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# Risk factors for earlier dementia onset in autopsy-confirmed Alzheimer's disease, mixed Alzheimer's disease with Lewy bodies, and pure Lewy body disease

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## Abstract

**Introduction:** Clinical Alzheimer's disease (AD) and dementia with Lewy bodies often have mixed AD and Lewy pathology, making it difficult to delineate risk factors.

**Methods:** Six risk factors for earlier dementia onset due to autopsy-confirmed AD (n = 647), mixed AD and Lewy body disease (AD+LBD) (n = 221), and LBD (n = 63) were entered into multiple linear regressions using data from the National Alzheimer's Coordinating Center.

**Results:** In AD and AD+LBD, male sex and *APOE* ε4 alleles each predicted a 2 to 3-year earlier onset, and depression predicted a 3-year earlier onset. In LBD, higher education predicted earlier onset, and depression predicted a 5.5-year earlier onset.

**Discussion:** Male sex and *APOE* ε4 alleles increase risk for earlier dementia onset in AD but not LBD. Depression increases risk for earlier dementia onset in AD, LBD, and AD+LBD, but evaluating the course, treatment, and severity is needed in future studies.

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**Keywords**

Alzheimer's disease; Lewy body disease; Risk factors; Dementia; Onset

## 1. Background

Alzheimer's disease (AD) is the most prevalent form of neurodegenerative dementia, accounting for 50-70% of cases [1], and is characterized neuropathologically by neurofibrillary tangles composed of hyperphosphorylated tau and neuritic plaques composed of both tau and amyloid β (Aβ) [2]. The reported prevalence of dementia with Lewy bodies (DLB) varies, but accounts for approximately 7.5% of all dementia cases [3]. Most cases of clinically diagnosed DLB are characterized neuropathologically by post-translationally modified alpha-synuclein that form insoluble fibrils [4] in the brain stem, limbic regions, and neocortex, and defined neuropathologically as cortical or diffuse Lewy body disease (LBD). However, many cases of clinically diagnosed DLB have both AD and LBD pathology (AD +LBD), and frequently the temporal onset of these separate pathologies remains unclear and clinical differentiation is often difficult.

Despite decades of research studying risk factors for dementia, there is still little known about risk factors for DLB. Several risk factors have been identified for developing dementia later in life, but only one study to date has evaluated a comprehensive set of risk factors for DLB and compared these to an AD cohort. Boot et al. (2013) found that when compared to an AD cohort (N=294), subjects clinically diagnosed with DLB (N = 147) were more likely to be male, younger, and more educated. In addition, those with DLB were more likely to have a history of depression and an absence of apolipoprotein (*APOE*) ε4 alleles. In contrast, many risk factors have been investigated for AD, including family history of AD [5], non-modifiable genetic factors such as *APOE* ε4 [6], modifiable life-style factors such as exercise and diet [7], and treatable medical factors such as hypertension, diabetes, and depression [8]. Despite reported differences in risk factors, there is a significant gap in research comparing risk factors between AD and DLB.

Most research examining risk factors for these neurodegenerative conditions rely on clinical diagnoses, which is not ideal for at least two reasons. First, clinical diagnoses are less accurate than histopathological examination. When comparing clinical diagnoses of dementias to histopathological examination, AD diagnoses are approximately 80% accurate [9] and accuracy for DLB is considerably lower (e.g., 53% in Alzheimer's Disease Centers) [10]. Second, mixed AD+LBD occurs with high frequency [11], making it difficult to arrive at clinical diagnoses *in vivo*. In one study, 77% of patients with autopsy-confirmed mixed AD+LBD (N = 248) were clinically diagnosed with AD only [10]. Taken together, relying exclusively on clinical diagnoses makes it difficult to isolate risk factors in these neuropathologically discrete conditions.

The vast majority of studies examining risk factors related to AD and DLB have focused on risk for development of these neurodegenerative conditions. Far fewer studies examined risk factors for earlier onset of dementia (i.e., age of dementia onset), especially in autopsy-confirmed samples. Age of onset is often related to the notion of "cognitive reserve", where

individuals may have hastened or delayed onset of cognitive impairments with similar brain pathology due to flexible factors such as education, premorbid intelligence, and occupational attainment [12]. Evaluating age of onset not only may help elucidate how various risk factors differentially impact AD versus LBD, but also offer insights into areas of intervention that may delay cognitive onset. As such, it was our aim to investigate modifiable and non-modifiable factors, such as demographics, family history, genetic, mood, and cardiovascular variables, as risk factors for earlier dementia onset in autopsy-confirmed samples of AD, mixed AD+LBD, and pure LBD.

## 2. Methods

### 2.1 Participants

Data for this study were obtained from the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) and Neuropathology Data Set (NPDS). Alzheimer's Disease Centers (ADCs) across the United States, funded by the National Institute of Aging (NIA), contribute data to NACC. Research using NACC data was approved by the University of Washington Institutional Review Board. Since 2005, NACC has collected clinical, autopsy, genetic, and demographic data on older adults and older adults with neurodegenerative conditions. NACC datasets (i.e., UDS and NPDS) were queried for individuals with clinically diagnosed dementia and an estimated age of onset after 40 years old. Data in this study were collected from 30 ADCs from 09/2005 through 08/2016.

### 2.2 Neuropathology

Three autopsy-confirmed groups were derived, and consisted of a pure AD group, a mixed AD+LBD group, and a pure LBD group. The AD group was defined as having Braak neurofibrillary tangle (NFT) stages from III-VI (i.e., limbic to neocortical involvement) in combination with moderate to frequent neuritic-type senile plaques, with Lewy bodies (LB) either absent or restricted to the brain stem. Mixed AD+LBD was defined as having AD neuropathology as described above, in addition to LB found in neocortical regions. In the pure LBD group, subjects had limbic or neocortical LB, with completely absent NFTs or NFTs confined to the transentorhinal cortex (i.e., Braak NFT stages 0-II) (see Table 1 for a reference of neuropathological criteria). However, it should be noted that reference to "limbic" Lewy-bodies may also contain amygdala-predominant LBD compared to "transitional" LBD, which neuropathologic diagnostic criteria recommend differentiating [4]. Unfortunately, NACC did not distinguish these two patterns of involvement until version 10 of the NPDS (2014), and exclusive use of data from version 10 would yield an untestable sample size. Thus, we used NACC's derived data across NPDS versions (i.e., Lewy bodies were labeled "limbic" if transitional or amygdala predominant Lewy bodies were found) in our pure LBD cohort to maximize our sample size. Of note, in the subsample of 17 cases from version 10 NPDS was used, when these 2 patterns of limbic involvement by LBD were differentiated, none had amygdala predominant Lewy bodies. Subjects were excluded if any of the following comorbid neuropathological findings were present: frontotemporal lobar degeneration and parkinsonism with tau-positive or argyophillic inclusions, Pick's disease, corticobasal degeneration, progressive supranuclear palsy, and prion disease. Additionally,

subjects with significant vascular disease or hippocampal sclerosis judged by the neuropathologist to relate to cognitive status were excluded.

### 2.3 Measures

At the time of dementia diagnosis, age of dementia onset was estimated by clinicians based on information obtained through subject and informant report, medical records, and/or observation, and defined as the age at which cognitive decline began. Modifiable and non-modifiable risk factors were obtained from NACC, primarily based on variables previously reported to be associated with AD or DLB, and examined to assess their potential influence on age of onset. These included sex, education, number of *APOE* ε4 alleles, depression, family history of dementia, and cardiovascular factors given these are well-established general risk factors for dementia. Sex, years of education (maximum of 20 years), and family history of dementia were obtained via subject or informant report at the time of the subject's first ADC visit. First-degree family history of dementia was coded in NACC as *present, absent,* or *unknown.* Within the UDS, "depressed mood" was defined as having been prescribed an anti-depressant medication, having been seen by a clinician for depressed mood, or having been diagnosed with a mood disorder (i.e., major depression, dysthymia, or bipolar disorder). "Depressed mood" was coded as *absent, present,* or *unknown* within the last 2 years of the subjects' ADC visit or more than 2 years prior to the subjects' ADC visit. In the present study, because the majority of subjects' clinic visits at the time of dementia diagnosis was more than 2 years after onset of symptoms, depression variables were combined to capture presence or absence of any history of depression. The majority of subjects underwent genetic (*APOE*) testing, and subjects were coded as non-carriers (0), heterozygous (1) carriers, or homozygous (2) carriers of *APOE* ε4 alleles. A cardiovascular risk factor index was computed based on the Cardiovascular Risk Factors, Aging, and Incidence of Dementia (CAIDE) risk score [13], and included education, body mass index, gender, systolic blood pressure, and hypercholesteremia (see Table 2).

### 2.4 Statistical Analyses

Multiple linear regression models were used to evaluate if risk factors for dementia predicted age of onset for each of the neuropathology groups (AD, AD+LBD, and LBD). Six predictors were entered simultaneously: sex (male/female), years of education (range: 0-20), cardiovascular risk score (table 2), family history of dementia (yes/no), history of depression (yes/no), and number of *APOE* ε4 alleles (0, 1, or 2). All assumptions for analyses were reviewed. Multivariate outliers were evaluated for each model by Mahalanobis distance and excluded if present. Heteroskedasticity (i.e., unequal variability of residuals) was assessed via the Koenker test. If violated, a transformed model was calculated to determine if findings remained [14]. Analyses were conducted using IBM SPSS Statistics version 24. Due to the exploratory nature of this study, $P < .05$ was used as the cutoff for significance.

## 3. Results

In total, 1,221 subjects met inclusion criteria. The largest group was the pure AD group (n = 852), followed by the AD+LBD group (n = 290), and finally the pure LBD group (n = 79). Missing data for the overall sample were as followed: cardiovascular risk factors (n = 12;

1%), family history of dementia (n = 112; 9%), *APOE* ε4 status (n = 174; 14%), and depression history (n = 16; 1%). Only one multivariate outlier was excluded. In total, this left 647 in the AD group, 221 in the AD+LBD group, and 63 in the LBD group. Sample characteristics for each neuropathological group are displayed in Table 3. Among subjects, 897 of 931 (96%) had an available informant, of which 609 were spouses (68%), 214 were children (24%), 36 were siblings or other relatives (4%), 19 were friends or close acquaintances (2%), and 6 were paid caregivers or health care providers (<1%).

Three standard multiple linear regressions were used to assess if risk factors were associated with age of onset among those with AD, AD+LBD, and LBD. Homoskedasticity testing using the Koenker test suggested a heteroskedastic distribution in the AD group ($\chi^2 = 16.82$, $P = .001$), but not in the AD+LBD ($\chi^2 = 9.68$, $P = .139$) or pure LBD ($\chi^2 = 4.42$, $P = .620$) groups. Thus, heteroskedastic-consistent Beta-coefficients were calculated [14] for the AD group, which did not suggest significant differences compared to the original model and the unadjusted model is reported below. Omnibus tests were significant in all models: AD, $F(6, 640) = 5.88$, $P < .001$; AD+LBD, $F(6, 214) = 5.13$, $P < .001$; LBD, $F(6, 56) = 2.47$, $P = .034$. Risk factors varied across groups. In AD, male sex and number of *APOE* ε4 alleles each predicted an approximately 2-year earlier onset, and depression predicted an approximately 3-year earlier onset ($P$'s < .05). Male sex, number of *APOE* ε4 alleles, and depression each predicted a 3-year earlier onset ($P$'s < .05) in the AD+LBD group. In the pure LBD group, each additional year of education was associated with earlier onset by 0.9 years, and depression predicted a 5.5-year earlier onset ($P$'s < .05). See Table 4 for predictors of earlier cognitive symptom onset among the three neuropathological groups.

## 4. Discussion

In this autopsy-confirmed sample of AD, AD+LBD, and LBD, risk factors for earlier onset of cognitive symptoms varied between groups. History of depression was associated with earlier onset in all three groups but was associated with the earliest onset in LBD. *APOE* ε4 alleles and male sex predicted earlier onset of AD and AD+LBD, but not LBD. Only in the LBD group was education associated with age of onset, and more years of education predicted earlier age of onset. Cardiovascular risk factors and family history of dementia did not predict age of onset in any group.

Male sex was associated with an approximately 2.5 year-earlier onset for AD and AD+LBD, but not LBD. This was unexpected because previous research has found male sex to be a risk factor for DLB [15] and Parkinson's disease (PD) [16]. However, this risk may be age-dependent, as incidence and age of DLB onset in men and women has been found to be similar when onset is less than 70-years-old [17]. In contrast, AD is more prevalent in women, but this may be due to life-expectancy differences or research cohort differences since studies in the U.S. have not consistently replicated this finding [18]. It remains unclear why men may experience earlier onset of AD and AD+LBD. Some have suspected hormonal differences may lead to neuroprotective effects in women [18], while others have found hippocampal atrophy is exhibited earlier in amyloid-positive normally aging older men [19]. Additionally, environmental factors such as sex differences in access to education, occupational history, and rates of exercise and smoking may influence cognitive reserve and

onset of AD [18]. Still, our findings suggest men display a 2- to 3-year earlier onset of AD but not LBD in models that account for education and cardiovascular health, warranting future study investigating potential mechanisms.

We found that each *APOE* ε4 allele predicted a 2- to 3-year earlier onset in those with AD pathology, consistent with previous findings that *APOE* ε4 carriers have earlier onset of AD [20]. In contrast, *APOE* ε4 did not appear to hasten onset in the pure LBD group, despite previous research suggesting *APOE* ε4 increases risk of dementia in autopsy-confirmed LBD [21]. In a study by Tsuang et al. (2013), *APOE* ε4 alleles led to increased risk of autopsy-confirmed AD (OR: 9.9), AD+LBD (OR: 12.6), and pure LBD (OR: 6.6) compared to controls. Although Tsuang et al. did not evaluate age of onset by *APOE* ε4 alleles, it is possible that *APOE* ε4 may increase overall risk of LBD, but not accelerate age of onset, although a mechanism for this association remains unclear. Their inclusion of NFT's within the occipital-temporal gyrus, rhinal sulcus, and entorhinal region (i.e., Braak Stage III) in their sample may have influenced findings since *APOE* ε4 has been associated with tau deposition and distribution [22]. Thus, it is possible that their findings were associated with tau versus Lewy pathology. Additionally, few homozygous *APOE* ε4 carriers in our LBD group, which is more associated with dementia risk, may have reduced power. In sum, the association between *APOE* ε4 and LBD is unclear and requires further investigation.

History of depression was associated with age of onset across all three groups, consistent with findings that depression can increase risk of dementia [23]. However, little research has been completed on depression and risk for DLB. Pathological studies have suggested neural substrates related to depression in LBD vs. AD, and a post mortem study by Piggott et al. (1999) found reductions in dopamine within the putamen of DLB and PD patients with no change in those with AD [24]. There is also evidence that serotonergic systems may be different in patients with DLB compared to AD, as well as the severity of depression reported [25]. Thus, differing neural mechanisms underlying depression may exert variable influences in the dementia process. Our findings are consistent with reports that a history of depression is a risk factor for earlier onset and may suggest a stronger association with LBD onset compared to AD and AD+LBD onset. However, it is important to note we could not differentiate temporal onset of depression with dementia and it is unknown whether depression was related to prodromal neurodegenerative disease. Additionally, the severity, course, and duration of symptoms of depression is unknown and requires further examination.

Higher levels of education have previously been associated with reduced dementia risk and delayed dementia onset [26, 27]. The current findings suggest higher education did not delay onset in AD or mixed AD+LBD, and instead, was associated with earlier LBD onset. While this appears to contrast the notion of "cognitive reserve," where individuals with higher educational attainment and/or occupational complexity can compensate for neuronal disruptions to delay dementia [28], a recent study suggests earlier trajectory of cognitive decline in some individuals with more education [29]. A 20-year population-based study in France showed that among individuals who developed dementia, isolated decline(s) on neuropsychological tests occurred several years earlier for those with higher education. Earlier cognitive changes, however, were better compensated by higher-educated

participants, subsequently delaying a dementia diagnosis. Although this may partly explain the link we observed between higher-education and earlier age LBD onset, there was no association in AD or AD+LBD. Clinical features of DLB involve cognitive fluctuations, visual hallucinations, and Parkinsonism, which may be more salient than the cognitive changes seen in AD. Higher educated patients and their families may then recognize and detect DLB symptoms earlier, potentially influencing when disease onset is identified. On the other hand, our LBD cohort contained a limited sample size of mostly high educated participants, and thus may be subject to an inflated false discovery rate. Nevertheless, Boot et. al found higher education to be more common in cases clinically diagnosed with DLB [15], indicating further investigation is needed.

The presence of various cardiovascular risk factors in midlife has been associated with increased risk of dementia [30], and this research has led various risk scores for early identification of those at increased risk for dementia. This study utilized a modified CAIDE risk score which has previously been shown to predict dementia 20 years later [31]. The present study did not find a relationship between cardiovascular risk and earlier dementia onset. This may be due to our attainment of cardiovascular variables at subjects' first visit, while the CAIDE risk score was based on presence of mid-life cardiovascular risk factors. In some cases, emergence of some cardiovascular risk factors (e.g., hypertension) in late life has actually been associated with reduced risk of dementia [32]. Furthermore, data on cardiovascular exercise was unavailable in NACC, which has shown to be protective against cognitive decline [8]. Thus, further examination of mid-life cardiovascular factors and their relation to age of onset is needed.

While family history of dementia is regarded as a risk factor for dementia, our findings suggest that 1$^{st}$-degree family history of dementia does not predict earlier onset of dementia. Studies suggest those with a family history of AD may have a three-fold increased risk of dementia compared to the general population [33], though if this risk is also associated with earlier dementia onset has not been established. Additionally, the relationship between family history of dementia and DLB is less certain. Woodruff et al. reported a higher percentage of patients with autopsy-confirmed LBD (N=18) had a family history of dementia (67%) compared to healthy controls (13%) [34] and Papapetropoulos et al. reported a family history of dementia was significantly more frequent in DLB subjects (N=25) compared to PD subjects (N=64) both with and without dementia and healthy controls [35]. However, Boot et al. did not find family history of dementia to be a risk factor for DLB [15]. In line with this research, we found family history of dementia did not predict earlier onset of LBD.

This study has several strengths, including the use of autopsy-confirmed cohorts, though there are also several limitations. First, although analysis of a subset of the data did not reveal any cases to have amygdala-predominant Lewy body inclusions, previous versions of NACC's NP dataset did not differentiate between limbic/transitional and amygdala-predominant involvement. Thus, it is possible that some individuals with subthreshold LBD may have been included, and their cognitive decline could be attributed to other unknown factors. Second, exercise, sleep apnea and other cardiovascular factors were unavailable, and their inclusion would likely influence cardiovascular risk. Third, depression was defined as

having been prescribed an anti-depressant medication, having been seen by a clinician for depressed mood, or having been diagnosed with a mood disorder (major depressive disorder, dysthymia, or bipolar disorder). NACC did not begin differentiating specific psychiatric diagnoses until UDS version 3 and we were unable to differentiate depression etiology further. Thus, results may have differed with the exclusion of bipolar disorder, although the magnitude remains unclear as bipolar disorder is a rare psychological condition. Fourth, despite the large overall autopsy-confirmed sample, a smaller LBD cohort led to a limited number of homozygous *APOE* ε4 carriers and females, and also precluded comparison of other risk factors such as traumatic brain injury, alcohol use disorder, etc. Our sample also consisted of largely well-educated non-Hispanic Caucasians, and replication in community-based samples is warranted. Fifth, our finding of increased education as a risk factor for earlier LBD onset was unexpected and contrasted the notion of cognitive reserve. Additionally, other variables related to cognitive reserve (e.g., occupational attainment and general intelligence) could not be evaluated in this study, and their inclusion may have altered results. Lastly, data were collected largely through self or informant report, which is subjective and could introduce the possibility of recall bias.

## 5. Conclusion

To our knowledge, this is the first study to compare multiple risk factors for earlier dementia onset in autopsy-confirmed AD, AD+LBD, and LBD. We found that *APOE* ε4, male sex, and depression predicted earlier onset of AD and AD+LBD, suggesting little difference in risk among these conditions. Higher education and depression predicted earlier onset of LBD. The severity, course, and treatment of depression was unknown and needs to be evaluated in future studies. We hope that future studies will examine risk factors for development, onset, and clinical progression among autopsy-confirmed cohorts, as clinical diagnoses to differentiate risk factors between AD and DLB are suboptimal.

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**Table 1.**

Neuropathological classification of Alzheimer's disease, Lewy body disease, and mixed groups

| | | Alzheimer's pathology | |
|---|---|---|---|
| | | **Braak stage 0-II** | **Braak stage III-VI** |
| **Lewy body pathology** | Neocortical | Pure LBD | Mixed AD+LBD |
| | Limbic | Pure LBD | |
| | Brainstem | | Pure AD |
| | None | | Pure AD |

NOTE: Mixed AD+LBD and pure AD also had moderate to frequent neuritic-type senile plaques.

**Table 2.**

Cardiovascular Risk Index computation using weights derived from the CAIDE risk score

| Risk Factor | Index Weighting |
|---|---|
| *Education ≥ 10 years | 0 |
| *Education 7 to 9 years | 2 |
| *Education ≤ 6 years | 3 |
| Female Sex | 0 |
| Male Sex | 1 |
| Systolic Blood Pressure < 141 | 0 |
| Systolic Blood Pressure ≥ 141 | 2 |
| Body Mass Index < 30 | 0 |
| Body Mass Index ≥ 30 | 2 |
| *No history of hypercholesterolemia | 0 |
| *Current or past hypercholesterolemia | 2 |

*Collected in the NACC database through self or informant report. The index score was computed using data available on the first ADC visit.

**Table 3.**

Sample characteristics by AD, AD+LBD, and LBD neuropathology

| | AD (N = 647) | AD+LBD (N = 221) | LBD (N = 63) | *p*-value |
|---|---|---|---|---|
| Age at Dementia Onset, M (SD) | 69.1 (10.9) | 68.2 (9.0) | 67.8 (9.9) | .381 |
| Age of Dementia Diagnosis, M (SD) | 75.3 (10.7) | 73.9 (9.2) | 73.7 (9.2) | .151 |
| Years from Onset to Death, M (SD) | 9.8 (4) | 8.9 (3.8) | 8.9 (4.4) | .009* |
| Male Sex, N (%) | 345 (53) | 137 (62) | 52 (83) | <.001** |
| Non-Hispanic Caucasian, N (%) | 588 (91) | 199 (90) | 62 (98) | .139 |
| Years of Education, M (SD) | 15.3 (3.2) | 15.4 (2.9) | 15.3 (3.2) | .933 |
| Cardiovascular Risk, M (SD) | 2.9 (1.9) | 2.95 (1.8) | 3.1 (1.8) | .843 |
| Family History of Dementia, N (%) | 389 (60) | 141 (66) | 39 (62) | .756 |
| *APOE* ε4 | | | | .003* |
| 0 *APOE* ε4 Alleles, N (%) | 279 (43) | 78 (35) | 39 (62) | |
| 1 *APOE* ε4 Alleles, N (%) | 287 (44) | 111 (50) | 22 (35) | |
| 2 *APOE* ε4 Alleles, N (%) | 81 (13) | 32 (15) | 2 (3) | |
| History of Depression, N (%) | 294 (45) | 125 (57) | 32 (51) | .016* |

*Note:* One-way analysis of variance and chi-square analyses were used to compare groups.

* = $p < .05$

** = $p < .001$

**Table 4.**

Predictors for age of cognitive symptom onset in dementia due to AD, AD+LBD, and LBD

| | AD (N=647) | | | | AD+LBD (N=221) | | | | LBD (N=63) | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Risk Factor** | **B** | **SE** | ***t*** | ***p*** | **B** | **SE** | ***t*** | ***p*** | **B** | **SE** | ***t*** | ***p*** |
| Male Sex | −2.19 | 0.91 | −2.41 | .016 | −2.86 | 1.35 | −2.13 | .035 | −0.51 | 3.34 | −0.15 | .880 |
| Years of Education | −0.01 | 0.14 | −0.05 | .963 | −0.17 | 0.21 | −0.81 | .417 | −0.92 | 0.41 | −2.25 | .028 |
| Cardiovascular Risk | −0.09 | 0.23 | −0.37 | .711 | 0.61 | 0.34 | 1.80 | .073 | −0.93 | 0.72 | −1.29 | .203 |
| Family History of Dementia | 0.91 | 0.87 | 1.04 | .297 | −1.20 | 1.23 | −0.98 | .329 | −3.94 | 2.61 | −1.51 | .137 |
| No. of *APOE* ε4 Alleles | −2.07 | 0.63 | −3.31 | .001 | −2.53 | 0.88 | −2.88 | .004 | −1.83 | 2.23 | −0.81 | .421 |
| History of Depression | −3.38 | 0.85 | −4.00 | <.001 | −3.13 | 1.18 | −2.66 | .008 | −5.59 | 2.49 | −2.25 | .029 |

*Note:* B = unstandardized beta; SE = standard error; *t* = t-statistic; *p* = *p*-value