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## APOE $\epsilon 4/\epsilon 4$ is associated with Aberrant Motor Behaviour through both Lewy Body and Cerebral Amyloid Angiopathy pathology in High Alzheimer's Disease pathological load

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### Abstract

**Background:** Aberrant Motor Behaviour (AMB) is a neuropsychiatric symptom (NPS) prevalent in Alzheimer's Disease (AD), known to cause great distress to both patients and caregivers. APOE4 is the most important genetic predictor of AD, and it has been associated with high NPS prevalence.

**Objective:** To investigate the neuropathological substrates and risk factors associated with AMB in AD patients.

**Methods:** Cases with Braak stage I-I and CERAD 0-1 were classified as Low AD (LAD), while Braak stage III-IV and CERAD 2 were grouped as Intermediate AD (IAD). Cases with Braak stage V-VI and CERAD 3 were classified as High AD (HAD) in accordance with NIA-Reagan criteria. All cases were stratified by APOE genotype, yielding No  $\epsilon 4$ ,  $\epsilon 4$  and  $\epsilon 4/\epsilon 4$  groups depending on  $\epsilon 4$  copy number within APOE. Presence of AMB was assessed using NPI-Q.

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#### CONFLICT OF INTEREST

The authors declare no conflict of interest.

**Results & Conclusion:** AMB increased in parallel with CERAD and Braak & Braak scores. Hypercholesterolemia, but no other Cardiovascular Risk Factors, was associated with AMB in HAD. AMB prevalence in HAD was significantly increased in the presence of two APOE  $\epsilon 4$  alleles as compared to No  $\epsilon 4$  &  $\epsilon 4$ . The relationship between homozygous APOE4 and AMB was strongly associated with the presence of both LB and CAA pathologies in both sexes.

### Keywords

Alzheimer's Disease; Neuropsychiatric symptoms; Aberrant Motor Behaviour; neuropathology; APOE gene; Lewy Bodies; Cerebral Amyloid Angiopathy

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## INTRODUCTION

Aberrant Motor Behaviour (AMB) is characterized by engagement in repetitive movements, inability to keep still and irregular pacing [1] among others. As a symptom, AMB has been strongly associated with Alzheimer's Disease (AD) [2-3], dementia and its several subtypes [4]. AMB is also one of the twelve neuropsychiatric symptoms (NPS) assessed through the Neuropsychiatric Inventory questionnaire (NPI) [2]. As a symptom, several studies report higher AMB prevalence scores in clinically diagnosed severe AD [3,5], with an overall 24.3% [6] to 32% prevalence [7]. AMB has also been associated with medium to high levels of caregiver burden and patient distress [8]. The  $\epsilon 4$  allele of the Apolipoprotein E (APOE) gene is the most important genetic predictor of late onset Alzheimer's Disease [9]. APOE4 has been associated with several neuropathological and clinical features of AD such as A $\beta$  plaque formation, disruption of synaptic plasticity [10-11] and accelerated dementia in a dose dependent manner [12]. In addition, APOE4 genotype has been repeatedly associated with a higher prevalence of all NPS [13]. Focused studies on depression [14], psychosis and its subtypes in severe AD have also reported an association with APOE4 [15]. In the aforementioned study, APOE4 effect on psychosis was found to be mediated by the presence of comorbid Lewy Body pathology (LB) [15].

Despite its prevalence and distressing effects on AD patients, the underlying mechanisms responsible for AMB are poorly understood. The goal of this study is to investigate the role of AD load and comorbid neuropathological substrates such as LB and Cerebrovascular Pathology play in the development of AMB. Furthermore, we seek to investigate the relationship between AMB prevalence and genetic and cardiovascular risk factors.

## MATERIALS AND METHODS

### Data and subject criteria

Data was obtained from the National Alzheimer's Coordinating Centre (NACC) dataset, which contains clinical and neuropathological data from Alzheimer's Disease Centres in the United States funded by the National Institute of Aging (NIA). The Uniform Data Set (UDS), the Neuropathological Data Set (NP), as well as the Research Data Dictionary-Genetic Data set (RDD-Gen) were used throughout the study. Demographical and clinical data, including gender and Cardiovascular Risk Factors such as Hypertension, Hypercholesterolemia, Diabetes and Smoking History were obtained from the UDS. AMB

presence was assessed using the Neuropsychiatric Inventory, Quick version (NPI-Q), evaluating the presence of motor disturbance within the month prior to a clinical visit. Criteria for motor disturbance within NPI-Q comprises, yet is not limited to, engaging in irregular pacing, repetitive set of movements and overall inability to keep still.

The NP was used to evaluate AD severity using neuropathological criteria. CERAD scores and Braak & Braak stage were used to assess density of neuritic plaques and neurofibrillary pathology respectively. NP was also used to gauge the presence of comorbid Lewy Body pathology (LB), as determined by positive immunohistochemical staining for alpha-synuclein at any cerebral site. Further LB quantification was not used. Cerebrovascular disease was assessed through the presence of Ischemic, Haemorrhagic and overall Vascular Pathology (IHVP), Cerebral amyloid angiopathy (CAA - including mild, moderate and severe CAA) and Subcortical arteriosclerotic leukocephalopathy (SAL).

The RDD- Gen was used to confirm patient's genetic background. The number of  $\epsilon 4$  alleles within APOE gene was used to classify cases according to their APOE4 genotype.

Cases with other primary etiological diagnoses such as Traumatic Brain Injury (TBI), CNS neoplasm, Down Syndrome, Huntington's Disease, Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), Prion Disease and Frontotemporal Dementia with or without ALS were excluded. Cases with Braak & Braak stage I & II and CERAD 1 and 0 were classified as Low AD pathological load (LAD), while Braak stage III & IV and CERAD 2 cases were classified as Intermediate AD pathological load (IAD), and cases with Braak stage V & VI and CERAD 3 were classified as High AD load (HAD), in accordance with NIA-Reagan criteria [16]. Cases with incongruent CERAD and Braak & Braak scores were excluded. Regarding APOE  $\epsilon 4$  status, cases were classified as No  $\epsilon 4$ , presence of one ( $\epsilon 4$ ) or two copies ( $\epsilon 4/\epsilon 4$ ) of the  $\epsilon 4$  allele; cases with unassessed APOE4 genotype were also excluded.

## Statistical analysis

Statistical analysis was performed using SPSS 23.0 software. Unadjusted logistic regression models were used to assess the relationship between AD pathological loads, gender, APOE4 genotype, preliminary associations, comorbid neuropathological substrates and AMB. Logistic regression results were reported as odds ratio (OR) with associated 95% confidence intervals (CI), as well as p-value. One-way ANOVA was used for direct comparisons between continuous data such as preliminary neuropathological associations coupled with risk estimate. Results were reported as p value, followed by OR with associated 95% CI. All statistical analyses were conducted using a  $\alpha = 0.05$  significance.

## RESULTS

### Subject demographics

We assessed AMB prevalence in an initial sample of 2959 cases in the NACC NP dataset. Cases were then classified using CERAD and Braak & Braak scores as described [16], yielding 831 LAD, 584 IAD and 1544 HAD cases. Because of their scarcity of  $\epsilon 4/\epsilon 4$  subjects, the LAD and IAD subsets were grouped into a Low to Intermediate AD group

(LIAD). After excluding those with unassessed APOE4 genotype, we identified 1218 LIAD and 1333 HAD cases. Further information regarding the demographic and clinical characteristics of LIAD and HAD groups can be found in Table 1.

### **Aberrant Motor Behaviour across CERAD, Braak & Braak scores and overall AD load**

First we assessed the prevalence of AMB in relation to AD pathology load, separately for plaques and neurofibrillary pathology, and then jointly. AMB prevalence significantly increased with CERAD scores ( $p=0.001$ , Figure 1a). CERAD 3 and CERAD 2 cases were significantly more likely to report present AMB compared to CERAD 0 (OR=3.928, 95% CI 2.897-5.326,  $p=0.001$ ; OR=2.433, 95% CI 1.724-3.433,  $p=0.01$  respectively). AMB prevalence increased along Braak & Braak stages as well ( $p=0.001$ , Figure 1.b), with Braak VI being significantly more likely to report AMB than Braak 0 (OR=2.268, 95% CI 1.349-3.813,  $p=0.002$ ). Interestingly, Braak II was significantly less likely to report AMB than Braak 0 (OR=0.520, 95% CI 0.282-0.958,  $p=0.036$ ). As seen in Figure 1.b, those 19 Braak 0 cases reported present AMB in an off-trend fashion, with their primary diagnosis being Lewy Body Disease (26.3%) and Cognitive impairment with unknown cause (26.3%).

AMB significantly increased across AD load ( $p=0.001$ , Figure 2), with HAD being significantly higher than LAD (OR=3.473, 95% CI 2.748-4.386,  $p=0.001$ ). AMB differences between IAD and LAD were also significant (OR=2.152, 95% CI 1.621-2.858,  $p=0.001$ ). Throughout AD load, gender did not influence AMB prevalence, as females were not more likely to report AMB compared to males (OR=0.878, 95% CI 0.742-1.039,  $p=0.129$ ).

### **APOE4 genotype is associated with AMB in HAD but not in LIAD load**

APOE4 genotype did not significantly influence AMB within LIAD ( $p=0.120$ , Table 3). Compared to No  $\epsilon 4$ ,  $\epsilon 4/\epsilon 4$  cases were not significantly more likely to report AMB in LIAD (OR=1.356, 95% CI 0.583-3.153,  $p=0.480$ ). Only 7 cases homozygous for APOE  $\epsilon 4$  genotype reported present AMB in LIAD, and thus we did not perform any further analysis in the LIAD group.

In HAD, APOE4 genotype did influence AMB prevalence ( $p=0.001$ , Table 3). Compared to No  $\epsilon 4$  only,  $\epsilon 4/\epsilon 4$  cases were significantly more likely to report AMB in HAD (OR=2.124, 95% CI 1.504-2.998,  $p=0.001$ , Table 3).  $\epsilon 4$  cases were also more likely to report present AMB compared to No  $\epsilon 4$  (OR=1.377, 95% CI 1.065-1.781,  $p=0.015$ ).

### **APOE $\epsilon 4/\epsilon 4$ is associated with AMB in HAD cases**

We then performed a regression analysis of the relationship between the presence of two copies of  $\epsilon 4$  in APOE4 and AMB prevalence in HAD.  $\epsilon 4/\epsilon 4$  cases were more likely to report AMB when analysed against one  $\epsilon 4$  copy only (OR=1.542, 95% CI 1.111-2.140,  $p=0.010$ , Table 3) and No  $\epsilon 4$  &  $\epsilon 4$  (OR=1.769, 95% CI 1.297-2.411,  $p=0.001$ ; Figure 3, 1.a). Given these results, the impact of APOE  $\epsilon 4$  allele on AMB prevalence was further assessed by grouping HAD cases into No  $\epsilon 4$  &  $\epsilon 4$  and  $\epsilon 4$  homozygous ( $\epsilon 4/\epsilon 4$ ) groups.  $\epsilon 4/\epsilon 4$  was more likely to report present AMB in both females (OR=1.923, 95% CI 1.175-3.149,  $p=0.009$ ; Table 4, Figure 3, 1.b) and males (OR=1.653, 95% CI 1.108-2.465,  $p=0.014$ ; Table 4, Figure 3, 1.c) compared to No  $\epsilon 4$  &  $\epsilon 4$  in HAD.

## **Hypercholesterolemia is the only vascular risk factor or lesion directly associated with AMB in HAD**

Prevalence of vascular lesions or risk factors in cases with AMB was then investigated. No direct significant associations were found between AMB and IHVP ( $p=0.603$ ,  $OR=1.285$ , 95% CI 0.499-3.307), CAA ( $p=0.065$ ,  $OR=1.317$ , 95% CI 0.982-1.765) and SAL ( $p=0.733$ ,  $OR=1.059$ , 95% CI 0.761-1.474) in HAD. Hypercholesterolemia was the only Cardiovascular Risk Factor significantly associated with AMB in HAD ( $p=0.035$ ,  $OR=1.279$ , 95% CI 1.017-1.607). AMB prevalence did not significantly differ in cases with Hypertension ( $p=0.506$ ,  $OR=0.927$ , 95% CI 0.741-1.159), Diabetes ( $p=0.968$ ,  $OR=1.007$ , 95% CI 0.704-1.442) or past smoking history ( $p=0.618$ ,  $OR=1.021$ , 95% CI 0.942-1.106) in HAD.

### ***In HAD, APOE $\epsilon 4/\epsilon 4$ is associated with AMB in cases with LB pathology in both sexes***

Lewy Body pathology was not directly associated with higher AMB prevalence in HAD ( $p=0.091$ ,  $OR=1.222$ , 95% CI 0.969-1.541). However, LB pathology was significantly associated with APOE  $\epsilon 4$  allele's copy number in HAD ( $p=0.006$ ), with homozygous APOE4 being significantly more likely to report present LB ( $OR=1.704$ , 95% CI 1.220-2.378,  $p=0.002$ ). Therefore, APOE4 effect on AMB was re-assessed upon stratification by LB. In HAD cases with comorbid LB, the presence of  $\epsilon 4/\epsilon 4$  in APOE significantly influenced AMB prevalence when analysed against No  $\epsilon 4$  &  $\epsilon 4$  ( $OR=2.390$ , 95% CI 1.535-3.722,  $p=0.001$ ; Table 4, Figure 3, 2.a). This association was maintained when females ( $OR=2.870$ , 95% CI 1.412-5.834,  $p=0.004$ ; Figure 3, 2.b) and males ( $OR=2.136$ , 95% CI 1.208-3.775,  $p=0.009$ ; Figure 3, 2.c) were analysed separately. In the absence of LB, AMB prevalence differences between  $\epsilon 4/\epsilon 4$  and No  $\epsilon 4$  &  $\epsilon 4$  were not significant ( $OR=1.269$ , 95% CI 0.810-1.987,  $p=0.298$ ; Table 4, Figure 3, 3.a). The association remained non-significant in both females ( $OR=1.405$ , 95% CI 0.692-2.852,  $p=0.347$ ; Figure 3, 3.b) and males ( $OR=1.225$ , 95% CI 0.683-2.197,  $p=0.497$ ; Figure 3, 3.c).

### ***In HAD, APOE $\epsilon 4/\epsilon 4$ is associated with AMB in cases with CAA in both sexes***

APOE4 genotype was not significantly associated with either IHVP or SAL in HAD ( $p=0.113$  and  $p=0.555$  respectively). In contrast,  $\epsilon 4$  copy number in APOE was significantly associated with CAA in HAD ( $p=0.001$ ), with homozygous APOE4 being significantly more likely to report CAA ( $OR=4.212$ , 95% CI 2.556-6.940,  $p=0.001$ ). The association between APOE4 and AMB was then re-assessed upon stratification by CAA. In the presence of comorbid CAA,  $\epsilon 4/\epsilon 4$  in APOE significantly influenced AMB prevalence when analysed against No  $\epsilon 4$  &  $\epsilon 4$  ( $OR=1.826$ , 95% CI 1.306-2.552,  $p=0.001$ ; Table 4, Figure 3, 4.a). This association was maintained in both females ( $OR=1.835$ , 95% CI 1.075-3.131,  $p=0.026$ ; Figure 3, 4.b) and males ( $OR=1.809$ , 95% CI 1.176-2.781,  $p=0.007$ ; Figure 3, 4.c).

In the absence of CAA, we found no significant differences in AMB prevalence based on APOE4 genotype ( $OR=0.811$ , 95% CI 0.417-3.052,  $p=0.811$ ; Table 4, Figure 3, 5a). This relationship remained non-significant in both females ( $OR=3.300$ , 95% CI 0.633-17.211,  $p=0.157$ ; Figure 3, 5.b) and males ( $OR=0.585$ , 95% CI 0.155-2.212,  $p=0.430$ ; Figure 3, 5.c).

**In HAD, APOE  $\epsilon 4/\epsilon 4$  is associated with AMB in cases with concurrent CAA and LB only**

Given our previous results on the relationship between APOE4 and both LB and CAA, the association between APOE4 and AMB was re-assessed upon double stratification by CAA and LB. In cases with presence of both LB and CAA, AMB prevalence in  $\epsilon 4/\epsilon 4$  was significantly greater than in No  $\epsilon 4$  &  $\epsilon 4$  (OR=2.681, 95% CI 1.663-4.322,  $p=0.001$ ; Table 5, Figure 4.a). We found no significant differences in AMB prevalence between  $\epsilon 4/\epsilon 4$  and No  $\epsilon 4$  &  $\epsilon 4$  in HAD cases with comorbid LB but absent CAA (OR=0.800, 95% CI 0.147-4.368,  $p=0.797$ ; Figure 4.b). The same trend was found in cases with absent LB but present CAA (OR=1.226, 95% CI 0.754-1.993,  $p=0.412$ ; Figure 4.c), as well as cases with both LB and CAA absent (OR=1.366, 95% CI 0.399-4.670,  $p=0.619$ ; Figure 4.d).

**DISCUSSION**

We found Aberrant Motor Behaviour prevalence to significantly increase along with AD pathological load. These results are consistent with others reporting an association between AMB and neurofibrillary pathology [17], although that study focused on AMB with comorbid agitation. Neurofibrillary tangle burden has also been linked to other NPS such as apathy [18] and psychosis [19]. We found SAL not significantly associated with either AMB or APOE genotype, unlike the findings of a study focused on psychosis [20]. However, there is mixed evidence regarding the relationships between specific NPS and white matter rarefaction in AD [21,22]. In High AD, the  $\epsilon 4$  allele of the APOE gene significantly influenced AMB prevalence in a strong recessive pattern. The literature offers mixed evidence regarding *APOE4*'s role in NPS development, with several studies reporting a non-significant [23], mixed [16] and a significant relationship between them [17]. This discrepancy could be explained by the reliance on clinical AD characterization [16,23], whereas our study used neuropathological post-mortem analysis. Interestingly, the relationship between NPS and APOE has mostly been assessed in APOE  $\epsilon 4$  carriers [17]. However, we found the association between homozygous APOE4 and AMB to be significant when analysed against cases with no copies of  $\epsilon 4$ , as well as cases with one copy of  $\epsilon 4$ , and both no copies and one copy together. These results agree with others reporting a specific APOE4 recessive effect in delusions [24] and anxiety prevalence [25] in AD.

We found Lewy Body pathology significantly associated with high AMB prevalence in homozygous APOE4 cases, thus agreeing with others on the importance of comorbid LB in the association between APOE4 genotype and NPS prevalence [26]. However, LB development has been associated with multiple genetic variants [27], and so the association between APOE4 and AMB might not be entirely mediated by LB. This observation is supported by our own findings on CAA, which was found to be significantly associated with a homozygous APOE4 effect on AMB. Although APOE4 has been extensively associated with CAA in AD [28,29], the relationship between CAA and NPS is not understood. Up to date, CAA has only been associated with psychosis in AD [30], as well as being reported in a clinical case with a patient presenting psychosis and depression [31]. To our knowledge, our study is the first one reporting Cerebral Amyloid Angiopathy presence as an additional pathological feature possibly mediating the association between APOE4 genotype and any NPS development.



Most importantly, our results suggest that the proven association between APOE4 and NPS is possibly influenced by several pathological substrates. A strong association between APOE4 homozygosity and AMB prevalence was only reported in the presence of both LB and CAA. If either of those pathological substrates was absent, differences in AMB prevalence became non-significant. High CAA prevalence has been previously associated with Lewy Body Disease [32] and Lewy Body Variant of AD [33]; however, no studies have focused on the functional consequences of CAA and LB comorbidity. To our knowledge, our study is the first one reporting comorbid LB and CAA as a pathological substrate possibly mediating the association between APOE4 homozygosity and any AD-related clinical outcome.

However, there are limitations to our study. The use of NIA-Reagan criteria to characterize High AD load could also be considered a limitation, for we excluded cases with discordant CERAD and Braak scores. The use of NPI-Q is also limiting in that it only considers a standardized recording of AMB within the last clinical visit, and thus data on AMB course was not reported. Additionally, presence of AMB was dependant on caregiver input, leaving room for possible confounds. It should also be noted that the NACC database is a voluntary sample set, and thus it might not be representative of the entire population suffering from AD. In summary, we demonstrate that Aberrant Motor Behaviour prevalence significantly increases with AD load, and that APOE4 genotype influenced AMB in a recessive pattern. This association was only found in the presence of concurrent LB and CAA pathology in both sexes, supporting the existence of multiple pathological substrates possibly mediating the association between APOE4 genotype and AMB prevalence. Further research is needed to clarify whether comorbid CAA and LB pathology influence other clinical manifestations of the disease.

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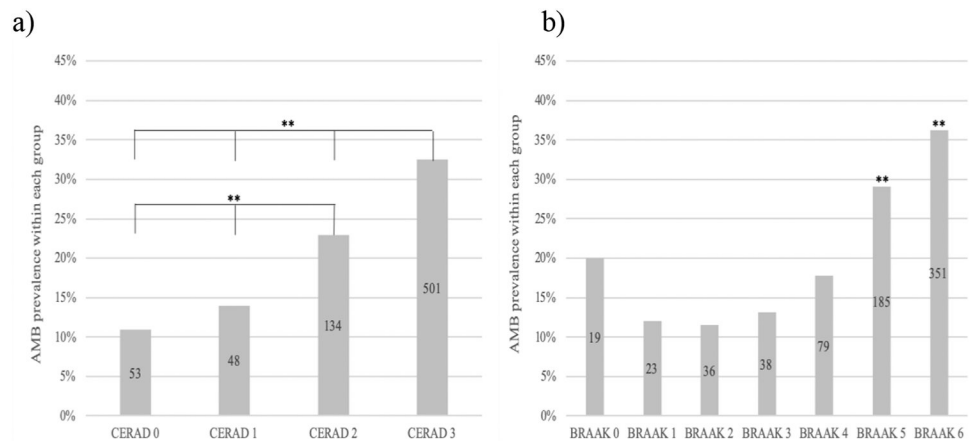
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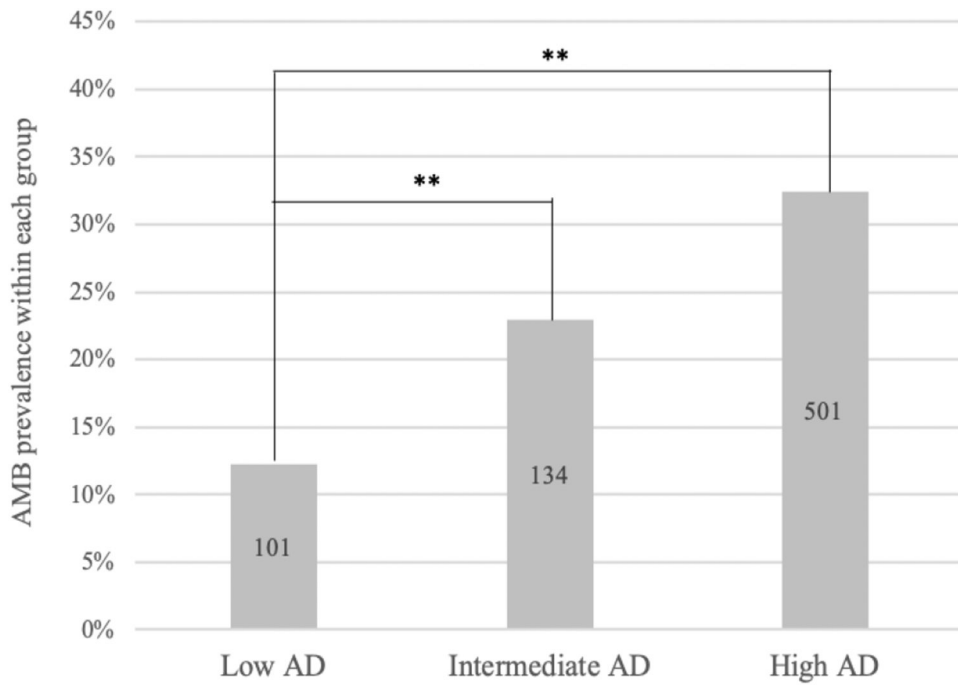
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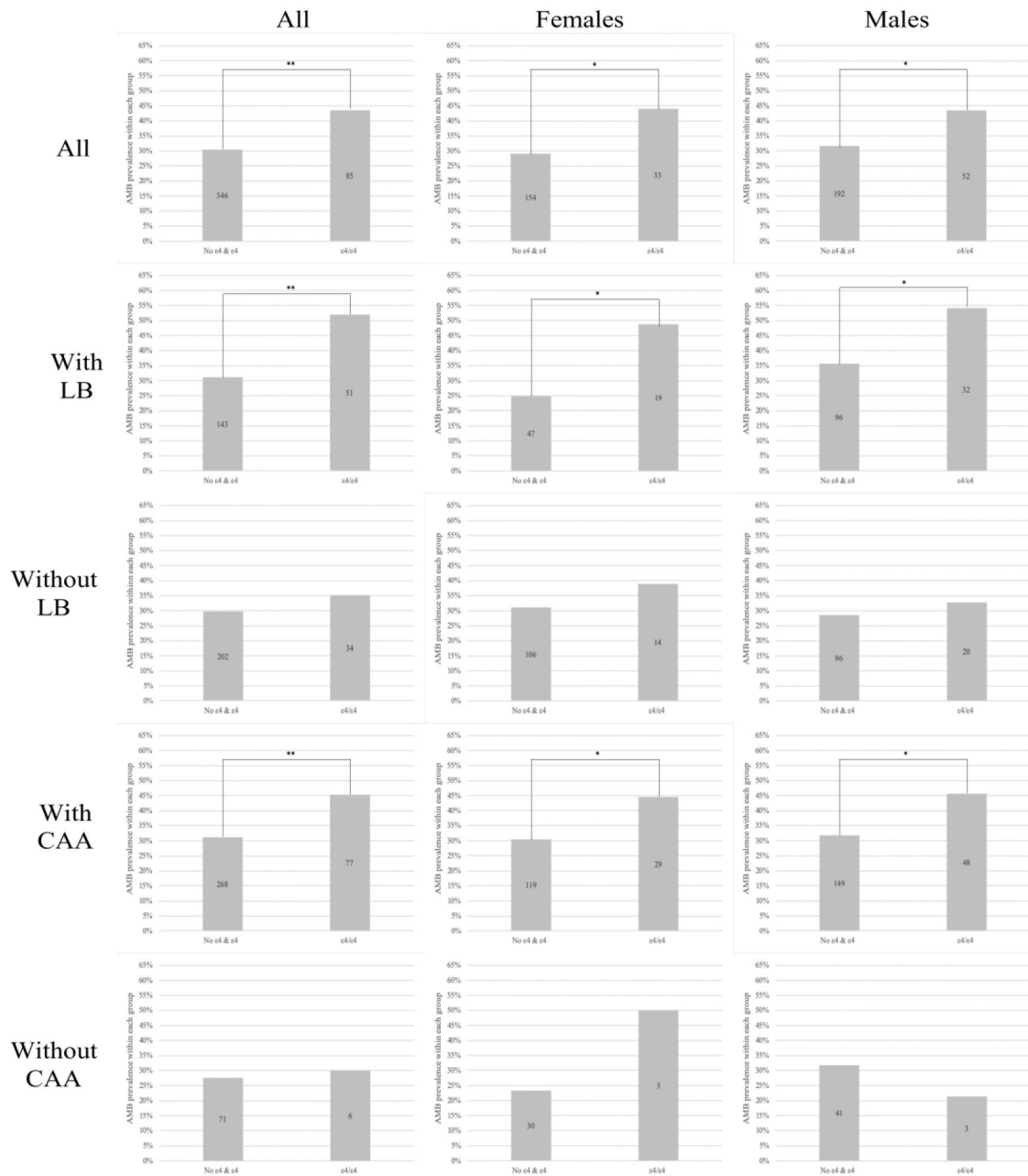
**FIGURE 1. AMB prevalence increases across neuropathological substrates**

Each column represents % of cases with present AMB in each pathological substrate group. Logistic regression was used to assess AMB prevalence differences between groups. Number of cases within group reflected in each bar. \*\* refers to  $p=0.001$ , \* refers to  $p < 0.050$  significance. AMB prevalence increases across a) CERAD scores and b) Braak & Braak stages (except Braak 0).



**FIGURE 2. AMB prevalence increases significantly across AD pathological load**

Each column represents percent of cases with present AMB in each AD load group. AMB prevalence differences were assessed with an unadjusted logistic regression model using LAD as an indicator. Number of cases within group reflected in each bar. \*\* refers to  $p=0.001$  significance.



**FIGURE 3. APOE  $\epsilon 4/\epsilon 4$  significantly increases AMB prevalence in the presence of individual neuropathological substrates in both genders in HAD**

Each column represents percent of cases with present AMB according to its APOE4 genotype-HAD group. AMB prevalence differences were assessed with an unadjusted logistic regression model using No  $\epsilon 4$  &  $\epsilon 4$  as an indicator. Number of cases within group reflected in each bar. First row represents all HAD cases, 2<sup>nd</sup> row represents HAD cases with comorbid LB, 3<sup>rd</sup> row represents HAD cases with absent LB, 4<sup>th</sup> row represents HAD cases with comorbid CAA and 5<sup>th</sup> row represents HAD cases with absent CAA. Column A represents both females and males, column B represents females only and column C represents males only. Each individual graph is labeled as *Figure 5 number.letter*, with

number referring to row and letter referring to column. \*\* refers to  $p=0.001$ , \* refers to  $p < 0.050$  significance.

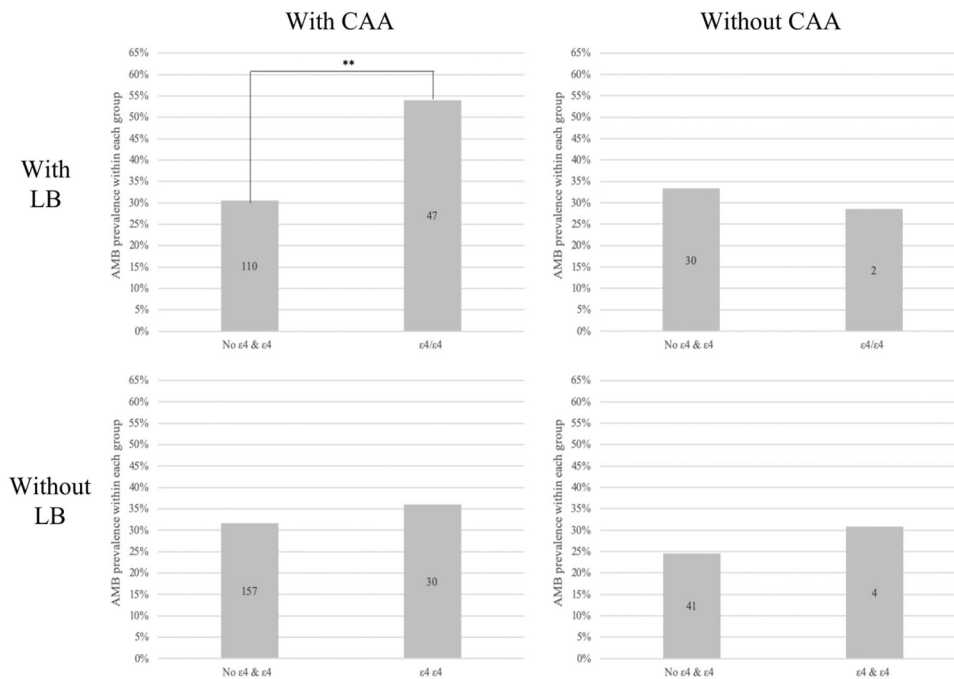
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**FIGURE 4. APOE  $\epsilon 4/\epsilon 4$  is associated with higher AMB prevalence only in cases with comorbid LB and CAA pathology in HAD**

Each column represents percent of cases with present AMB according to its APOE4 genotype-HAD group. AMB prevalence differences were assessed with an unadjusted logistic regression model using No  $\epsilon 4$  &  $\epsilon 4$  as an indicator. Number of cases within group reflected within each bar. a) The presence of two copies of  $\epsilon 4$  within APOE is significantly associated with AMB prevalence in HAD cases with comorbid LB and CAA (top, left). The presence of two copies of APOE  $\epsilon 4$  does is not significantly associated with higher AMB prevalence in HAD cases with b) present LB but absent CAA (top, right), c) absent LB but present CAA (bottom, left) and d) absent LB and CAA pathology (bottom, right). \*\* refers to  $p=0.001$  significance.

**TABLE 1**

## Demographic and Clinical characteristics

|                            | AD pathological load       |                           |
|----------------------------|----------------------------|---------------------------|
|                            | LIAD<br>N = 1218<br>N/Mean | HAD<br>N = 1333<br>N/Mean |
| Sex                        |                            |                           |
| Male                       | 648                        | 727                       |
| Female                     | 570                        | 606                       |
| Age at last clinical visit | 83.45                      | 78.38                     |
| Age at death               | 84.57                      | 79.86                     |
| Years of education         | 15.73                      | 15.78                     |
| APOE4 status               |                            |                           |
| No e4                      | 858                        | 506                       |
| e4                         | 323                        | 632                       |
| e4/e4                      | 37                         | 195                       |

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**TABLE 2**

Regression analysis of the relationship between AMB prevalence and AD neuropathological load

| Predictors          | Odds Ratio<br>(95% CI) | P value |
|---------------------|------------------------|---------|
| CERAD 0 (indicator) |                        |         |
| CERAD 1             | 1.325<br>(0.873-2.011) | 0.187   |
| CERAD 2             | 2.433<br>(1.724-3.433) | 0.001   |
| CERAD 3             | 3.928<br>(2.897-5.326) | 0.001   |
| BRAAK 0 (indicator) |                        |         |
| BRAAK 1             | 0.548<br>(0.282-1.065) | 0.076   |
| BRAAK 2             | 0.520<br>(0.282-0.958) | 0.036   |
| BRAAK 3             | 0.606<br>(0.330-1.112) | 0.106   |
| BRAAK 4             | 0.868<br>(0.497-1.518) | 0.620   |
| BRAAK 5             | 1.644<br>(0.967-2.797) | 0.066   |
| BRAAK 6             | 2.268<br>(1.349-3.813) | 0.002   |
| LAD (indicator)     |                        |         |
| IAD                 | 2.152<br>(1.621-2.858) | 0.001   |
| HAD                 | 3.472<br>(2.748-4.386) | 0.001   |

Table representing the relationship between AD pathological load, separately and jointly, and AMB prevalence. Predictors referred to presence of neuritic plaques (CERAD score), neurofibrillary pathology (Braak & Braak score) or joint AD pathological load (LAD-HAD). Numerical values within each column represent Odds Ratio (OR) with associated 95% Confidence Interval (95% CI) and p value. The relationship between AD neuropathological load and AMB was assessed in an unadjusted logistic regression model.

**TABLE 3**

Regression analysis of the relationship between APOE4 genotype and presence of AMB in LIAD and High AD load

| Predictors                                 | Odds Ratio<br>(95% CI) | P value |
|--|------------------------|---------|
| <b>LIAD</b>                                |                        | 0.120   |
| No $\epsilon 4$ (indicator)                |                        |         |
| $\epsilon 4$                               | 1.408<br>(1.008-1.966) | 0.045   |
| $\epsilon 4/\epsilon 4$                    | 1.356<br>(0.583-3.153) | 0.480   |
| <b>HAD</b>                                 |                        |         |
| No $\epsilon 4$ (indicator)                |                        | 0.001   |
| $\epsilon 4$                               | 1.377<br>(1.065-1.781) | 0.015   |
| $\epsilon 4/\epsilon 4$                    | 2.124<br>(1.504-2.998) | 0.001   |
| $\epsilon 4$ only (indicator)              |                        |         |
| $\epsilon 4/\epsilon 4$                    | 1.542<br>(1.111-2.140) | 0.010   |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 1.769<br>(1.297-2.411) | 0.001   |

Table representing the relationship between APOE4 genotype and AMB prevalence in different AD pathological loads. Predictors referred to the presence of one ( $\epsilon 4$ ) or two ( $\epsilon 4/\epsilon 4$ ) copies of the  $\epsilon 4$  allele of the APOE gene in cases with Low to Intermediate AD load (LIAD) or High AD load (HAD). Numerical values within each column represent Odds Ratio (OR) with associated 95% Confidence Interval (95% CI) and p value. The relationship between APOE4 genotype and AMB prevalence was assessed in an unadjusted logistic regression model.

TABLE 4

*Regression analysis of the relationship between APOE  $\epsilon 4/\epsilon 4$  genotype and presence of AMB with comorbid neuropathological substrates in HAD*

| Predictors                                 | Odds Ratio<br>(95% CI) | P value |
|--|------------------------|---------|
| <b>HAD females</b>                         |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 1.923<br>(1.175-3.149) | 0.009   |
| <b>HAD males</b>                           |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 1.653<br>(1.108-2.465) | 0.014   |
| <b>HAD with LB</b>                         |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 2.390<br>(1.535-3.722) | 0.001   |
| <b>HAD with LB, females</b>                |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 2.870<br>(1.412-5.834) | 0.004   |
| <b>HAD with LB, males</b>                  |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 2.136<br>(1.208-3.775) | 0.009   |
| <b>HAD without LB</b>                      |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 1.269<br>(0.810-1.987) | 0.298   |
| <b>HAD without LB, females</b>             |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 1.405<br>(0.692-2.852) | 0.347   |
| <b>HAD without LB, males</b>               |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 1.225<br>(0.683-2.197) | 0.497   |
| <b>HAD with CAA</b>                        |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 1.826<br>(1.306-2.552) | 0.001   |
| <b>HAD with CAA, females</b>               |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 1.835<br>(1.075-3.131) | 0.026   |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |

| Predictors                                 | Odds Ratio<br>(95% CI)  | P value |
|--|-------------------------|---------|
| $\epsilon 4/\epsilon 4$                    | 1.809<br>(1.176-2.781)  | 0.007   |
| <b>HAD without CAA</b>                     |                         |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                         |         |
| $\epsilon 4/\epsilon 4$                    | 1.129<br>(0.417-3.052)  | 0.811   |
| <b>HAD without CAA, females</b>            |                         |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                         |         |
| $\epsilon 4/\epsilon 4$                    | 3.300<br>(0.633-17.211) | 0.157   |
| <b>HAD without CAA, males</b>              |                         |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                         |         |
| $\epsilon 4/\epsilon 4$                    | 0.585<br>(0.155-2.212)  | 0.430   |

Table representing LB and CAA's impact as separate comorbid neuropathological substrates on the relationship between APOE4 and AMB in HAD. Predictors referred to presence of two ( $\epsilon 4/\epsilon 4$ ) copies of the  $\epsilon 4$  allele of the APOE gene in HAD cases with or without Lewy Bodies (LB), as well as with or without Cerebral Amyloid Angiopathy (CAA). Numerical values within each column represent Odds Ratio (OR) with associated 95% Confidence Interval (95% CI) and p value. The relationship between APOE4 genotype and AMB prevalence was assessed in an unadjusted logistic regression model.



**TABLE 5**

*Regression analysis of the relationship between APOE  $\epsilon 4/\epsilon 4$  genotype and presence of AMB with concurrent LB and CAA pathology in HAD*

| Predictors                                 | Odds Ratio<br>(95% CI) | P value |
|--|------------------------|---------|
| <b>HAD with LB and CAA</b>                 |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 2.681<br>(1.663-4.322) | 0.001   |
| <b>HAD with LB &amp; without CAA</b>       |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 0.800<br>(0.147-4.368) | 0.797   |
| <b>HAD without LB &amp; with CAA</b>       |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 1.226<br>(0.754-1.993) | 0.412   |
| <b>HAD without LB &amp; CAA</b>            |                        |         |
| No $\epsilon 4$ & $\epsilon 4$ (indicator) |                        |         |
| $\epsilon 4/\epsilon 4$                    | 1.366<br>(0.399-4.670) | 0.619   |

Table representing the effect of LB and CAA as concurrent neuropathological substrates on the relationship between APOE4 and AMB in HAD. Predictors referred to presence of two ( $\epsilon 4/\epsilon 4$ ) copies of the  $\epsilon 4$  allele of the APOE gene in HAD cases with or without Lewy Bodies (LB), as well as with or without Cerebral Amyloid Angiopathy (CAA). Numerical values within each column represent Odds Ratio (OR) with associated 95% Confidence Interval (95% CI) and p value. The relationship between APOE4 genotype and AMB prevalence was assessed in an unadjusted logistic regression model.