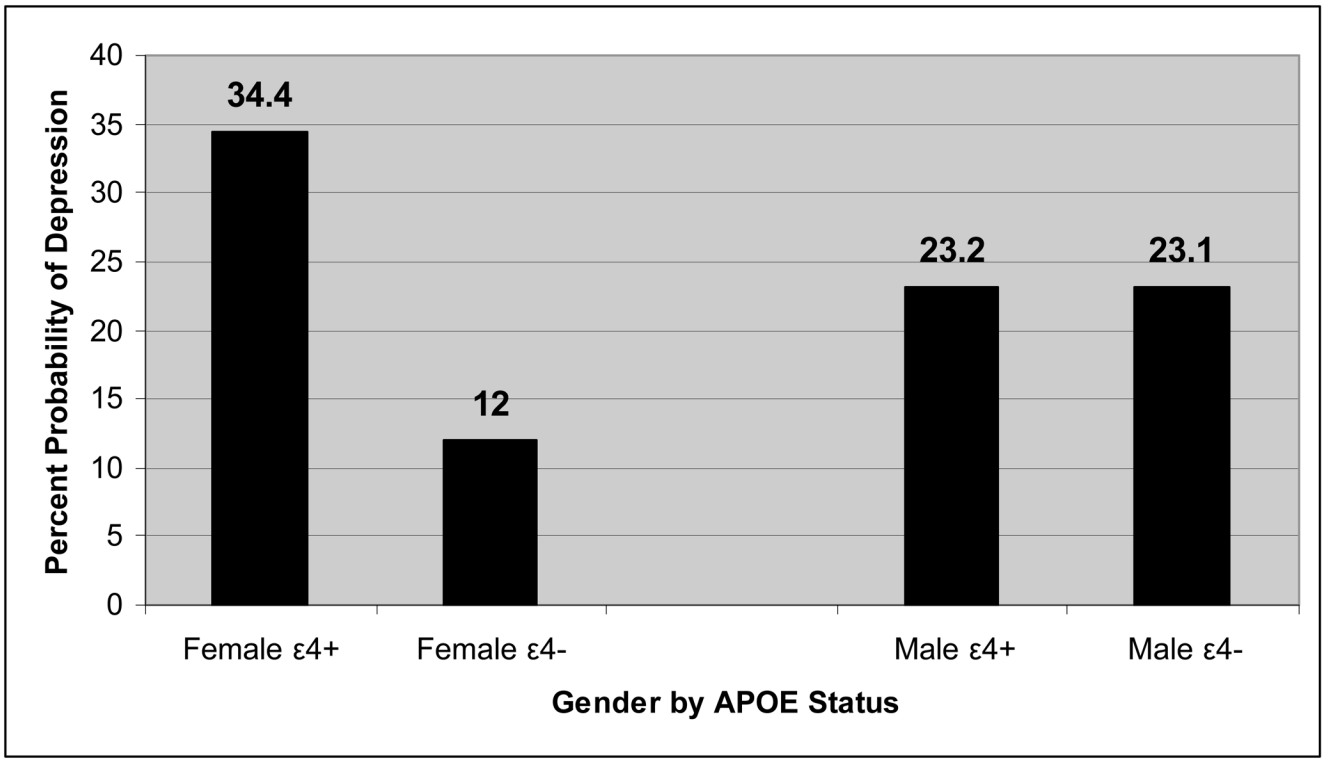

Figure 1.
Plot of Apolipoprotein-E (APOE) status X Gender interaction on probability of depression for AD sample
*Controlled for Education and Years of AD Duration

Table 1

Demographic, Cognitive, and Apolipoprotein-E (APOE) ε4 Comparisons by Depression Status and Gender

	AD Groups by Depression Status			AD Groups by Gender		
	Clinically Depressed(N=61)	**Not Depressed (N=262)**	**p-value***	**Women (N=160)**	**Men (N=163)**	**p-value**
Demographics						
Age, mean (SD)	72.1 (7.0)	72.7 (9.7)	0.657	72.9 (10.8)	72.3 (7.5)	0.586
Female, %	54.1	48.5	0.429	-	-	-
Education, mean (SD)	12.8 (4.1)	13.2 (4.1)	0.445	12.2 (3.8)	14.0 (4.2)	<0.001
Clinical Features						
Depressed, %	-	-		20.6	17.2	0.429
Years of AD, mean (SD)	4.3 (2.5)	3.7 (2.4)	0.087	3.7 (2.3)	4.0 (2.6)	0.198
DRS, mean (SD)	102.1 (25.7)	103.0 (21.1)	0.765	102.5 (22.0)	103.2 (22.2)	0.783
MMSE, mean (SD)	20.9 (5.7)	20.3 (5.4)	0.484	20.0 (5.4)	20.8 (5.6)	0.185
APOE Status						
APOE ε4 Positive, %	77.0	58.0	0.042	64.4	57.1	0.178

Table 2

Multivariate Regression: Depressed versus Non-Depressed by Apolipoprotein-E (APOE) ε4 Status

	OR (95% CI)	Coefficent*	p-value
APOE ε4 Positive	1.00 (0.44, 2.31)	0.004	0.992
Female Gender	0.46 (0.15, 1.42)	−0.787	0.176
APOE ε4 Positive x Female Gender	3.83 (1.02, 14.4)	1.342	0.047
Years of AD Duration	1.10 (1.0, 1.3)	0.095	0.088
Education (years)	0.95 (0.87, 1.03)	−0.054	0.185

* Coefficient estimate for linear model, not yet converted to odds ratios. For example, the odds of depression for a female subject who is APOE ε4 positive is exp (0.004− 0.787+1.342)=1.75. Coefficient for model intercept = −1.204.