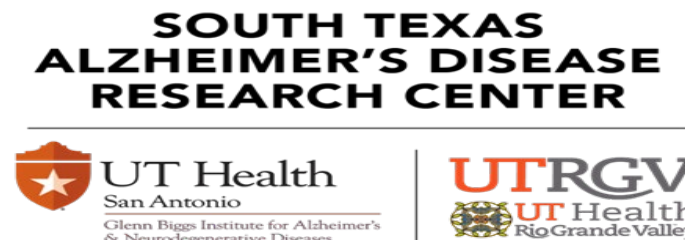


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on behalf of the African Initiative on Bioinformatics Online Training in Neurodegenerative Diseases (AI-BOND), The University of Texas Health Science Center at San Antonio, and South Texas Alzheimer's Disease Research Center.



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INTRODUCTION

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-β plaques and tau neurofibrillary tangles, and frequently co-occurs with additional brain co-pathologies, including Lewy body pathology (LBP). Whether LBP modifies the association between APOE genotype and AD neuropathology remains unclear.

We examined whether LBP modifies the association between APOE genotype and Alzheimer-related neuropathologic measures using National Alzheimer’s Coordinating Center (NACC) dataset.

We hypothesized that LBP attenuates the strength of association between APOE genotype and AD neuropathologic burden, reflecting interactions between co-occurring proteinopathies.

METHODS

We evaluate the modifying effect of LBP on the relationship between APOE genotype and AD neuropathologic burden: AD neuropathologic change score, Thal phase, CERAD neuritic plaque density, diffuse plaques, and Braak tangle stage.

We included NACC autopsied participants with complete AD neuropathologic and LBP assessments. Participants were classified by APOE genotype as ε4 noncarriers (ε22, ε23, ε33), ε4 heterozygote (ε24, ε34), or ε4 homozygotes (ε44). LBP was defined as presence or absence.

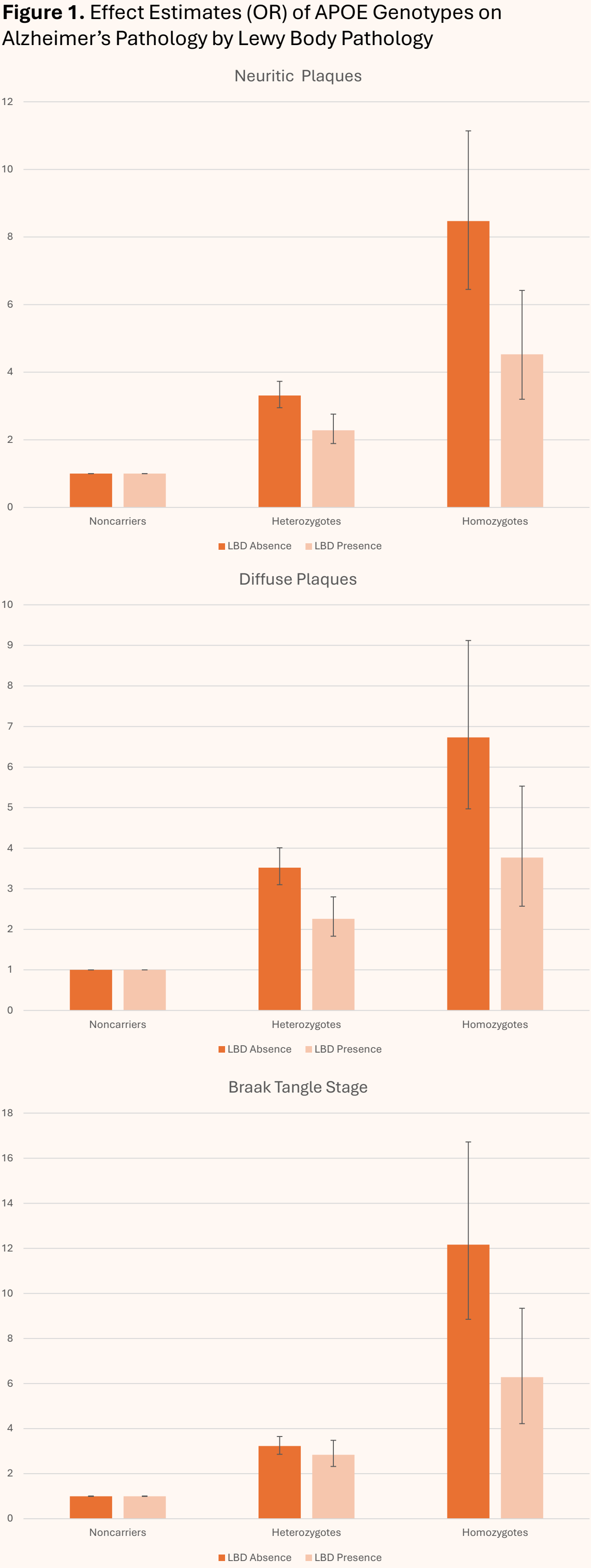
Ordinal or simple Logistic regression models adjusting for age, age-squared, sex, self-reported ancestry, and education were used. Odds ratios compared ε4 heterozygotes and homozygotes with noncarriers.

Statistical significance was set at false discovery rate-corrected α=0.05.



RESULTS

Table 1. Participants Characteristic				
Characteristic	Overall	APOE ε4 Allele		
		ε33, ε22	ε24, ε34	ε44
N	7153	3998	2567	588
Age, years, mean (SD)	79 (12)	80 (12)	78 (11)	75 (9)
Female	3405 (48)	1924 (48)	1218 (47)	263 (45)
Education, years				
Up to High School	1629 (23)	913 (23)	592 (23)	124 (21)
Some College	1298 (18)	738 (18)	442 (17)	118 (20)
Bachelor’s Degree	2034 (28)	1113 (28)	756 (30)	165 (28)
Postgraduate Degree	2192 (31)	1234 (31)	777 (30)	181 (31)
Self-reported Ancestry				
White	6758 (95)	3800 (95)	2414 (94)	544 (93)
Black or African American	303 (4)	134 (3)	130 (5)	39 (6)
Other	92 (1)	64 (2)	23 (1)	5 (1)
Hispanic or Latino	225 (3)	140 (4)	69 (3)	16 (3)
Systolic Blood Pressure, mean (SD)	131 (20)	131 (20)	131 (20)	130 (19)
Diastolic Blood Pressure, mean (SD)	73 (11)	73 (11)	73 (11)	74 (10)
Smoking Status	3207 (46)	1835 (47)	1127 (46)	245 (44)
Lipid Lowering Medication Use	2425 (35)	1296 (33)	911 (36)	218 (37)
Hypertension Treatment	193 (3)	109 (3)	70 (3)	14 (2)
Alzheimer’s Disease Neuropathologic Change (ADNC)				
No or low ADNC	1338 (31)	1089 (46)	236 (15)	13 (4)
Intermediate or High ADNC	2921 (69)	1286 (54)	1298 (85)	337 (96)
Thal Phase				
Phase 0	582 (14)	530 (22)	49 (3)	3 (1)
Phase 1 and 2	618 (14)	458 (19)	149 (10)	11 (3)
Phase 3	510 (12)	334 (14)	158 (10)	18 (5)
Phase 4	2602 (60)	1094 (45)	1189 (77)	319 (91)
Neuritic Plaques				
None	1695 (24)	1427 (36)	258 (11)	10 (2)
Sparse	917 (13)	558 (14)	319 (12)	40 (7)
Moderate	1345 (18)	765 (19)	496 (19)	84 (14)
Frequent	3196 (45)	1248 (31)	1494 (58)	454 (77)
Diffuse Plaques				
None	998 (15)	865 (24)	123 (5)	10 (2)
Sparse	854 (13)	592 (16)	233 (10)	29 (5)
Moderate	1087 (16)	652 (18)	371 (15)	64 (12)
Frequent	3675 (56)	1569 (42)	1667 (70)	439 (81)
Braak Tangle Stage				
Stage 0	383 (5)	319 (8)	64 (3)	0
Stage I and Stage II	1333 (19)	1042 (27)	272 (11)	19 (3)
Stage III and Stage IV	1716 (24)	1114 (29)	536 (21)	66 (11)
Stage V and Stage VI	3606 (51)	1431 (37)	1675 (66)	500 (86)
Other Brain Pathologies				
Lewy Body Pathology	2006 (29)	905 (23)	850 (35)	251 (46)
Numbers are reported as n(%), unless otherwise stated.				



CONCLUSIONS

Our findings suggest that LBP, modifies the association between APOE ε4 and AD-related neuropathology: APOE ε4 heterozygotes and homozygotes showed significant associations with parenchymal amyloid and tau pathology both in the presence and absence of LBP, but the strength of these associations was attenuated among individuals with LBP.

Further clarifying APOE–LBP relationships may improve understanding of how co-occurring proteinopathy shape disease severity and progression, inform clinicopathologic heterogeneity in mixed AD/LBD, and aid in the stratification of participants in biomarkers and therapeutic trials where co-pathologies may influence APOE-related associations.

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REFERENCES

- Walker et al., 2023. Cognitive resistance to and resilience against multiple comorbid neurodegenerative pathologies and the impact of APOE status. Journal of Neuropathology & Experimental Neurology. 82(2):110-119
- Robinson et al., 2021. The development and convergence of co-pathologies in Alzheimer's disease. Brain. 144(3):953-962.
- Talyansky et al 2023 APOE-ε4 and BIN1 increase risk of Alzheimer’s disease pathology but not specifically of Lewy body pathology. Journal of Acta Neuropathologica Communications 11, 149.
- Alzheimer's Disease Research Center. (n.d.). Uniform data set (UDS) 3.0: Researcher data dictionary (RDD). University of Washington. Retrieved from <https://files.alz.washington.edu/documentation/uds3-rdd.pdf>
- Alzheimer's Disease Research Center. (n.d.). Researcher data dictionary: Neuropsychology (RDD-NP). University of Washington. Retrieved from <https://files.alz.washington.edu/documentation/rdd-np.pdf>