

Biological Sex And APOE4 As Determinants Of Apathy Presence And Severity In Alzheimer’s Disease

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Introduction

- **Apathy** is a core neuropsychiatric symptom in Alzheimer’s disease (AD), characterized by a loss of motivation affecting behaviour, cognition, and emotion.
- Despite affecting ~65% of individuals with AD, apathy is frequently overlooked, yet it is an independent contributor to functional decline, increased caregiver dependence, and greater care burden beyond cognitive impairment alone.
- While **APOE4** is strongly linked to increased AD risk and earlier disease onset, its relationship with apathy appears largely indirect and mediated by overall disease severity.

Gap: The role of APOE4 in apathy has not been well characterized.

Objective: To investigate whether sex, APOE4 carrier status, and AD-related blood biomarkers are associated with apathy presence in individuals with AD.

Hypothesis: Male APOE4 carriers would show a higher likelihood of apathy presence and severity.

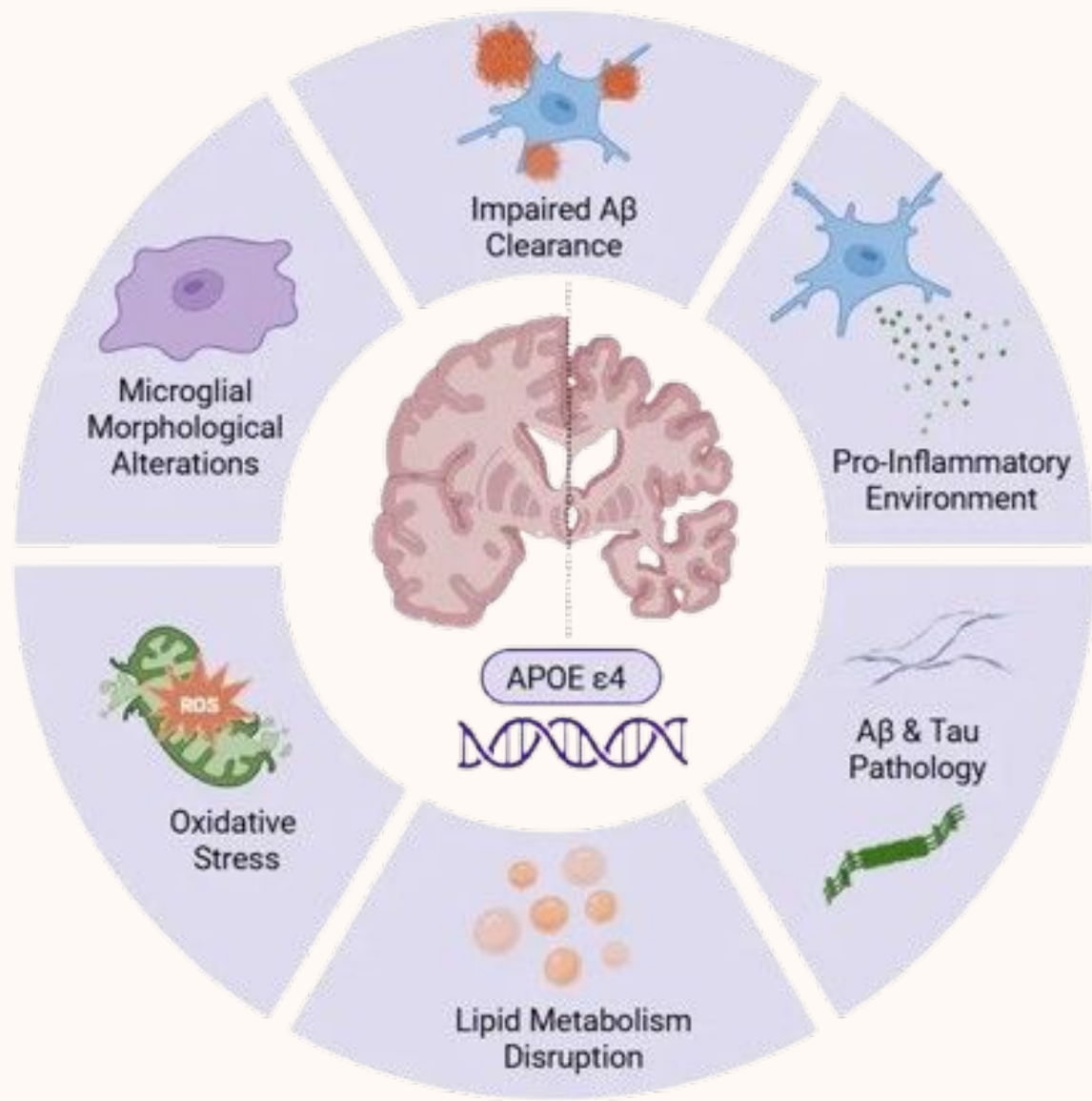


Figure 1. Summary of the effects of APOE4 in Alzheimer's disease risk, neuropathology, and brain structure reported in the literature.

Methods

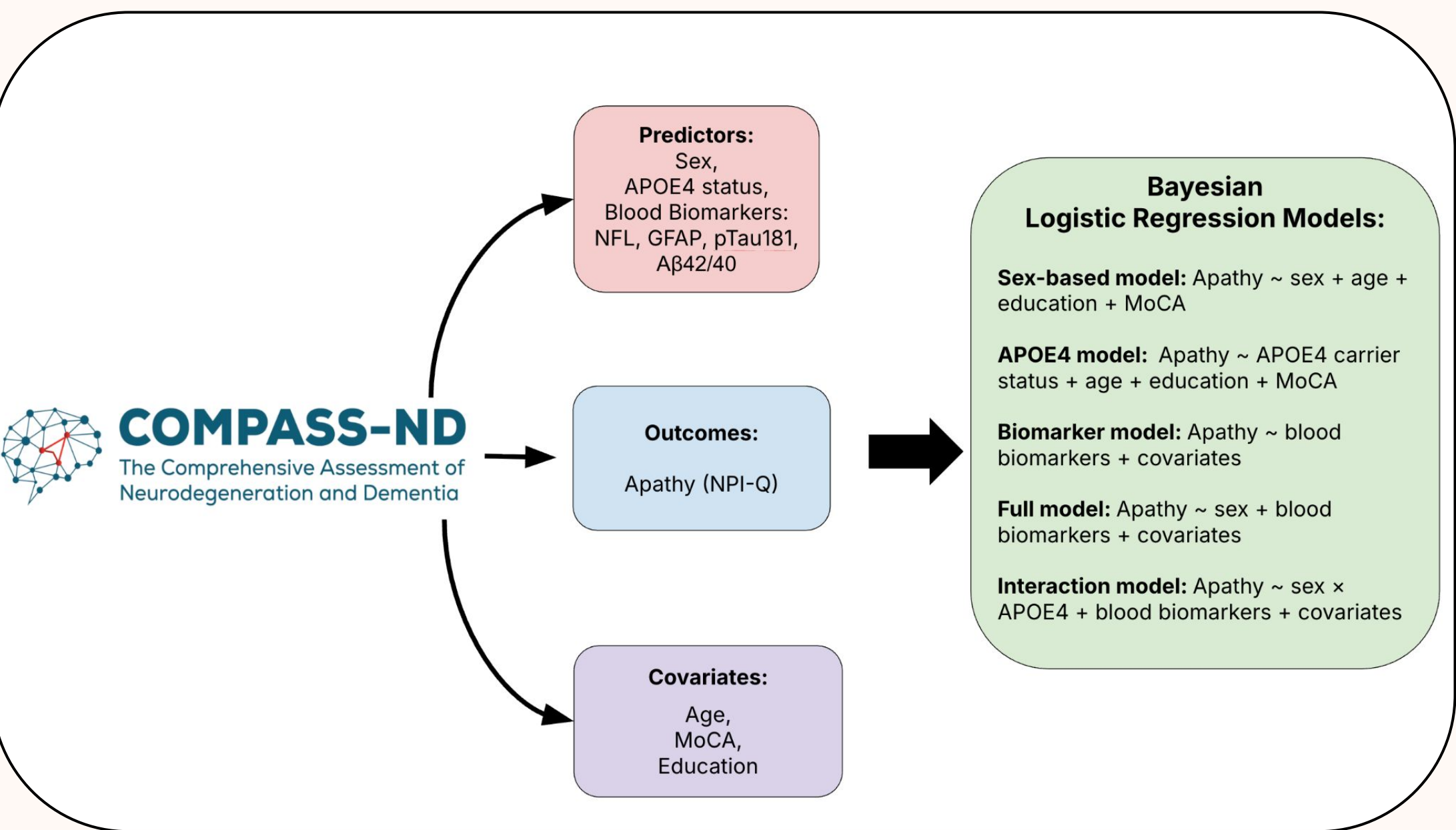


Figure 2 - Flowchart illustrating the predictors, covariates, and outcome used in the statistical analysis of apathy in AD among individuals within the COMPASS-ND cohort

Results

	Females (n = 80)	Males (n = 99)	Effect Size	Significance
Demographic Variables				
Age, years (mean ± SD)	75 ± 8	76 ± 7	$d = -.12$	NS
MOCA score (mean ± SD)	17.20 ± 4	18.90 ± 3.9	$d = -.45$	NS
Years of Education (mean ± SD)	14.49 ± 2.71	15.39 ± 3.14	$d = -.31$	$p < .001$
Clinical Variables				
APOE4 homozygotes (%)	13.75	13.13	$V = -.025$	NS
Apathy (NPI-Q; %)	38	55	$\phi = 0.17$	$p < .05$
NPS Burden (NPI-Q; mean ± SD)	2.49 ± 1.64	2.55 ± 1.59	$d = -.04$	NS
Distribution of Blood Biomarkers (SIMOA)				
Neurofilament Light Chains (NFL; mean ± SD)	36 ± 21	31 ± 18	$d = .25$	$p < .01$
Glial Fibrillary Acidic Protein (GFAP; mean ± SD)	279 ± 124	207 ± 120	$d = .59$	$p < .001$
Phosphorylated Tau 181 (pTau181; mean ± SD)	4.40 ± 1.49	4.16 ± 2.14	$d = 0.13$	NS
Amyloid 42/40 Ratio (Aβ42/40; mean ± SD)	0.058 ± 0.007	0.061 ± 0.016	$d = -0.20$	NS

Table 1. Participant Demographics and Clinical Characteristics. Males had significantly more years of education ($p < .001$) and a higher prevalence of apathy ($p < .05$). Females exhibited significantly higher concentrations of NFL ($p < .01$) and GFAP ($p < .001$), with a moderate effect size observed for GFAP ($d = 0.59$).

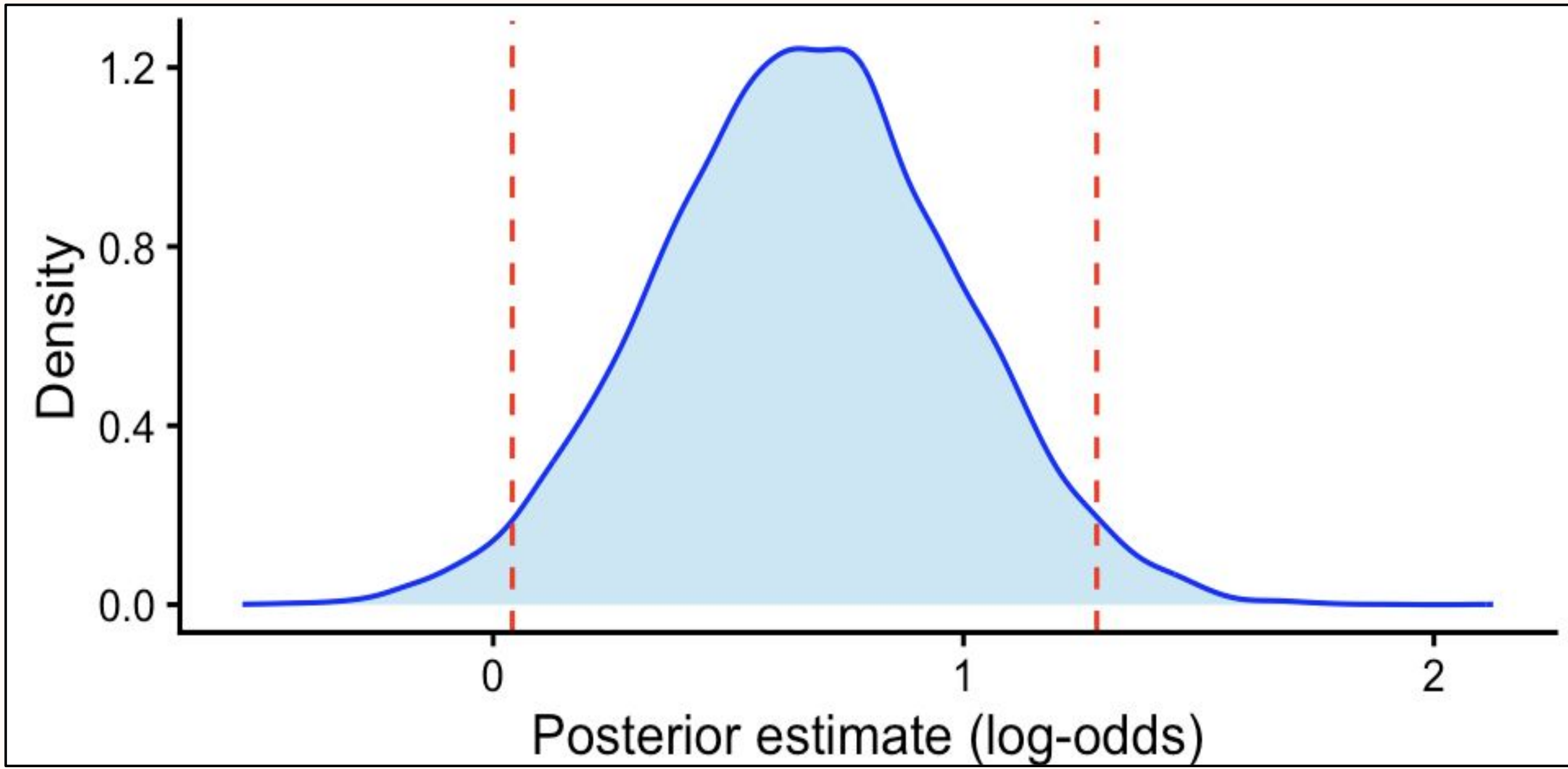


Figure 3. Posterior Estimates of Predictors of Apathy Presence. Male sex was associated with greater odds of apathy ($\beta = 0.66$, 95% CrI [0.04, 1.28], $P(\beta > 0) > 0.95$).

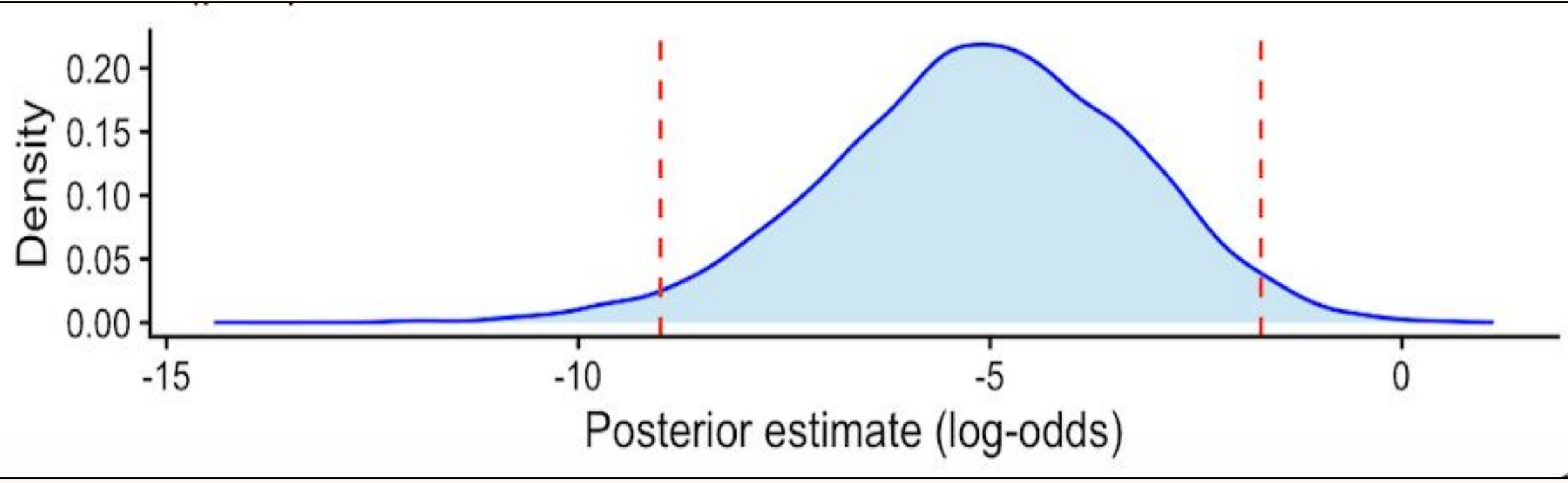


Figure 4. Posterior Distribution of the Sex × APOE4 Interaction Effect on Apathy Severity. Posterior distribution of the sex × APOE4 interaction term from a Bayesian regression model predicting apathy severity, shows a strong negative association ($\beta = -5.12$, 95% CrI [-9.00, -1.71], $P(\beta < 0) > 0.95$).

Discussion

- Sex consistently predicted apathy, with males showing higher posterior probabilities of increased apathy across models, and this effect remaining robust after adjustment for demographic and biomarker variables.
- Evidence of effect modification by sex was observed for APOE4, with a strong interaction signal in the full model, indicating that APOE4–apathy associations may differ by sex.
- Biomarker associations were generally modest but suggestive, with NFL and GFAP showing the most consistent positive directional effects across models, although uncertainty remained and credible intervals often included zero.

Future Directions

- Integrate multimodal biomarker frameworks, combining fluid biomarkers with neuroimaging and cognitive profiles to better capture the neurobiological substrates of apathy.
- Longitudinal modelling is needed to clarify directionality, as current cross-sectional associations cannot distinguish whether sex, APOE4 status, or biomarkers such as NFL and GFAP contribute to the development versus progression of apathy over time.

Acknowledgements

Data used in this study were obtained from the COMPASS-ND cohort, a part of the Canadian Consortium on Neurodegeneration in Aging (CCNA). The CCNA is supported by a grant (CNA-137794, CNA-163902) from the Canadian Institutes of Health Research, with additional support from the BRAIN grant (BDO-148341). Data are hosted via the LORIS neuroinformatics platform.

We would also like to acknowledge the contributions of Team 11, whose work and support were instrumental to this project.