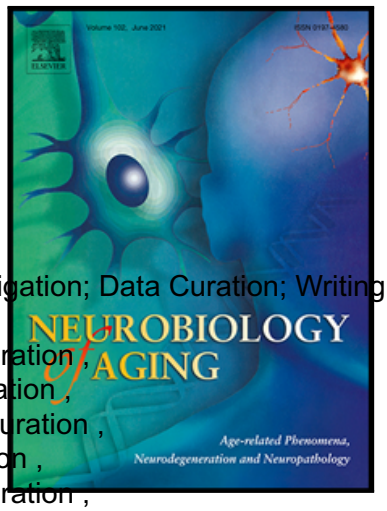

Apolipoprotein E4, amyloid, and cognition in Alzheimer's and Lewy body disease

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Apolipoprotein E4, amyloid, and cognition in Alzheimer's and Lewy body disease

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Highlights

- *APOE4* is associated with increased risks of AD and LBD with β-amyloid deposition.
- *APOE4* is not associated with the risk of pure LBD without β-amyloid deposition.
- Typical AD interacts with *APOE4* to worsen memory dysfunction and left hippocampal atrophy.
- Typical LBD interacts with *APOE4* to increase occipital β-amyloid deposition.

Abstract

The role of apolipoprotein E4 (*APOE4*) in the risk of Alzheimer's disease (AD) and Lewy body disease (LBD), and their relationship with β-amyloid deposition and cognitive dysfunction, remain unclear. Using amyloid and dopamine transporter imaging, we enrolled 126 controls and 208 patients with typical AD (pure AD and Lewy body variant of AD), AD with dementia with Lewy bodies (DLB), or typical LBD (DLB with amyloid deposition and pure LBD). *APOE4* was associated with an increased risk of all disease subtypes except pure LBD. *APOE4* was associated with increased frontal β-amyloid burden, and typical LBD was associated with increased occipital β-amyloid levels through its interaction with *APOE4*. *APOE4* was associated with deteriorated general cognition and memory dysfunction via its interaction with typical LBD and AD, respectively. In conclusion, the impact of *APOE4* on disease risk depends on its effects on β-amyloid deposition, and *APOE4* is associated with β-amyloid deposition regardless of the clinical diagnosis. However, it interacts with typical LBD to cause occipital β-amyloid deposition.

Keywords

Apolipoprotein E; Alzheimer's disease; β-amyloid; cognition; Lewy body disease; Mixed dementia

Abbreviations: AD, Alzheimer's disease; ADCI, AD-related cognitive impairment; *APOE4*, apolipoprotein E4; CDR-SOB, Clinical Dementia Rating Sum of Boxes; DLB, dementia with Lewy bodies; DLBA, DLB with amyloid deposition; FP-CIT, 18F-fluorinated N-3 fluoropropyl-2-beta-carboxy-methoxy-3-beta-(4-iodophenyl) nortropane; ICV, intracranial volume; K-MMSE, Korean version of Mini-Mental State Examination; LBCI, LBD-related cognitive impairment; LBD, Lewy body disease; LBVAD, LB variant of AD; MRI, magnetic resonance imaging; NC, normal cognition; PDD, PD dementia; PET, positron emission tomography; PLBD, pure LBD; PWMH, Periventricular WMH; SUVR, standardized uptake value ratios; UPDRS, Unified Parkinson's Disease Rating Scale; WMH, white matter hyperintensity.

1. Introduction

Alzheimer's disease (AD) and Lewy body disease (LBD) are the two most common causes of dementia. Apolipoprotein E4 (*APOE4*) allele is a genetic risk factor for AD (Corder et al., 1993; Farrer et al., 1997), which increases β-amyloid accumulation (Drzezga et al., 2009; Polvikoski et al., 1995) or induces a non-amyloidogenic mechanism that contributes to neurodegeneration by interacting with tau (Therriault et al., 2019). Furthermore, *APOE4* is a genetic risk factor for LBD (Bras et al., 2014; Tsuang et al., 2013). Previous autopsy studies have reported that *APOE4* increases the pathologic α-synuclein burden (Davis et al., 2020; Ruffmann et al., 2016), while others have not (Colom-Cadena et al., 2013; Vefring et al., 2010). Frequent AD and LBD co-occurrence in patients with cognitive impairment (Chung et al., 2015; Hamilton, 2000) could be attributed to the association between *APOE4* and LBD risk (Prokopenko et al., 2019). Advances in amyloid and dopamine transporter imaging have allowed *in vivo* diagnosis of AD (McKhann et al., 2011), LBD (McKeith et al., 2017), and their mixed disease (Burke et al., 2011). However, the role of *APOE4* in AD and LBD risk, considering their mixed diseases, remains unclear.

β-amyloid accumulation is a key phenomenon in patients with AD (Pascoal et al., 2017) and LBD (Gomperts et al., 2008). Given the association of *APOE4* with α-synuclein spreading (Davis et al., 2020; Zhao et al., 2020) and the interaction between α-synuclein and β-amyloid (Gallardo et al., 2008), *APOE4* could be involved in the relationship between α-synuclein and β-amyloid deposition. Development of amyloid positron emission tomography (PET) has allowed *in vivo* β-amyloid burden quantification (Sabri et al., 2015). However, there is no reliable *in vivo* biomarker for α-synuclein quantification or LB pathology; nevertheless, sufficient LB pathology that causes cognitive dysfunction can be detected based on the clinical diagnostic criteria and dopamine transporter imaging, which have high specificity for detecting dementia with Lewy bodies (DLB) (McKeith et al., 2017). Amyloid PET outperforms autopsy evaluation with regard to thorough topographical β-amyloid quantification without *a priori* evaluation for specific AD pathology sites. Therefore, we hypothesized that amyloid PET could be used to determine the effects of LBD, *APOE*, and their interaction on regional β-amyloid deposition.

Tau, α-synuclein, and β-amyloid interact synergistically in cognitive decline (Clinton et al., 2010). AD and LBD independently contribute to cognitive dysfunction (Kang et al., 2019); however, the role of *APOE4* in cognitive dysfunction with AD and LBD considered simultaneously remains unclear. We aimed to determine the effects of *APOE4* on the risk of each disease subtype, as well as on cognitive dysfunction, hippocampal volume, and β-amyloid deposition after adjusting for AD and LBD. We hypothesized that the association between disease risks and *APOE4* is dependent on β-amyloid deposition and that *APOE4* is associated with β-amyloid deposition regardless of the

clinical diagnosis. Moreover, we hypothesized that *APOE4* interacts with AD or LBD to increase β-amyloid deposition, hippocampal atrophy, and cognitive dysfunction.

2. Methods

2.1 Participants

We enrolled 126 participants with normal cognition (NC) and 208 patients with cognitive impairment. The NC participants lacked any subjective cognitive impairment symptoms or a history of neurologic or psychiatric illnesses and underwent neurological and neuropsychological examination, brain magnetic resonance imaging (MRI), and *APOE* genotyping. Their neurological and neuropsychological findings were normal, and they lacked structural brain lesions. Eleven NC participants underwent ^{18}F-Florbetaben (FBB)-PET, and no significant β-amyloid deposition was noted.

Patients with AD and/or LBD underwent neurological examination, *APOE* genotyping, neuropsychological tests, 3T MRI, FDG PET, and FBB PET scans at the dementia and movement clinics of Yonsei University Severance Hospital, Seoul, Korea, between April 2012 and May 2019. Using semi-structured questionnaires, caregivers evaluated clinical AD features, including slow-progressive memory dysfunction, and those of LBD, including parkinsonism, rapid eye movement sleep behavior disorder, visual hallucinations, and cognitive fluctuation. Parkinsonism severity was assessed using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (UPDRS) motor score with a score > 16 being considered moderate. The exclusion criteria were pure vascular cognitive impairment; other degenerative dementia causes, including frontotemporal dementia, corticobasal degeneration, and progressive supranuclear palsy; drug-induced cognitive impairment; and other adequate cognitive impairment causes, including epilepsy, psychiatric disorder, normal-pressure hydrocephalus, and structural brain lesions (e.g., tumor or hemorrhage).

All patients with AD dementia met the probable AD dementia criteria with high levels of biomarker evidence (McKhann et al., 2011), while all patients with mild cognitive impairment (MCI) due to AD met the high likelihood of MCI due to AD criteria based on the National Institute on Aging-Alzheimer's Association workgroups guidelines for AD (Albert et al., 2011). These patients were considered to have "typical AD." Specifically, all the patients with typical AD had progressive memory problems with insidious onset, biomarker evidence

of neuronal injury based on FDG PET, and significant cerebral β-amyloid deposition confirmed by global FBB standardized uptake value ratios (SUVR) > 1.478 (Sabri et al., 2015).

All patients with PD satisfied the United Kingdom PD Brain Bank diagnostic criteria (Gibb and Lees, 1988) and presented decreased dopamine transporter uptake on ^{18}F-fluorinated N-3 fluoropropyl-2-beta-carboxy-methoxy-3-beta-(4-iodophenyl) nortropane (FP-CIT) PET scans. Patients with PD-MCI and PD dementia (PDD) met the Movement Disorder Society criteria for PD-MCI (Litvan et al., 2012) and probable PDD (Emre et al., 2007), respectively. All the patients with DLB fulfilled the 2017 revised criteria for probable DLB (McKeith et al., 2017) and showed decreased dopamine transporter uptake on FP-CIT PET scans. To ascertain early brain changes in patients with DLB, we included patients with MCI (Petersen et al., 1999) who met all diagnostic criteria for probable DLB, except for dementia presence. These patients with PD-MCI, PDD, DLB-MCI, and DLB were considered to have LBD-related cognitive impairment (LBCI).

Based on clinical features and biomarker evidence, patients with mixed disease were placed in the AD-dominant, LBD-dominant, and equally dominant mixed disease subgroups (Figure 1). Patients with LBCI who presented β-amyloid deposition but did not have memory problems as their chief complaint and entorhinal hypometabolism were considered to have LBD-dominant mixed disease or DLB with amyloid deposition. Conversely, patients with typical AD who showed moderate/severe Parkinsonism and abnormal FP-CIT PET scans but lacked other LBD features, including cognitive fluctuation and visual hallucination, were considered to have AD-dominant mixed disease or LB variant of AD (LBVAD) (Hansen et al., 1990). If patients with typical AD satisfied the diagnostic criteria for DLB based on cognitive fluctuation or visual hallucination, they were regarded to have an equally dominant mixed disease or AD/DLB. Finally, there were 57, 32, 56, 21, and 42 patients with pure AD (PAD), LBVAD, pure LBD (PLBD), DLB with amyloid deposition (DLBA), and AD/DLB, respectively. Patients with PAD and LBVAD were regarded to have typical AD; patients with PLBD and DLBA, typical LBD; and patients with AD/DLB, both typical AD and typical LBD.

AD-related cognitive impairment (ADCI) was defined to include patients with PAD, LBVAD, AD/DLB, and LBDA. Given the progressive AD nature (Dubois et al., 2016), we defined ADCI solely based on amyloid PET-positivity and differentiated it from typical AD that corresponds to the symptomatic AD stage. Similarly, we defined LBCI for patients with LBVAD, AD/LBD, LBDA, and PLBD to differentiate it from typical LBD corresponding to LBD-dominant disease.

2.2 *APOE* genotyping

Genomic DNA was extracted from peripheral blood leukocytes using the DiaPlexQ^{TM} ApoE Genotyping Kit following the manufacturer's instructions (SolGent co., Ltd.). Two single nucleotide polymorphisms (rs429358 for codon 112 and rs7412 for codon 158) in the *APOE* gene were genotyped using a CFX 96 Real-time PCR system (Bio-Rad) per the manufacturer's instructions.

2.3 MRI acquisition, regional white matter hyperintensity (WMH) measurement, and lacune counting

All MRI scans were acquired using the same 3T MRI scanner (Philips Achieva; Philips Medical System, Best, The Netherlands) with a SENSE head coil (SENSE factor = 2). A visual rating scale of WMHs was modified from the Fazekas scale (Fazekas et al., 1987). Periventricular WMH (PWMH) areas were classified as P1 (cap and band < 5 mm), P2 (5 mm ≤ cap or band < 10 mm), and P3 (10 mm ≤ cap or band), and deep WMH (DWMH) areas as D1 (maximum diameter of deep white matter lesion < 10 mm), D2 (10 mm ≤ lesion < 25 mm), and D3 (≥ 25 mm). Supplementary Method S1 presents detailed methods for MRI acquisition and manual lacune counting.

2.4 Hippocampal segmentation and volume measurement

We used FMRIB's integrated registration and segmentation tool to determine the hippocampal volume in mm^3 (Patenaude et al., 2011). Each intensity bias-corrected T1-weighted image was registered to the MNI standard space, and the hippocampal mesh structure was fitted to the image. Boundary correction was applied for volumetric output. To account for individual brain size differences, we measured intracranial volume (ICV), defined as the sum of gray matter, white matter, and cerebrospinal fluid volumes.

2.5 Acquisition and assessment of ^{18}F-FBB and ^{18}F-FP-CIT PET imaging

PET scans were obtained using a Discovery 600 system (GE Healthcare, Milwaukee, WI). FP-CIT PET was interpreted through visual rating as previously described (Lee et al., 2018). Regarding FBB PET, amyloid-positivity was identified through global FBB SUVR obtained via

surface-based FBB PET analysis methods (Lee et al., 2018), where global FBB SUVR > 1.478 indicated amyloid-positivity (Sabri et al., 2015). Supplementary Method S2 presents detailed methods for the acquisition and preprocessing of PET images.

2.6 Quality assurance for image processing

All MRI scans and processing results were visually inspected by three researchers blinded to participant information (J.H.J., S.J., and B.S.Y.) for quality assurance.

2.7 Neuropsychological evaluation

All participants were assessed using the standardized Seoul Neuropsychological Screening Battery (Ahn et al., 2010). Supplementary Method S3 presents details regarding the measurement of the Korean version of Mini-Mental State Examination (K-MMSE) scores; Clinical Dementia Rating Sum of Boxes (CDR-SOB); and domain-specific scores for attention, language, visuospatial function, memory, and frontal/executive function.

2.8 Statistical analysis

An analysis of variance and a χ^2 test were performed for cross-group comparisons of clinical features. Logistic regression analyses were performed to evaluate the *APOE4* (carrier vs. non-carrier) effect on disease risk. Covariates for logistic regression analyses and other analyses included age, sex, education, hypertension, diabetes mellitus, hyperlipidemia, DWMH, PWMH, and the lacune number. Model 1 analyses evaluated the *APOE4* effect on each disease's risk (PAD, LBVAD, AD/LBD, DLBA, PLBD, ADCI, LBCI, typical AD or typical LBD) in a combined NC and each disease group. Model 2 analyses evaluated the *APOE4* effect on the ADCI or LBCI risk in all participants after adjusting for LBCI or ADCI, respectively. Model 3 analyses evaluated the *APOE4* effect on the typical AD or typical LBD risk in all study participants after adjusting for typical LBD or typical AD, respectively.

To determine the *APOE4* effect on cognitive dysfunction, the effects of *APOE4*, typical AD, and typical LBD on composite cognitive scores were evaluated with general linear models. Model 1 analyses evaluated the independent effects of *APOE4*, typical AD, and typical LBD. Given the significant interaction effects of AD and LBD on neuropsychological test scores, the interaction term of typical AD * typical LBD was further included in Model 1 analyses (Kang et al., 2019). Model 2 analyses tested the significance of interaction terms, including *APOE4* * typical AD and *APOE4* * typical LBD. Model 3 analyses were based on general linear models using *APOE4*, typical LBD, typical AD, typical AD * typical LBD, and significant interaction terms from Model 2 as predictors.

To assess the effects of *APOE4*, typical AD, and typical LBD on hippocampal volume, we performed general linear models for the left, right, and mean hippocampal volume further including ICV as a covariate. As typical AD * typical LBD effect was significant on hippocampal volume, *APOE4*, typical AD, typical LBD, and typical AD * typical LBD were included as predictors for Model 1. Model 2 tested the significance of the interaction terms (*APOE4* * typical AD or *APOE4* * typical LBD) by adding one of the two interaction terms as a predictor to Model 1. Model 3 used *APOE4*, typical AD, typical LBD, typical AD*typical LBD, and the significant interaction terms in Model 2 as predictors. Ten NC participants were excluded from these analyses because 3D T1 images were unavailable. Hippocampal volume could not be assessed because of issues with preprocessing quality in two, three, one, and two participants of the PAD, AD/DLB, PLBD, and NC groups, respectively. Finally, 114, 55, 32, 39, 21, and 55 participants with NC, PAD, LBVAD, AD/DLB, DLBA, and PLBD, respectively, were included.

To determine the *APOE4* effect on β-amyloid deposition, we used general linear models to investigate the independent and interactive effects of *APOE4*, typical AD, and typical LBD on the global and mean FBB SUVR in the frontal, temporal, parietal, and occipital cortices. Given the small sample size of the NC group that underwent FBB-PET (n = 11), these analyses were performed after excluding NC participants. Model 1 analyses evaluated the independent effects of *APOE4*, typical AD, and typical LBD. Model 2 analyses tested the significance of each pair of interaction terms, including *APOE4* * typical AD and *APOE4* * typical LBD. Model 3 analyses showed the results of general linear models using *APOE4*, typical LBD, typical AD, and significant interaction terms from Model 2 as predictors. Statistical analyses were performed using SPSS software (version 23.0; IBM Corp., Armonk, NY, USA) with significance set at $p < 0.05$.

MATLAB-based SurfStat toolbox was used for statistical analyses of vertex-wise FBB uptake (Worsley et al., 2009). To identify regional β-amyloid deposition patterns associated with *APOE4*, the independent and interactive effects of *APOE4*, typical AD, and typical LBD on the vertex-wise FBB SUVR were investigated using typical AD and typical LBD in general linear models after adjustment for similar

covariates as global and lobar FBB SUVR. As with the analyses on the mean FBB SUVR, this analysis was performed after excluding 11 NC participants. Given the significant interaction effects of *APOE4* * typical LBD on the mean lobar FBB SUVR, it was included in the models. As a sensitivity analysis, a further analysis including NC participants was performed (Supplementary Table 1 and Supplementary Figure 1).

3. Results

3.1 Demographic and clinical characteristics

Table 1 represents the demographic and clinical characteristics of participants. The AD/DLB, LBVAD, and PLBD groups were older than the control group; however, there was no significant among-group age difference. Male patients were more common in the LBVAD and DLBA groups than in the NC group. There was no significant among-group difference in education, hypertension, and hyperlipidemia; however, diabetes mellitus was more common in the PLBD group than in the NC, PAD, and AD/DLB groups. The lacune number and DWMH severity were comparable. Compared to the NC group, the AD/DLB group had more severe PWMH, which was similar across the remaining groups. The proportion of patients with dementia was higher in the AD/DLB group than in the PAD, LBVAD, and PLBD groups. Moreover, it was higher in the DLBA group than in the PAD group. All the disease groups showed worse K-MMSE and CDR-SOB scores than those of the NC group. The AD/DLB group had worse K-MMSE scores than did the PAD, LBVAD, and PLBD groups. The AD/DLB and DLBA groups had higher mean CDR-SOB scores than did the PAD and LBVAD groups; moreover, the PLBD group had a higher mean CDR-SOB score than did the PAD group. Compared with the NC and PLBD groups, the PAD, LBVAD, AD/DLB, and DLBA groups showed higher global, frontal, parietal, temporal, and occipital FBB SUVR. The *APOE4* carrier proportion was highest in the pure AD group (73.7%), followed by the AD with LBD (59.5%), LBVAD (53.1%), LBD with amyloid (47.6%), PLBD (19.6%), and NC (17.5%) groups. The PAD, LBVAD, AD/DLB, and DLBA groups had a higher proportion of *APOE4* carriers than did the NC and PLBD groups. However, the PLBD group had a comparable proportion of *APOE4* carriers to that in the NC group. All 11 NC participants who underwent FBB-PET scans were amyloid-negative according to the visual rating scale and had a global FBB SUVR < 1.478. Five of the 11 NC participants were *APOE4* heterozygotes and there were no *APOE4* homozygotes.

3.2 Effects of *APOE* genotypes on disease risk

Table 2 shows the associations between *APOE* genotype and each disease's risk compared with that in the NC group (Model 1). *APOE4* was associated with increased PAD, LBVAD, AD/DLB, and DLBA risks but not PLBD risk. The odds ratio (OR) of each disease group associated with *APOE4* was highest for PAD (OR, 95% confidence interval [CI] = 14.71, 6.54–33.10), followed by AD/DLB (OR, 95% CI = 9.07, 3.52–23.37), LBVAD (OR, 95% CI = 7.73, 2.85–21.02), and DLBA (OR, 95% CI = 5.52, 1.68–18.13). *APOE4* was associated with an increased risk of ADCI (OR, 95% CI = 8.90, 4.78–16.56), LBCI (OR, 95% CI = 4.06, 2.13-7.74), typical AD (9.39, 4.98–17.71), and typical LBD (OR, 95% CI = 3.58, 1.80–7.10). *APOE2* effect on PAD risk was not evaluated since there were no *APOE2* carriers in the PAD group. Further, *APOE2* was not associated with LBVAD, AD/DLB, DLBA, and PLBD risk. However, *APOE2* was associated with a decreased risk of ADCI (OR, 95% CI = 0.29, 0.11–0.73) and typical AD (OR, 95% CI = 0.24, 0.09–0.70). Sensitivity analysis involving the evaluation of the association between *APOE4* and LBCI after excluding patients with typical AD showed that *APOE4* was associated with an increased LBCI risk (OR, 95% CI = 2.30, 1.04–5.08). However, sensitivity analysis without patients with ADCI showed that *APOE4* was not associated with LBCI risk (OR, 95% CI = 1.37, 0.54–3.47).

The assessment of the *APOE4* effect on ADCI and typical AD risk (Model 2 and Model 3) showed that *APOE4* was associated with an increased ADCI and typical AD risk after controlling for LBCI and typical LBD, respectively. Meanwhile, *APOE4* was not associated with LBCI nor typical LBD risk after controlling for ADCI and typical AD, respectively. *APOE2* was associated with a lower ADCI and typical AD risk after controlling for LBCI and typical LBD, respectively. However, *APOE2* was not associated with LBCI or typical LBD risk after controlling for ADCI and typical AD, respectively.

3.3 *APOE4*, typical AD, and typical LBD on cognition

Model 1 analyses showed that typical AD and typical LBD were independently associated with worse cognitive scores in all neuropsychological domains, as well as K-MMSE and CDR-SOB scores. Further, *APOE4* was independently associated with worse CDR-SOB scores (Table 3). Typical AD and typical LBD had significant interaction effects on all neuropsychological domains except for the attention domain. However, the interaction direction implied that the cognitive dysfunction degree was comparable across the typical AD, typical LBD, and typical AD/typical LBD groups. Model 2 analyses showed that *APOE4* and typical AD were interactively associated with

worse memory scores, while *APOE4* and typical LBD were interactively associated with worse CDR-SOB scores. Model 3 showed similar effects of typical AD and typical LBD, as well as the interaction effect of typical AD * typical LBD, to those in Model 1.

3.4 Effects of *APOE4*, typical AD, and typical LBD on hippocampal volume

Model 1 analyses showed that typical AD and typical LBD were independently associated with a lower mean, left, and right hippocampal volumes (Table 4). Typical AD and typical LBD had significant interaction effects on hippocampal volumes in that the degree of hippocampal atrophy was comparable across the typical AD, typical LBD, and typical AD/typical LBD groups. Although *APOE4* had no significant independent effect on hippocampal volume in Model 1, Models 2 and 3 showed that *APOE4* and typical AD were interactively associated with a low left hippocampal volume. There was no significant interaction effect between *APOE4* and typical LBD on hippocampal volumes.

3.5 Effects of *APOE4*, AD, and LBD on global and regional FBB SUVR

The effects of *APOE4*, typical AD, and typical LBD on global and regional FBB SUVR were evaluated in patients with AD and/or LBD (Table 5). Model 1 analyses revealed that typical AD was associated with global SUVR and mean lobar SUVR in all four lobar regions. Typical LBD was not associated with FBB SUVR in any region, but *APOE4* was associated with mean frontal SUVR. Model 2 analyses showed that *APOE4* and typical LBD were interactively associated with a high mean occipital SUVR. Model 3 analyses showed that typical AD and *APOE4* * typical LBD were independently associated with a higher mean occipital SUVR.

There was a significant interaction effect between typical LBD and *APOE4* on occipital β-amyloid (Figure 2A). Typical AD had a significant effect on whole-brain cortices (Figure 2B), while typical LBD and *APOE4* independently did not have effects on vertex-wise FBB SUVR. Sensitivity analyses including 11 NC subjects revealed similar results to the original results (Supplementary Table 1 and Supplementary Figure 1).

4. Discussion

We assessed the relationship between *APOE4*, AD, LBD, β-amyloid deposition, and cognition in patients with cognitive impairment and NC participants who were diagnosed using careful clinical assessment and imaging biomarkers of FDG PET, amyloid PET, and dopamine transporter PET. *APOE4* increased the PAD, AD/DLB, LBVAD, and DLBA risks, but not the PLBD risk. The interaction of *APOE4* with typical LBD was associated with worse CDR-SOB, while that of *APOE4* and typical AD was associated with more severe memory dysfunction and left hippocampal atrophy. Furthermore, typical LBD was associated with increased occipital β-amyloid burden through its interaction with *APOE4*. This suggests that the *APOE4* effect on disease risk is dependent on β-amyloid deposition; however, *APOE4* interacts with typical LBD to worsen general cognition and increase occipital β-amyloid deposition. It also interacts with typical AD to worsen memory dysfunction and left hippocampal atrophy.

It remains unclear whether *APOE4* is associated with an increased risk of PLBD (Prokopenko et al., 2019; Tsuang et al., 2013). In contrast to our study results, a previous autopsy study with a relatively large sample size (Tsuang et al., 2013) demonstrated *APOE4*-associated increased risk of neuropathologically-identified DLB and PDD without AD pathology and suggested the *APOE4*-associated risk for DLB might be unrelated to amyloid mechanisms. However, the autopsy study identified concomitant AD pathology based on the Braak neurofibrillary tangle stage > III and the Consortium to Establish a Registry for Alzheimer's Disease plaque score of C, which consider diffuse plaque only β-amyloid deposition as a lack of AD pathology. As β-amyloid ligands bind to diffuse as well as neuritic plaques (Burack et al., 2010; Kantarci et al., 2020; Sabri et al., 2015), patients with DLB with amyloid in our study could have been classified into pure LBD group in the previous study. In a similar vein, antemortem amyloid PET scans of autopsy-confirmed pure LBD cases were found to be amyloid-positive with a diffuse plaque being the primary contributor (Burack et al., 2010; Kantarci et al., 2020). This perspective is consistent with our sensitivity analyses excluding patients with typical AD or ADCI. *APOE4* was significantly associated with LBCI risk after excluding patients with typical AD, but not after excluding patients with ADCI. Therefore, the *APOE4* effect on disease risk across AD and LBD depends on β-amyloid deposition.

APOE4 was associated with increased occipital β-amyloid deposition in the presence of typical LBD. Notably, the association was independent of the presence of typical AD. Since *APOE4* is also involved in the spread of α-synuclein or LB pathology (Davis et al., 2020; Dickson et al., 2018; Emamzadeh et al., 2016; Zhao et al., 2020) and the co-existence of α-synuclein and β-amyloid pathologies (Chung et al., 2015; Robinson et al., 2018), *APOE4* could play a pivotal role in the interaction between α-synuclein and β-amyloid (Gallardo et al., 2008).

The precise mechanism for the regional preference to occipital cortex in *APOE4* interaction with LBD remains unclear but is consistent with the fact that the occipital cortex is the converging region of various degenerative phenomena including hypoperfusion (Lobotesis et al., 2001), gray matter reduction (Lee et al., 2010), and hypometabolism (McKeith et al., 2017) in LBD. Given that an autopsy study comparing antemortem amyloid PET suggested LBD-associated occipital β-amyloid sparing (Kantarci et al., 2020), typical LBD with *APOE4* can be a distinct subtype of LBD showing accentuated occipital β-amyloid deposition. Additionally, the clinical classification considering the presence of visual hallucination or cognitive fluctuation could account for the differences (Figure 1). In our study, the interaction of *APOE4* with LBD was associated with worse CDR-SOB scores. Notably, no specific cognitive domains were affected by the interaction effect. Since general cognition in patients with LBD is affected by several factors, including visual hallucination, cognitive fluctuation, Parkinsonism severity, and various psychiatric symptoms, there is a need for further studies to address the association between *APOE4* and other LBD features.

The interaction of *APOE4* with typical AD was associated with worsened memory dysfunction and decreased left hippocampal volume. Although we could not perform tau imaging, all patients with typical AD presented typical clinical AD features and significant β-amyloid deposition. Furthermore, FDG PET confirmed that they had AD-relevant neurodegeneration (Figure 1). Given the close correlation of tau accumulation with clinical and neurodegenerative changes in AD (Ossenkoppele et al., 2016; Whitwell et al., 2018), typical AD in our study could be considered to involve AD-specific tau accumulation. Therefore, our findings may represent indirect clinical evidence of the interaction between *APOE4* and tau pathology, which is consistent with previous reports of a direct interaction of *APOE4* with tau (Strittmatter et al., 1994) and tau phosphorylation (Brecht et al., 2004), as well as of a significant association between *APOE4* and medial temporal lobe tau independent of β-amyloid burden (Therriault et al., 2019). Our sensitivity analysis could support the possible amyloid independent interaction between *APOE4* and tau pathology in worsening memory scores. After further adjusting for global FBB-SUVR, the interaction effect of *APOE4* * typical AD on memory scores remained significant (β [SE] = -0.59 [0.25], p = 0.019). Further studies are warranted to confirm the interaction of *APOE4* with quantified tau-burden on memory dysfunction. In our study, the *APOE4* effect on hippocampal volume was dependent on the presence of typical AD. However, a previous study showed that hippocampal volumes are smaller with increasing *APOE4* dosages, regardless of diagnosis within the AD/DLB spectrum (Saeed et al., 2018). This discrepancy might be attributed to whether there is a consideration for the mixed disease of AD and LBD. As concomitant AD pathology is frequently observed in LBD patients, the confounding effect of AD could explain the association between *APOE4* and hippocampal atrophy in LBD.

This study had several limitations. First, we did not perform tau PET nor measure the LB pathology burden, thereby limiting the establishment of a dose-dependent relationship of AD and LB pathologies with cognitive dysfunction and β-amyloid burden. Second, since

only 11 of 126 NC participants underwent FBB-PET, we could not include them in the models using global and regional FBB-SUVR as outcomes. Third, a previous study showed that *APOE4* influenced the association between WMH and cognitive performance in AD and DLB (Mirza et al., 2019); however, in our data, there was no significant interaction between *APOE4* and lacune number, DWMH, or PWMH on the cognitive scores (data not shown). Different methods for WMH rating (semi-automated volume measurement vs. visual rating), different demographic and ethnic backgrounds, and the inclusion of patients with mixed disease could be possible explanations for these differences. This being said, further studies are warranted to evaluate the differential role of *APOE4* with and without significant vascular burden. Fourth, LBVAD under-diagnosis could have occurred since we did not perform dopamine transporter PET for patients with PAD without significant parkinsonism (UPDRS motor scale score > 16). Moreover, dopamine transporter PET has suboptimal sensitivity for LBD detection (McKeith et al., 2007), in particular if LB pathology does not involve the nigrostriatal dopaminergic system (Zaccai et al., 2008). Inconsistent with our findings of the PAD group having the highest *APOE4* prevalence, a previous autopsy study reported that the *APOE4* prevalence was highest in the AD with LB group, followed by the pure AD group (Chung et al., 2015). This inconsistency could be attributed to our possible LBVAD underestimation.

Our findings suggest that the *APOE4* effect on disease risk is dependent on its effects on β-amyloid deposition. However, *APOE4* further interacts with typical LBD to induce worse general cognition and higher occipital β-amyloid deposition. This study highlights the possible interaction of β-amyloid and LBD pathologies converging in the occipital cortex.

Disclosure statement

Nothing to report

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Data availability: For purposes of replicating procedures and results, any qualified investigator can request anonymized data after ethics clearance and approval by all authors.

Ethics approval: This study was approved by the Institutional Review Board of the Yonsei University Medical Center. Since this was a retrospective study, the requirement for patient consent was waived

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References

Ahn, H.J., Chin, J., Park, A., Lee, B.H., Suh, M.K., Seo, S.W., Na, D.L., 2010. Seoul Neuropsychological Screening Battery-dementia version (SNSB-D): a useful tool for assessing and monitoring cognitive impairments in dementia patients. Journal of Korean medical science 25(7), 1071-1076.

Albert, M.S., DeKosky, S.T., Dickson, D., Dubois, B., Feldman, H.H., Fox, N.C., Gamst, A., Holtzman, D.M., Jagust, W.J., Petersen, R.C., Snyder, P.J., Carrillo, M.C., Thies, B., Phelps, C.H., 2011. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7(3), 270-279.

Bras, J., Guerreiro, R., Darwent, L., Parkkinen, L., Ansorge, O., Escott-Price, V., Hernandez, D.G., Nalls, M.A., Clark, L.N., Honig, L.S., Marder, K., Van Der Flier, W.M., Lemstra, A., Scheltens, P., Rogaeva, E., St George-Hyslop, P., Londos, E., Zetterberg, H., Ortega-Cubero, S., Pastor, P., Ferman, T.J., Graff-Radford, N.R., Ross, O.A., Barber, I., Braae, A., Brown, K., Morgan, K., Maetzler, W., Berg, D., Troakes, C., Al-Sarraj, S., Lashley, T., Compta, Y., Revesz, T., Lees, A., Cairns, N., Halliday, G.M., Mann, D., Pickering-Brown, S., Dickson, D.W., Singleton, A., Hardy, J., 2014. Genetic analysis implicates APOE, SNCA and suggests lysosomal dysfunction in the etiology of dementia with Lewy bodies. Hum Mol Genet 23(23), 6139-6146.

Brecht, W.J., Harris, F.M., Chang, S., Tesseur, I., Yu, G.-Q., Xu, Q., Dee Fish, J., Wyss-Coray, T., Buttini, M., Mucke, L., Mahley, R.W., Huang, Y., 2004. Neuron-Specific Apolipoprotein E4 Proteolysis Is Associated with Increased Tau Phosphorylation in Brains of Transgenic Mice. 24(10), 2527-2534.

Burack, M.A., Hartlein, J., Flores, H.P., Taylor-Reinwald, L., Perlmutter, J.S., Cairns, N.J., 2010. In vivo amyloid imaging in autopsy-confirmed Parkinson disease with dementia. Neurology 74(1), 77-84.

Burke, J.F., Albin, R.L., Koeppe, R.A., Giordani, B., Kilbourn, M.R., Gilman, S., Frey, K.A., 2011. Assessment of mild dementia with amyloid and dopamine terminal positron emission tomography. Brain 134(6), 1647-1657.

Chung, E.J., Babulal, G.M., Monsell, S.E., Cairns, N.J., Roe, C.M., Morris, J.C., 2015. Clinical Features of Alzheimer Disease With and Without Lewy Bodies. JAMA neurology 72(7), 789-796.

Clinton, L.K., Blurton-Jones, M., Myczek, K., Trojanowski, J.Q., LaFerla, F.M., 2010. Synergistic Interactions between Abeta, tau, and alpha-synuclein: acceleration of neuropathology and cognitive decline. J Neurosci 30(21), 7281-7289.

Colom-Cadena, M., Gelpi, E., Charif, S., Belbin, O., Blesa, R., Marti, M.J., Clarimon, J., Lleo, A., 2013. Confluence of alpha-synuclein, tau, and beta-amyloid pathologies in dementia with Lewy bodies. J Neuropathol Exp Neurol 72(12), 1203-1212.

Corder, E.H., Saunders, A.M., Strittmatter, W.J., Schmechel, D.E., Gaskell, P.C., Small, G.W., Roses, A.D., Haines, J.L., Pericak-Vance, M.A., 1993. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science (New York, N.Y.) 261(5123), 921-923.

Davis, A.A., Inman, C.E., Wargel, Z.M., Dube, U., Freeberg, B.M., Galluppi, A., Haines, J.N., Dhavale, D.D., Miller, R., Choudhury, F.A., Sullivan, P.M., Cruchaga, C., Perlmutter, J.S., Ulrich, J.D., Benitez, B.A., Kotzbauer, P.T., Holtzman, D.M., 2020. APOE genotype regulates pathology and disease progression in synucleinopathy. Sci Transl Med 12(529).

Dickson, D.W., Heckman, M.G., Murray, M.E., Soto, A.I., Walton, R.L., Diehl, N.N., van Gerpen, J.A., Uitti, R.J., Wszolek, Z.K., Ertekin-Taner, N., Knopman, D.S., Petersen, R.C., Graff-Radford, N.R., Boeve, B.F., Bu, G., Ferman, T.J., Ross, O.A., 2018. APOE ε4 is associated with severity of Lewy body pathology independent of Alzheimer pathology. Neurology 91(12), e1182-e1195.

Drzezga, A., Grimmer, T., Henriksen, G., Muhlau, M., Perneczky, R., Miederer, I., Praus, C., Sorg, C., Wohlschlager, A., Riemenschneider, M., Wester, H.J., Foerstl, H., Schwaiger, M., Kurz, A., 2009. Effect of APOE genotype on amyloid plaque load and gray matter volume in Alzheimer disease. Neurology 72(17), 1487-1494.

Dubois, B., Hampel, H., Feldman, H.H., Scheltens, P., Aisen, P., Andrieu, S., Bakardjian, H., Benali, H., Bertram, L., Blennow, K., Broich, K., Cavedo, E., Crutch, S., Dartigues, J.F., Duyckaerts, C., Epelbaum, S., Frisoni, G.B., Gauthier, S., Genthon, R., Gouw, A.A., Habert,

M.O., Holtzman, D.M., Kivipelto, M., Lista, S., Molinuevo, J.L., O'Bryant, S.E., Rabinovici, G.D., Rowe, C., Salloway, S., Schneider, L.S., Sperling, R., Teichmann, M., Carrillo, M.C., Cummings, J., Jack, C.R., Jr., 2016. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. Alzheimers Dement 12(3), 292-323.

Emamzadeh, F.N., Aojula, H., McHugh, P.C., Allsop, D., 2016. Effects of different isoforms of apoE on aggregation of the alpha-synuclein protein implicated in Parkinson's disease. Neuroscience letters 618, 146-151.

Emre, M., Aarsland, D., Brown, R., Burn, D.J., Duyckaerts, C., Mizuno, Y., Broe, G.A., Cummings, J., Dickson, D.W., Gauthier, S., Goldman, J., Goetz, C., Korczyn, A., Lees, A., Levy, R., Litvan, I., McKeith, I., Olanow, W., Poewe, W., Quinn, N., Sampaio, C., Tolosa, E., Dubois, B., 2007. Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 22(12), 1689-1707; quiz 1837.

Farrer, L.A., Cupples, L.A., Haines, J.L., Hyman, B., Kukull, W.A., Mayeux, R., Myers, R.H., Pericak-Vance, M.A., Risch, N., van Duijn, C.M., 1997. 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 278(16), 1349-1356.

Fazekas, F., Chawluk, J.B., Alavi, A., Hurtig, H.I., Zimmerman, R.A., 1987. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. AJR. American journal of roentgenology 149(2), 351-356.

Gallardo, G., Schluter, O.M., Sudhof, T.C., 2008. A molecular pathway of neurodegeneration linking alpha-synuclein to ApoE and Abeta peptides. Nat Neurosci 11(3), 301-308.

Gibb, W.R., Lees, A.J., 1988. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson's disease. J Neurol Neurosurg Psychiatry 51(6), 745-752.

Gomperts, S.N., Rentz, D.M., Moran, E., Becker, J.A., Locascio, J.J., Klunk, W.E., Mathis, C.A., Elmaleh, D.R., Shoup, T., Fischman, A.J., Hyman, B.T., Growdon, J.H., Johnson, K.A., 2008. Imaging amyloid deposition in Lewy body diseases. Neurology 71(12), 903-910.

Hamilton, R.L., 2000. Lewy bodies in Alzheimer's disease: a neuropathological review of 145 cases using alpha-synuclein immunohistochemistry. Brain Pathol 10(3), 378-384.

Hansen, L., Salmon, D., Galasko, D., Masliah, E., Katzman, R., DeTeresa, R., Thal, L., Pay, M.M., Hofstetter, R., Klauber, M., et al., 1990. The Lewy body variant of Alzheimer's disease: a clinical and pathologic entity. Neurology 40(1), 1-8.

Kang, S.W., Jeon, S., Yoo, H.S., Chung, S.J., Lee, P.H., Sohn, Y.H., Yun, M., Evans, A.C., Ye, B.S., 2019. Effects of Lewy body disease and Alzheimer disease on brain atrophy and cognitive dysfunction. Neurology, 10.1212/WNL.0000000000007373.

Kantarci, K., Lowe, V.J., Chen, Q., Przybelski, S.A., Lesnick, T.G., Schwarz, C.G., Senjem, M.L., Gunter, J.L., Jack, C.R., Jr., Graff-Radford, J., Jones, D.T., Knopman, D.S., Graff-Radford, N., Ferman, T.J., Parisi, J.E., Dickson, D.W., Petersen, R.C., Boeve, B.F., Murray, M.E., 2020. β-Amyloid PET and neuropathology in dementia with Lewy bodies. Neurology 94(3), e282-e291.

Lee, J.E., Park, B., Song, S.K., Sohn, Y.H., Park, H.J., Lee, P.H., 2010. A comparison of gray and white matter density in patients with Parkinson's disease dementia and dementia with Lewy bodies using voxel-based morphometry. Mov Disord 25(1), 28-34.

Lee, Y.G., Jeon, S., Yoo, H.S., Chung, S.J., Lee, S.K., Lee, P.H., Sohn, Y.H., Yun, M., Evans, A.C., Ye, B.S., 2018. Amyloid-beta-related and unrelated cortical thinning in dementia with Lewy bodies. Neurobiol Aging 72, 32-39.

Litvan, I., Goldman, J.G., Troster, A.I., Schmand, B.A., Weintraub, D., Petersen, R.C., Mollenhauer, B., Adler, C.H., Marder, K., Williams-Gray, C.H., Aarsland, D., Kulisevsky, J., Rodriguez-Oroz, M.C., Burn, D.J., Barker, R.A., Emre, M., 2012. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord 27(3), 349-356.

Lobotesis, K., Fenwick, J.D., Phipps, A., Ryman, A., Swann, A., Ballard, C., McKeith, I.G., O'Brien, J.T., 2001. Occipital hypoperfusion on SPECT in dementia with Lewy bodies but not AD. Neurology 56(5), 643-649.

McKeith, I., O'Brien, J., Walker, Z., Tatsch, K., Booij, J., Darcourt, J., Padovani, A., Giubbini, R., Bonuccelli, U., Volterrani, D., Holmes, C., Kemp, P., Tabet, N., Meyer, I., Reininger, C., 2007. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. Lancet Neurol 6(4), 305-313.

McKeith, I.G., Boeve, B.F., Dickson, D.W., Halliday, G., Taylor, J.P., Weintraub, D., Aarsland, D., Galvin, J., Attems, J., Ballard, C.G., Bayston, A., Beach, T.G., Blanc, F., Bohnen, N., Bonanni, L., Bras, J., Brundin, P., Burn, D., Chen-Plotkin, A., Duda, J.E., El-Agnaf, O., Feldman, H., Ferman, T.J., Ffytche, D., Fujishiro, H., Galasko, D., Goldman, J.G., Gomperts, S.N., Graff-Radford, N.R., Honig, L.S., Iranzo, A., Kantarci, K., Kaufer, D., Kukull, W., Lee, V.M.Y., Leverenz, J.B., Lewis, S., Lippa, C., Lunde, A., Masellis, M., Masliah, E., McLean, P., Mollenhauer, B., Montine, T.J., Moreno, E., Mori, E., Murray, M., O'Brien, J.T., Orimo, S., Postuma, R.B., Ramaswamy, S., Ross, O.A., Salmon, D.P., Singleton, A., Taylor, A., Thomas, A., Tiraboschi, P., Toledo, J.B., Trojanowski, J.Q., Tsuang, D., Walker, Z., Yamada, M., Kosaka, K., 2017. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. Neurology 89(1), 88-100.

McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R., Jr., Kawas, C.H., Klunk, W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N., Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S., Phelps, C.H., 2011. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7(3), 263-269.

Mirza, S.S., Saeed, U., Knight, J., Ramirez, J., Stuss, D.T., Keith, J., Nestor, S.M., Yu, D., Swardfager, W., Rogaeva, E., St. George Hyslop, P., Black, S.E., Masellis, M., 2019. APOE ε4, white matter hyperintensities, and cognition in Alzheimer and Lewy body dementia. Neurology 93(19), e1807-e1819.

Ossenkoppele, R., Schonhaut, D.R., Schöll, M., Lockhart, S.N., Ayakta, N., Baker, S.L., O'Neil, J.P., Janabi, M., Lazaris, A., Cantwell, A., Vogel, J., Santos, M., Miller, Z.A., Bettcher, B.M., Vossel, K.A., Kramer, J.H., Gorno-Tempini, M.L., Miller, B.L., Jagust, W.J., Rabinovici, G.D., 2016. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. Brain 139(Pt 5), 1551-1567.

Pascoal, T.A., Mathotaarachchi, S., Shin, M., Benedet, A.L., Mohades, S., Wang, S., Beaudry, T., Kang, M.S., Soucy, J.P., Labbe, A., Gauthier, S., Rosa-Neto, P., 2017. Synergistic interaction between amyloid and tau predicts the progression to dementia. Alzheimers Dement 13(6), 644-653.

Patenaude, B., Smith, S.M., Kennedy, D.N., Jenkinson, M., 2011. A Bayesian model of shape and appearance for subcortical brain segmentation. Neuroimage 56(3), 907-922.

Petersen, R.C., Smith, G.E., Waring, S.C., Ivnik, R.J., Tangalos, E.G., Kokmen, E., 1999. Mild cognitive impairment: clinical characterization and outcome. Arch Neurol 56(3), 303-308.

Polvikoski, T., Sulkava, R., Haltia, M., Kainulainen, K., Vuorio, A., Verkkoniemi, A., Niinisto, L., Halonen, P., Kontula, K., 1995. Apolipoprotein E, dementia, and cortical deposition of beta-amyloid protein. The New England journal of medicine 333(19), 1242-1247.

Prokopenko, I., Miyakawa, G., Zheng, B., Heikkinen, J., Petrova Quayle, D., Udeh-Momoh, C., Claringbould, A., Neumann, J., Haytural, H., Kaakinen, M.A., Loizidou, E., Meissner, E., Bertram, L., Gveric, D.O., Gentleman, S.M., Attems, J., Perneczky, R., Arzberger, T., Muglia, P., Lill, C.M., Parkkinen, L., Middleton, L.T., 2019. Alzheimer's disease pathology explains association between dementia with Lewy bodies and APOE-epsilon4/TOMM40 long poly-T repeat allele variants. Alzheimers Dement (N Y) 5, 814-824.

Robinson, J.L., Lee, E.B., Xie, S.X., Rennert, L., Suh, E., Bredenberg, C., Caswell, C., Van Deerlin, V.M., Yan, N., Yousef, A., Hurtig, H.I., Siderowf, A., Grossman, M., McMillan, C.T., Miller, B., Duda, J.E., Irwin, D.J., Wolk, D., Elman, L., McCluskey, L., Chen-Plotkin, A., Weintraub, D., Arnold, S.E., Brettschneider, J., Lee, V.M., Trojanowski, J.Q., 2018. Neurodegenerative disease concomitant proteinopathies are prevalent, age-related and APOE4-associated. Brain : a journal of neurology 141(7), 2181-2193.

Ruffmann, C., Calboli, F.C., Bravi, I., Gveric, D., Curry, L.K., de Smith, A., Pavlou, S., Buxton, J.L., Blakemore, A.I., Takousis, P., Molloy, S., Piccini, P., Dexter, D.T., Roncaroli, F., Gentleman, S.M., Middleton, L.T., 2016. Cortical Lewy bodies and Abeta burden are associated with prevalence and timing of dementia in Lewy body diseases. Neuropathol Appl Neurobiol 42(5), 436-450.

Sabri, O., Sabbagh, M.N., Seibyl, J., Barthel, H., Akatsu, H., Ouchi, Y., Senda, K., Murayama, S., Ishii, K., Takao, M., Beach, T.G., Rowe, C.C., Leverenz, J.B., Ghetti, B., Ironside, J.W., Catafau, A.M., Stephens, A.W., Mueller, A., Koglin, N., Hoffmann, A., Roth, K., Reininger, C., Schulz-Schaeffer, W.J., 2015. Florbetaben PET imaging to detect amyloid beta plaques in Alzheimer's disease: phase 3 study. Alzheimers Dement 11(8), 964-974.

Saeed, U., Mirza, S.S., MacIntosh, B.J., Herrmann, N., Keith, J., Ramirez, J., Nestor, S.M., Yu, Q., Knight, J., Swardfager, W., Potkin, S.G., Rogaeva, E., St George-Hyslop, P., Black, S.E., Masellis, M., 2018. APOE-ε4 associates with hippocampal volume, learning, and memory across the spectrum of Alzheimer's disease and dementia with Lewy bodies. Alzheimers Dement 14(9), 1137-1147.

Strittmatter, W.J., Saunders, A.M., Goedert, M., Weisgraber, K.H., Dong, L.M., Jakes, R., Huang, D.Y., Pericak-Vance, M., Schmechel, D., Roses, A.D., 1994. Isoform-specific interactions of apolipoprotein E with microtubule-associated protein tau: implications for Alzheimer disease. 91(23), 11183-11186.

Therriault, J., Benedet, A.L., Pascoal, T.A., Mathotaarachchi, S., Chamoun, M., Savard, M., Thomas, E., Kang, M.S., Lussier, F., Tissot, C., Parsons, M., Qureshi, M.N.I., Vitali, P., Massarweh, G., Soucy, J.P., Rej, S., Saha-Chaudhuri, P., Gauthier, S., Rosa-Neto, P., 2019. Association of Apolipoprotein E epsilon4 With Medial Temporal Tau Independent of Amyloid-beta. JAMA Neurol.

Tsuang, D., Leverenz, J.B., Lopez, O.L., Hamilton, R.L., Bennett, D.A., Schneider, J.A., Buchman, A.S., Larson, E.B., Crane, P.K., Kaye, J.A., Kramer, P., Woltjer, R., Trojanowski, J.Q., Weintraub, D., Chen-Plotkin, A.S., Irwin, D.J., Rick, J., Schellenberg, G.D., Watson, G.S., Kukull, W., Nelson, P.T., Jicha, G.A., Neltner, J.H., Galasko, D., Masliah, E., Quinn, J.F., Chung, K.A., Yearout, D., Mata, I.F., Wan, J.Y., Edwards, K.L., Montine, T.J., Zabetian, C.P., 2013. APOE epsilon4 increases risk for dementia in pure synucleinopathies. JAMA Neurol 70(2), 223-228.

Vefring, H., Haugarvoll, K., Tysnes, O.B., Larsen, J.P., Kurz, M.W., 2010. The role of APOE alleles in incident Parkinson's disease. The Norwegian ParkWest Study. Acta Neurol Scand 122(6), 438-441.

Whitwell, J.L., Graff-Radford, J., Tosakulwong, N., Weigand, S.D., Machulda, M.M., Senjem, M.L., Spychalla, A.J., Vemuri, P., Jones, D.T., Drubach, D.A., Knopman, D.S., Boeve, B.F., Ertekin-Taner, N., Petersen, R.C., Lowe, V.J., Jack, C.R., Jr., Josephs, K.A., 2018. Imaging correlations of tau, amyloid, metabolism, and atrophy in typical and atypical Alzheimer's disease. Alzheimers Dement 14(8), 1005-1014.

Worsley, K.J., E. Taylor, J., Carbonell, F., Chung, M., Duerden, E., Bernhardt, B., Oc, L., Boucher, M., Evans, A., 2009. SurfStat: A Matlab toolbox for the statistical analysis of univariate and multivariate surface and volumetric data using linear mixed effects models and random field theory.

Zaccai, J., Brayne, C., McKeith, I., Matthews, F., Ince, P.G., 2008. Patterns and stages of alpha-synucleinopathy: Relevance in a population-based cohort. Neurology 70(13), 1042-1048.

Zhao, N., Attrebi, O.N., Ren, Y., Qiao, W., Sonustun, B., Martens, Y.A., Meneses, A.D., Li, F., Shue, F., Zheng, J., Van Ingelgom, A.J., Davis, M.D., Kurti, A., Knight, J.A., Linares, C., Chen, Y., Delenclos, M., Liu, C.C., Fryer, J.D., Asmann, Y.W., McLean, P.J., Dickson, D.W., Ross, O.A., Bu, G., 2020. APOE4 exacerbates alpha-synuclein pathology and related toxicity independent of amyloid. Sci Transl Med 12(529).

Figure 1. Diagram representing participant classification

Abbreviations: AD, Alzheimer's disease; LBD, Lewy body disease; LB, Lewy body; LB variant AD, Lewy body variant of Alzheimer's disease = AD + PD; DLB, dementia with Lewy bodies; PD, Parkinson's disease; UPDRS, unified Parkinson's disease rating scale; DAT, dopamine transporter; PDRP, Parkinson's disease-related metabolic pattern; FDG, Fluorine-18-fluorodeoxyglucose.

Figure 2. Effects of *APOE4*, typical Alzheimer's disease, and typical Lewy body disease on regional amyloid deposition

Statistical map showing cortical regions with (A) a significant interaction effect between *APOE4* and typical Lewy body disease and (B) a significant independent effect of typical Alzheimer's disease on cortical amyloid deposition. There was no region showing a significant independent effect of *APOE4* or that of typical Lewy body disease. Results are based on a general linear model. Covariates include age, sex, education, hypertension, diabetes mellitus type 2, dyslipidemia, number of lacunes, and deep and periventricular white matter hyperintensities. This analysis was performed for all participants except normal controls.. The color scale represents t-values with areas bounded by the white line showing statistically significant regions (corrected $p < 0.05$, false discovery rate).

Abbreviations: *APOE4*, apolipoprotein E4; LBD, Lewy body disease; FBB, ^{18}F-Florbetaben; FDR, false discovery rate.

Table 1. Demographic characteristics of the study participants

	NC	PAD	LBVAD	AD/DLB	DLBA	PLBD	p^1	p^2
Number	126	57	32	42	21	56		
Age (years)	68.5 ± 8.3[c,d,f]	71.7 ± 7.7	73.3 ± 8.1[a]	75.1 ± 7.2[a]	73.13 ± 7.0	75.02 ± 7.3[a]	<0.001	0.114
Sex, female	91 (72.2)[c,e]	39 (68.4)	16 (50.0)[a]	26 (61.9)	8 (38.1)[a]	33 (58.9)	0.017	0.132
Education (years)	10.7 ± 4.5	10.6 ± 4.5	9.4 ± 5.5	8.9 ± 5.9	11.4 ± 5.8	9.3 ± 5.1	0.152	0.281
Vascular risk factors, n (%)								
Hypertension	65 (51.6)	25 (43.9)	16 (50.0)	24 (57.1)	9 (42.9)	35 (62.5)	0.396	0.272
Diabetes mellitus	25 (19.8)[f]	10 (17.5)[f]	6 (18.8)	7 (16.7)[f]	6 (28.6)	22 (39.3)[a,b,d]	0.037	0.035
Dyslipidemia	48 (38.1)	26 (56.6)	14 (43.8)	13 (31.0)	7 (33.3)	18 (32.1)	0.591	0.448
Cognitive status							NA	0.009
Non-demented	NA	38 (66.7)[d,e]	19 (59.4)[d]	14 (33.4)[b,c,f]	8 (38.1)[b]	30 (55.4)[d]		
Dementia	NA	19 (33.3)[d,e]	13 (40.6)[d]	28 (66.7)[b,c,f]	13 (61.9)[b]	25 (44.6)[d]		
K-MMSE	27.7 ± 2.0[b,c,d,e,f]	23.4 ± 3.3[a,d]	22.5 ± 3.1[a,d]	19.8 ± 4.8[a,b,c,f]	21.5 ± 6.1[a]	22.4 ± 4.5[a,d]	<0.001	0.002
CDR-SOB	0[b,c,d,e,f]	2.5 ± 1.5[a,d,e,f]	3.1 ± 2.1[a,d,e]	4.7 ± 3.2[a,b,c]	5.2 ± 3.7[a,b,c]	3.67± 2.8[a,b]	<0.001	<0.001

Vascular MRI markers								
Number of lacunes	0.9 ± 2.00	1.0 ± 1.7	1.6 ± 2.3	1.8 ± 2.9	1.8 ± 2.8	1.5 ± 2.5	0.189	0.563
PWMH	1.4 ± 0.6[d]	1.5 ± 0.7	1.7 ±0.7	1.8 ± 0.7[a]	1.5 ± 0.7	1.7 ± 0.7	0.009	0.248
DWMH	1.3 ± 0.6	1.4 ± 0.7	1.4 ± 0.6	1.5 ± 0.6	1.3 ± 0.5	1.3 ± 0.5	0.713	0.681
FBB-PET[3]								
Global FBB SUVR	1.2 ± 0.1[b,c,d,e]	1.9 ± 0.2[a,f]	2.0 ± 0.3[a,f]	1.9 ± 0.3[a,f]	1.9 ± 0.4[a,f]	1.3 ± 0.9[b,c,d,e]	<0.001	<0.001
Frontal SUVR	1.2 ± 0.1[b,c,d,e]	2.0 ± 0.3[a,f]	2.0 ± 0.4[a,f]	2.0 ± 0.3[a,f]	1.9 ± 0.4[a,f]	1.3 ± 0.1[b,c,d,e]	<0.001	<0.001
Parietal SUVR	1.2 ± 0.1[b,c,d,e]	1.9 ± 0.2[a,f]	2.0 ± 0.3[a,f]	1.9 ± 0.3[a,f]	1.9 ± 0.4[a,f]	1.3 ± 0.1[b,c,d,e]	<0.001	<0.001
Temporal SUVR	1.2 ± 0.1[b,c,d,e]	1.9 ± 0.3 [a,f]	1.9 ± 0.3[a,f]	1.9 ± 0.3[a,f]	1.9 ± 0.3[a,f]	1.3 ± 0.1[b,c,d,e]	<0.001	<0.001
Occipital SUVR	1.3 ± 0.1[b,c,d,e]	1.7 ± 0.2[a,f]	1.8 ± 0.3[a,f]	1.8 ± 0.3[a,f]	1.9 ± 0.3[a,f]	1.4 ± 0.1[b,c,d,e]	<0.001	<0.001
Positivity on visual rating	0 (0)	55 (96.5)	32 (100)	41 (97.6)	19 (90.5)	7 (12.5)		
Global SUVR > 1.478	0 (0)	54 (100)	30 (100)	40 (100)	20 (100)	0 (0)		
APOE4 homozygote	0 (0)[b,c]	4 (7.0)[a]	5 (15.6)[a,f]	1 (2.4)	0 (0)	1 (1.8)[c]	<0.001	0.056
APOE2 carrier	22 (17.5)[b,d]	0[a,c,f]	4 (12.5)[b]	1 (2.4)[a,f]	2 (9.5)	9 (16.1)[b,d]	0.001	0.003

Abbreviations: *APOE* = apolipoprotein E; AD = Alzheimer's disease; PAD = pure Alzheimer's disease; AD/DLB = Alzheimer's disease with dementia with Lewy bodies; DLBA = dementia with Lewy bodies with amyloid deposition; PLBD = pure Lewy body disease; NC = normal cognition; FBB = Florbetaben; PET = positron emission tomography; DWMH = deep white matter hyperintensity; PWMH = periventricular white matter hyperintensities; K-MMSE = Korean version of the Mini-Mental State Examination; CDR-SOB = Clinical Dementia Rating Sum of Boxes; MRI = magnetic resonance imaging; SUVR = standardized uptake value ratio.

[1] *p* values are results of comparisons among all six study groups.

[2] *p* values are the results of comparisons among the five disease groups.

[3] A total of 11 of 126 (8.3%) NC participants and all patients with cognitive impairment underwent FBB-PET scans. Global FBB SUVR was not calculated because of issues with imaging quality in three, two, two, one, and two patients with PAD, LBVAD, AD/DLB, DLBA, and PLBD, respectively. In these patients, amyloid-positivity and -negativity was determined based on the visual rating scale.

[a] Significantly different compared to the NC group.

[b] Significantly different compared to the PAD group.

[c] Significantly different compared to the LBVAD group.

[d] Significantly different compared to the AD/DLB group.

[e] Significantly different compared to the DLBA group.

[f] Significantly different compared to the PLBD group.

Table 2. Effect of *APOE* on the risk of cognitive impairment in specific disease groups

	APOE4		*APOE2*	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Model 1 (control + each disease group)				
PAD	14.71 (6.54-33.10)	<0.001	NA	NA
LBVAD	7.73 (2.85-21.02)	<0.001	1.01 (0.28-3.57)	0.994
AD/DLB	9.07 (3.52-	<0.001	0.21 (0.26-	0.153

	23.37)		1.78)	
DLBA	5.52 (1.68-18.13)	0.005	0.71 (0.14-3.67)	0.680
PLBD	1.37 (0.54-3.47)	0.511	1.15 (0.42-3.16)	0.786
Model 1 (control + combined disease groups)				
ADCI (PAD + LBVAD + AD/DLB + DLBA)	8.90 (4.78-16.56)	<0.001	0.29 (0.11-0.73)	0.009
LBCI (LBVAD + AD/DLB + DLBA + PLBD)	4.06 (2.13-7.74)	<0.001	0.69 (0.31-1.52)	0.359
Typical AD (PAD + LBVAD + AD/DLB)	9.39 (4.98-17.71)	<0.001	0.24 (0.09-0.70)	0.009
Typical LBD (AD/DLB + DLBA + PLBD)	3.58 (1.80-7.10)	<0.001	0.62 (0.26-1.47)	0.277
Model 2 (all participants)				
ADCI	8.41 (4.81-14.71)	<0.001	0.20 (0.08-0.50)	0.001
LBCI	0.71 (0.40-1.27)	0.251	1.75 (0.77-3.98)	0.180
Model 3 (all participants)				
Typical AD	7.01 (4.18-	<0.001	0.21 (0.08-	0.002

	11.76)		0.56)	
Typical LBD	1.34 (0.76-2.34)	0.310	0.86 (0.38-1.94)	0.712

Abbreviations: *APOE* = apolipoprotein E; AD = Alzheimer's disease; LBD = Lewy body disease; ADCI = Alzheimer's disease-related cognitive impairment; LBCI = Lewy body disease-related cognitive impairment; PAD = pure Alzheimer's disease; LBVAD = Lewy body variant of Alzheimer's disease; AD/DLB = Alzheimer's disease with dementia with Lewy bodies; DLBA = dementia with Lewy bodies with amyloid deposition; PLBD = pure Lewy body disease; OR = odds ratio; CI = confidence interval; DWMH = deep white matter hyperintensities; PWMH = periventricular white matter hyperintensities.

Model 1 involved logistic regression analyses for the presence of each disease performed using all of the study participants with *APOE* genotype as a predictor. Model 2 involved logistic regression analyses for the presence of ADCI or LBCI while Model 3 involved logistic regression analyses for the presence of typical AD or typical LBD in all study participants. Covariates included age, sex, education, hypertension, diabetes mellitus, dyslipidemia, DWMH, PWMH, and the lacune number. Model 2 analyses for ADCI and LBCI were further controlled for LBCI and ADCI presence, respectively. Model 3 analyses for typical AD and typical LBD were further controlled for the presence of typical LBD and typical AD, respectively.

Table 3. Effects of *APOE4*, typical Alzheimer's disease, and typical Lewy body disease on neuropsychological test scores

Predictor	*APOE4*		Typical AD		Typical LBD		Typical AD * Typical LBD		*APOE4* * Typical LBD		*APOE4* * Typical AD	
Cognitive domain	β (SE)	*p* value	β (SE)	*p* value	β (SE)	*p* value	β (SE)	*p* value	β (SE)	*p* value	β (SE)	*p* value
Model 1												
Attention	0.16 (0.15)	0.272	-0.57 (0.18)	0.002	-0.99 (0.18)	<0.001	0.47 (0.28)	0.096				
Language	0.01 (0.16)	0.938	-1.36 (0.20)	<0.001	-1.65 (0.20)	<0.001	1.22 (0.31)	<0.001				
Visuospatial	-0.06 (0.33)	0.856	-1.27 (0.33)	<0.001	-2.86 (0.34)	<0.001	1.12 (0.53)	0.035				
Memory	0.14 (0.5)	0.351	-1.71 (0.13)	<0.001	-1.75 (0.12)	<0.001	1.73 (0.18)	<0.001				
Executive	0.05 (0.12)	0.664	-1.16 (0.12)	<0.001	-1.58 (0.12)	<0.001	1.10 (0.19)	<0.001				

K-MMSE	-0.40 (0.42)	0.339	-4.10 (0.52)	<0.001	-4.99 (0.52)	<0.001[a]	2.19 (0.80)	0.007				
CDR-SOB	0.89 (0.26)	0.001	1.76 (0.32)	<0.001	3.46 (0.32)	<0.001	-1.47 (0.50)	0.003				
Model 2												
Attention									0.39 (0.30)	0.200	-0.47 (0.30)	0.115
Language									-0.28 (0.33)	0.400	0.05 (0.32)	0.870
Visuospatial									0.54 (0.53)	0.306	-0.72 (0.52)	0.164
Memory									0.02 (0.18)	0.932	-0.52 (0.18)	0.003
Executive									-0.06 (0.19)	0.767	-0.25 (0.18)	0.169
K-MMSE									-0.97 (0.86)	0.262	-1.62 (0.84)	0.055
CDR-SOB									1.46 (0.53)	0.006	0.48 (0.52)	0.359
Model 3												
Memory	0.11 (0.12)	0.345	-1.71 (0.13)	<0.001	-1.76 (0.11)	<0.001	1.71 (0.17)	<0.001			-0.52 (0.18)	0.003
CDR-SOB	0.30 (0.33)	0.363	2.04 (0.33)	<0.001	3.12 (0.34)	<0.001	-2.03 (0.53)	<0.001	1.46 (0.53)	0.006		

Abbreviations: *APOE4* = apolipoprotein E4; AD = Alzheimer's disease; LBD = Lewy body disease; DWMH = deep white matter hyperintensities; PWMH = periventricular white matter hyperintensities.

Data represent results of general linear models for neuropsychological test scores after controlling for age, sex, education, hypertension, diabetes mellitus type 2, hyperlipidemia, DWMH, PWMH, and the lacune number. Model 1 used *APOE4*, typical LBD, typical AD, and typical AD * typical LBD as predictors. Model 2 tested the significance of *APOE4* * typical AD and *APOE4* * typical LBD by adding one of the two interaction terms as a predictor to Model 1. Model 3 used *APOE4*, typical LBD, typical AD, and the significant interaction terms from Model 2 as predictors.

Table 4. Effects of *APOE4*, Alzheimer's disease, and Lewy body disease on hippocampal volume

Predictors	Mean hippocampal volume		Right hippocampal volume		Left hippocampal volume	

	β (SE)	*p* value	β (SE)	*p* value	β (SE)	*p* value
Model 1						
APOE4	-9.39 (46.99)	0.842	-0.44 (52.79)	0.993	-18.34 (47.63)	0.700
Typical AD	-568.99 (57.47)	<0.001	-581.83 (64.56)	<0.001	-556.15 (58.25)	<0.001
Typical LBD	-329.74 (57.08)	<0.001	-365.47 (64.12)	<0.001	-294.01 (57.85)	<0.001
Typical AD * Typical LBD	391.73 (89.90)	<0.001	453.19 (101.00)	<0.001	330.27 (91.12)	<0.001
Model 2						
APOE4 * Typical AD	-152.43 (94.25)	0.107	-112.04 (106.15)	0.292	-192.82 (95.29)	0.044
APOE4 * Typical LBD	114.68 (96.12)	0.234	139.85 (107.94)	0.196	89.50 (97.53)	0.359
Model 3						
APOE4	-9.39 (46.99)	0.842	-0.44 (52.79)	0.993	71.10 (64.80)	0.273
Typical AD	-568.99 (57.47)	<0.001	-581.83 (64.56)	<0.001	-473.87 (70.79)	<0.001
Typical LBD	-329.74 (57.08)	<0.001	-365.47 (64.12)	<0.001	-303.20 (57.74)	<0.001
Typical AD * Typical LBD	391.73 (89.90)	<0.001	453.19 (101.00)	<0.001	335.76 (90.70)	<0.001
APOE4 * Typical AD					-192.82 (95.29)	0.044

Abbreviations: *APOE4* = apolipoprotein E4; AD = Alzheimer's disease; LBD = Lewy body disease; FBB = ^{18}F-Florbetaben; ICV = intracranial volume; SUVR = standardized uptake value ratio; SE = standard error; DWMH = deep white matter hyperintensities; PWMH = periventricular white matter hyperintensities.

Data represent results of general linear models for the mean, right, or left hippocampal volume after controlling for age, sex, education, hypertension, diabetes mellitus type 2, dyslipidemia, DWMH, PWMH, lacune number, and ICV. Model 1 used *APOE4*, typical AD, typical LBD, and typical AD*typical LBD as predictors. Model 2 tested the significance of the interaction terms (*APOE4* * typical AD or *APOE4* * typical LBD) by adding one of the two interaction terms as a predictor to Model 1. Model 3 used *APOE4*, typical AD, typical LBD, typical AD * typical LBD and the significant interaction terms in Model 2 as predictors. Ten participants in the healthy control group were excluded from this analysis because no 3D T1 image was taken. Hippocampal volume could not be extracted because of issues with preprocessing quality in two, three, one, and two participants of PAD, AD/DLB, PLBD, and healthy control groups, respectively. Finally, 114, 55, 32, 39, 21, and 55 participants with normal cognition, PAD, LBVAD, AD/DLB, DLBA, and PLBD, respectively, were included.

Table 5. Effects of *APOE4*, Alzheimer's disease, and Lewy body disease on the regional ^{18}F-Florbetaben standardized uptake value ratio

Predictors	Global SUVR		Frontal SUVR		Temporal SUVR		Parietal SUVR		Occipital SUVR	
	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value
Model 1										
APOE4	0.09 (0.05)	0.058	0.10 (0.05)	0.039	0.06 (0.05)	0.223	0.08 (0.05)	0.079	0.02 (0.04)	0.574
Typical AD	0.46 (0.06)	<0.001	0.47 (0.06)	<0.001	0.42 (0.06)	<0.001	0.45 (0.06)	<0.001	0.28 (0.06)	< 0.001
Typical LBD	0.00 (0.06)	0.987	-0.02 (0.06)	0.779	0.02 (0.60)	0.764	0.01 (0.06)	0.929	0.06 (0.06)	0.265
Model 2										

APOE4 * Typical AD	-0.13 (0.10)	0.171	-0.10 (0.10)	0.318	-0.13 (0.10)	0.194	-0.16 (0.10)	0.096	-0.13 (0.09)	0.148
APOE4 * Typical LBD	0.13 (0.09)	0.171	0.11 (0.10)	0.278	0.12 (0.09)	0.207	0.14 (0.09)	0.133	0.25 (0.08)	0.004
Model 3										
APOE4	0.09 (0.05)	0.058	0.10 (0.05)	0.039	0.06 (0.05)	0.223	0.08 (0.05)	0.079	-0.12 (0.06)	0.069
Typical AD	0.46 (0.06)	<0.001	0.47 (0.06)	<0.001	0.42 (0.06)	<0.001	0.45 (0.06)	<0.001	0.25 (0.06)	< 0.001
Typical LBD	0.00 (0.06)	0.987	-0.02 (0.06)	0.779	0.02 (0.60)	0.764	0.01 (0.06)	0.929	-0.09 (0.08)	0.223
APOE4 * Typical LBD									0.25 (0.08)	0.004

Abbreviations: *APOE4* = *apolipoprotein E4*; AD = Alzheimer's disease; LBD = Lewy body disease; FBB = ^{18}F-Florbetaben; SUVR = standardized uptake value ratio; SE = standard error; DWMH = deep white matter hyperintensities; PWMH = periventricular white matter hyperintensities.

Data represent results of general linear models for global or mean lobar FBB SUVR after controlling for age, sex, education, hypertension, diabetes mellitus type 2, dyslipidemia, DWMH, PWMH, and the lacune number. This analysis was performed for all participants except normal controls. The result of analysis performed for all participants including normal controls is provided in Supplementary Table 1. Model 1 used *APOE4*, typical LBD, and typical AD as predictors. Model 2 tested the significance of the interaction terms (*APOE4* * typical AD or *APOE4* * typical LBD) by adding one of the two interaction terms as a predictor to Model 1. Model 3 used *APOE4*, typical LBD, typical AD, and the significant interaction terms in Model 2 as predictors.