



Sex differences for clinical impact of *APOEε4* mediated by Alzheimer's pathology in people with Lewy body pathology

Ece Bayram¹ (drecebayram@gmail.com), Brianne Bettcher¹, Samantha Holden¹ | ¹Department of Neurology, University of Colorado Anschutz, Aurora, CO, USA

Background

- In Alzheimer's disease (AD), *APOEε4* is associated with worse cognition for females.
- APOEε4* impacts phenotype of Lewy body (LB) disease (LBD) through both direct and indirect AD pathology-related mechanisms.
- As clinical correlations of AD and LB pathologies differ by sex, *APOEε4* effect on clinical profile may differ by sex in LBD in relation to these pathologies.

Objective: Assess whether AD or LB pathologies mediate the association between *APOEε4* and clinical profile differently for females and males with LB pathology

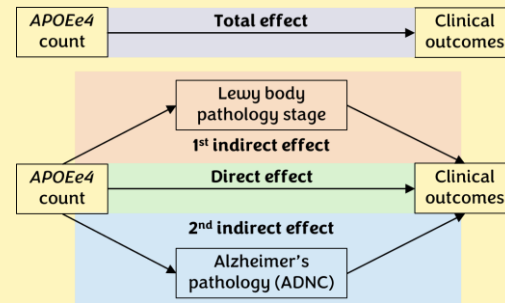
Methods

- 178 females, 293 males with LB pathology and no other neurodegenerative pathology from National Alzheimer's Coordinating Center

	Females (n=178)	Males (n=293)
Age at last visit	75.52 (11.43)	73.71 (10.31)
Age at death	78.29 (11.06)	76.24 (9.86)
Years of education *	15.11 (2.86)	16.31 (2.92)
<i>APOEε4</i> count		
-0	69 (38.8)	127 (43.3)
-1	82 (46.1)	127 (43.3)
-2	27 (15.2)	39 (13.3)
Lewy body pathology stage		
-Olfactory	47 (26.4)	61 (20.8)
-Amygdala	21 (11.8)	18 (6.1)
-Brainstem	15 (8.4)	36 (12.3)
-Limbic	30 (16.9)	43 (14.7)
-Neocortical	65 (36.5)	135 (46.1)
NIA-AA Alzheimer's disease neuropathologic change score (ADNC) *		
-0	4 (2.2)	13 (4.4)
-1	8 (4.5)	37 (12.6)
-2	33 (18.5)	62 (21.2)
-3	133 (74.7)	181 (61.8)
Clinical diagnosis of Lewy body disease *	36 (20.2)	108 (36.9)
Clinical diagnosis of Alzheimer's disease	137 (77)	196 (66.9)

Variables are reported as mean (standard deviation) or count (percentage).
Statistical significance marked with * for false discovery rate-adjusted $q < .05$.

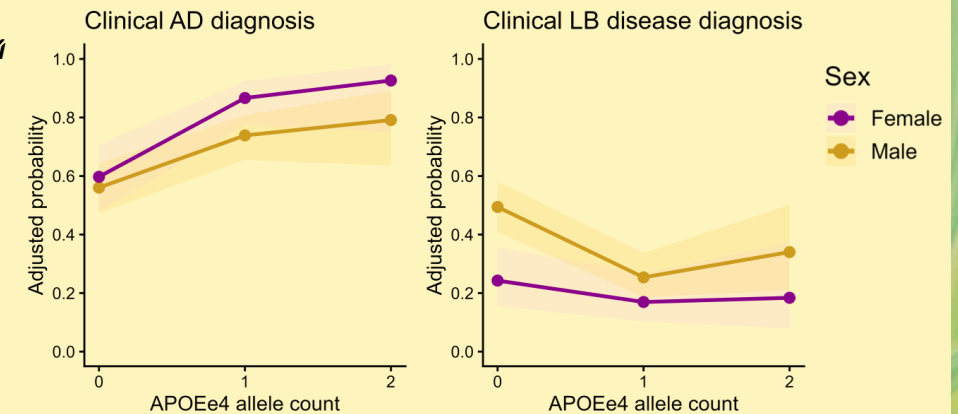
- Parallel mediation models with nonparametric bootstrapping (1000 iterations) including age at last visit as covariate to assess whether *APOEε4* effect on clinical outcomes at last visit is mediated by LB or AD pathology (ADNC).
- False discovery rate used for multiple comparisons.



Results

- APOEε4* was associated with lower likelihood of parkinsonism and higher likelihood of memory decline, delusions, clinical AD diagnosis for females; lower likelihood of gait changes, bradykinesia, clinical LBD diagnosis and higher likelihood of orientation, language decline, clinical AD diagnosis for males.

- Compared to males, *APOEε4* association with higher likelihood for clinical AD diagnosis was stronger; clinical LBD diagnosis was weaker for females.



- For females, *APOEε4* association with clinical AD diagnosis was partially mediated by AD pathology. For males, *APOEε4* associations with bradykinesia, language, clinical diagnoses were mediated by AD pathology.
- LB pathology was not a significant mediator.

Conclusions

- For people with LB pathology, *APOEε4* can have sex-specific effects on clinical profile mediated by AD pathology.
- Sex differences should be considered to improve the determination of genetic and pathology targets for risk and treatments in LBD.

Acknowledgments: This work was supported by research funding from NIA R00AG073453. The NACC database is funded by NIA/NIH Grant U24 AG072122. NACC data are contributed by the NIA-funded ADCRs: P30 AG062421 (PI James Brewer, MD, PhD), P30 AG066468 (PI Oscar Lopez, MD), P30 AG062421 (PI Teresa Gomez-Isla, MD), P30 AG066509 (PI Thomas Grabowski, MD), P30 AG066514 (PI Mary Sano, PhD), P30 AG066530 (PI Helena Chui, MD, Arthur Toga, PhD), P30 AG066507 (PI Marilyn Albert, PhD), P30 AG066444 (PI David Holtzman, MD), P30 AG066518 (PI Lisa Silbert, MD, Kevin Duff, PhD), P30 AG066512 (PI Thomas Wisniewski, MD), P30 AG066462 (PI Scott Small, MD), P30 AG072979 (PI David Wolk, MD), P30 AG072972 (PI Charles DeCarli, MD, Rachel Whitmer, PhD), P30 AG072976 (PI Andrew Saykin, PhD), P30 AG072975 (PI Julie Schneider, MD, MS), P30 AG072978 (PI Ann McKee, MD), P30 AG072977 (PI Robert Vassar, PhD), P30 AG066519 (PI Joshua Grill, PhD), P30 AG062677 (PI Brad Boeve, MD, Ronald Petersen, MD, PhD), P30 AG079280 (PI Jessica Langbaum, PhD), P30 AG062422 (PI Gil Rabinouici, MD), P30 AG066511 (PI Allan Levey, MD, PhD), P30 AG072946 (PI Linda Van Eldik, PhD), P30 AG062715 (PI Sanjay Asthana, MD, FRCP), P30 AG072973 (PI Russell Swerdlow, MD), P30 AG066506 (PI Glenn Smith, PhD, ABPP, David Lowenstein, PhD, Ranjan Duara, MD), P30 AG066508 (PI Stephen Strittmatter, MD, PhD, Christopher Van Dyck, MD), P30 AG066515 (PI Victor Henderson, MD, MS), P30 AG072947 (PI Suzanne Craft, PhD), P30 AG072931 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI Sudha Seshadri, MD, Gladys Maestre, MD, PhD), P30 AG086401 (PI Erik Roberson, MD, PhD), P30 AG086404 (PI Gary Rosenberg, MD), P30 AG086403 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD, Gwenn Garden, MD, PhD), P30 AG072959 (PI Jagan Pillai, MD, PhD), P30 AG092752 (Ihab Hajjar, MD, MS).