

Background: In previous work we found that Colombian PSEN1 asymptomatic carriers had small negative mutation effects on thalamic, but not basal forebrain or hippocampal volumes, contrasting with sporadic AD evidence^[1-3]. Here, we aimed to extend this work using Bayesian statistics and include our prior knowledge.

Methods: We analyzed DIAN baseline cases with complete imaging and genetic data (PSEN1: n = 258, 73.7%; PSEN2: n = 27, 7.7%; APP: n = 65, 18.6%) (**Table**). Hippocampal and thalamic volumes were extracted in FreeSurfer. Basal forebrain was segmented in CAT12. Volumes were intracranial-volume corrected and z-standardized. Bayesian multilevel models estimated carrier effects adjusted for sex, age, education. Prior sensitivity was assessed using flat informative and informed priors derived from our previous Colombian PSEN1 findings. Sensitivity analysis stratified results for Clinical Dementia Rating (CDR)’s stages.

Characteristic	Overall	Carrier	Non-carrier
Sex: male	246 (42.6%)	150 (42.9%)	96 (42.3%)
Sex: female	331 (57.4%)	200 (57.1%)	131 (57.7%)
Age at visit, years*	36.00 [29.00, 45.00]	36.00 [29.00, 46.00]	36.00 [29.00, 43.50]
Education, years*	14.00 [12.00, 16.00]	14.00 [12.00, 16.00]	15.00 [13.00, 16.00]
CDR: Preclinical CDR=0	449 (77.8%)	234 (66.9%)	215 (94.7%)
CDR: Prodromal CDR=0.5	84 (14.6%)	72 (20.6%)	12 (5.3%)
CDR: Clinical CDR>0.5	44 (7.6%)	44 (12.6%)	0 (0.0%)
N	577	350	227

Table. Demographic characteristics. (*) Here are reported median and interquartal ranges [IQR]

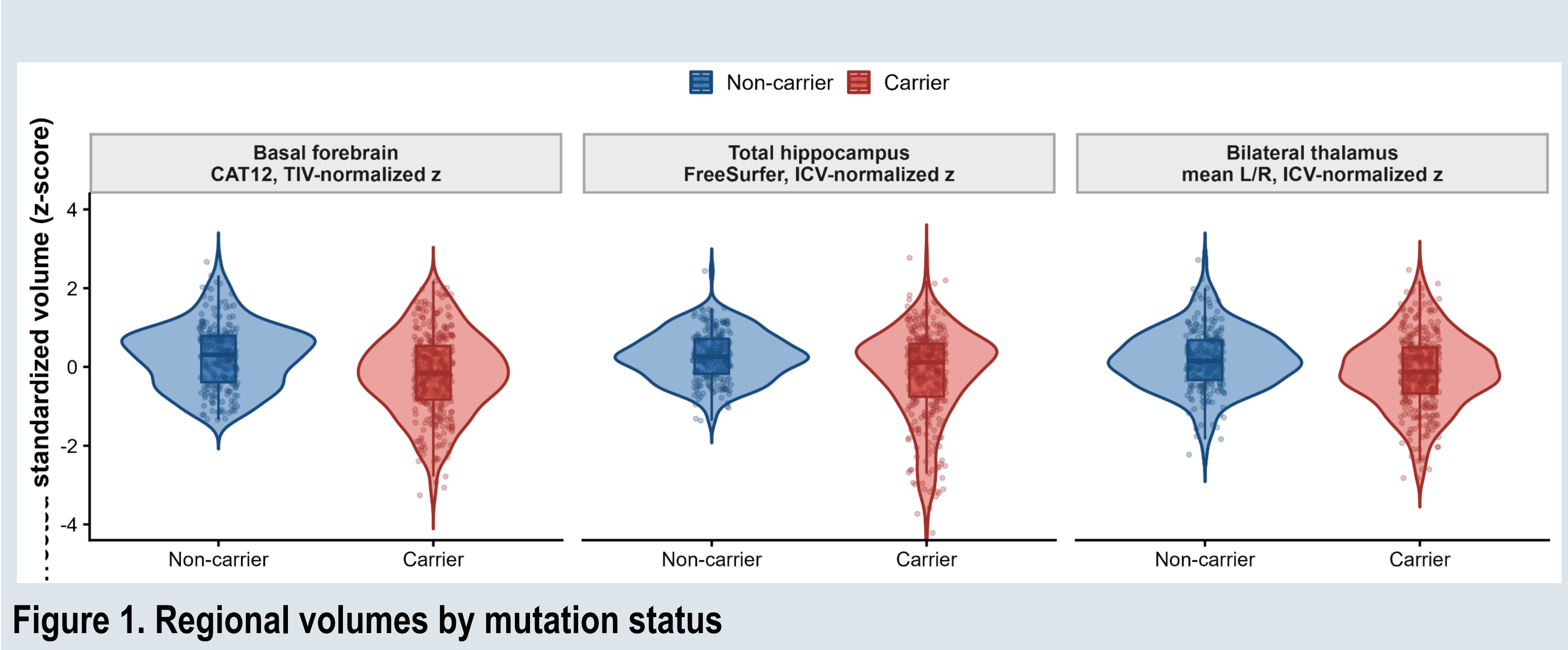


Figure 1. Regional volumes by mutation status

Conclusions: We replicated our prior Colombian PSEN1 findings of lower thalamic volumes and extended them by demonstrating robust hippocampal and basal forebrain volume reductions in the DIAN-ADAD cohort. Bayesian prior analyses confirmed that these effects were stable across flat/weak and informed priors, supporting evidence for shared subcortical vulnerability between ADAD and sporadic AD. Sensitivity analyses indicated early signs of volume reduction, with progressively greater reductions from preclinical to prodromal and clinical stages.

References: ^[1]Teipel, S., Grazia, A., Dyrba, M. *et al. Sci Rep* (2024); ^[2]Grazia, A., Dyrba, M., Pomara, N., *et al. JPAD* (2025); ^[3]Teipel, S., Baena, A., He, B. *et al.DADM* (2025).

Results: Mutation carriers showed consistently lower regional volumes than non-carriers across basal forebrain, hippocampal and thalamic ROIs (**Figure 1**). Basal forebrain showed a robust negative carrier effect under both the flat/weak prior, $\beta = -0.406$ $[-0.539, -0.271]$, $P(\beta < 0) > .999$, and the informed prior, $\beta = -0.370$ $[-0.492, -0.247]$, $P(\beta < 0) > .999$. Similar negative effects were observed for left, right, and total hippocampal volumes, with informed-prior estimates ranging from $\beta = -0.336$ to -0.352 . Thalamic effects were also negative, with a smaller effect in the left thalamus, $\beta = -0.178$ $[-0.320, -0.036]$, $P(\beta < 0) = .994$, and a stronger effect in the right thalamus, $\beta = -0.321$ $[-0.448, -0.194]$, $P(\beta < 0) > .999$ (**Figure 2**).

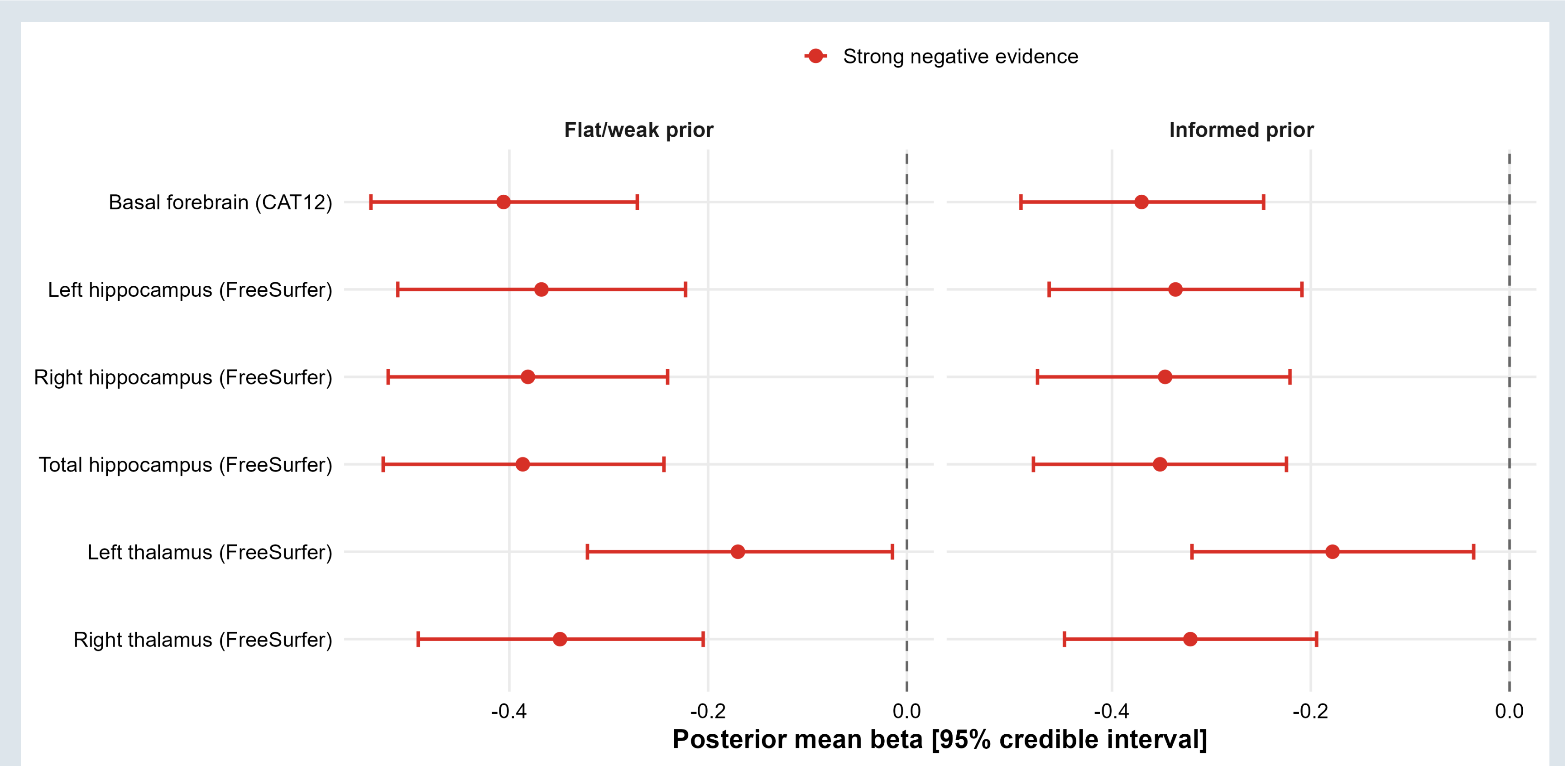


Figure 2. Bayesian carrier effects across regions. Points show posterior mean β and bars show 95% credible intervals; values below zero indicate lower regional volumes in mutation carriers.

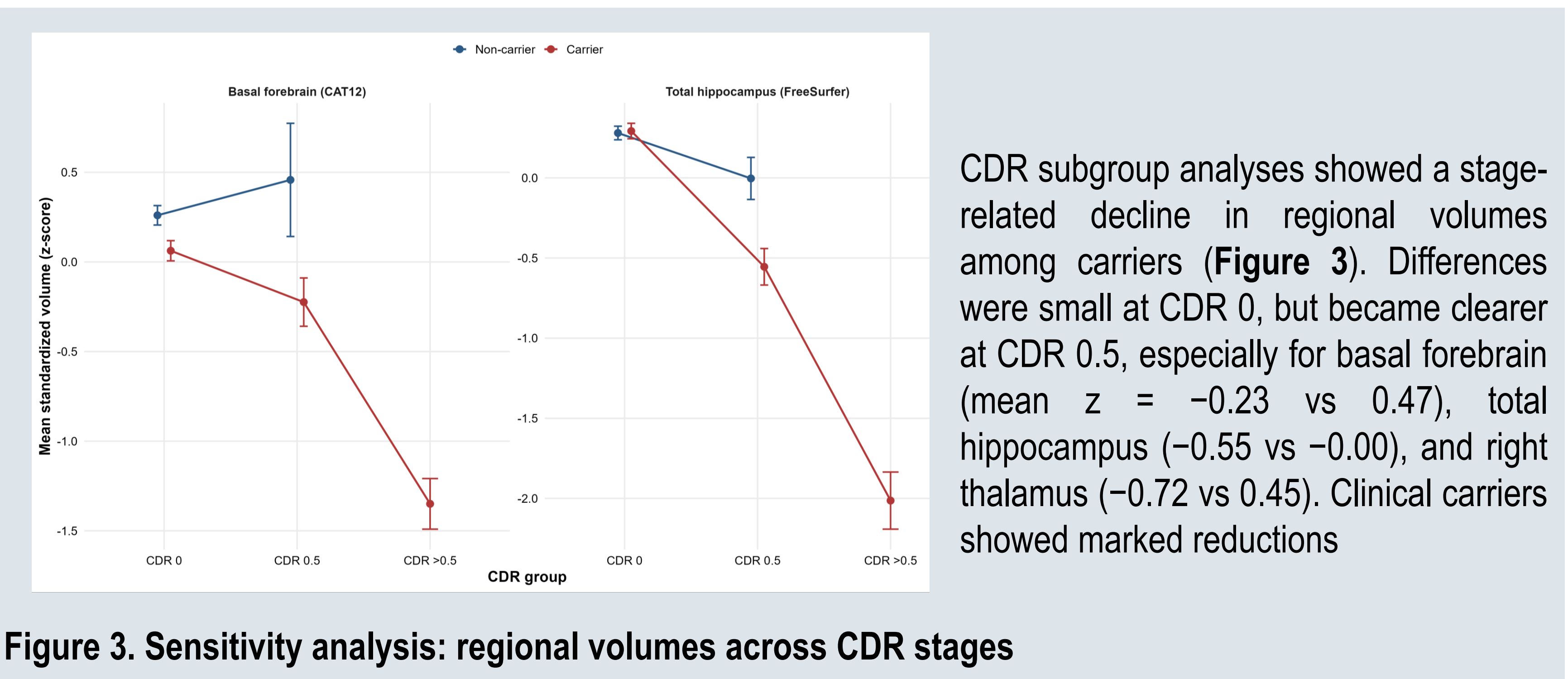


Figure 3. Sensitivity analysis: regional volumes across CDR stages

CDR subgroup analyses showed a stage-related decline in regional volumes among carriers (**Figure 3**). Differences were small at CDR 0, but became clearer at CDR 0.5, especially for basal forebrain (mean $z = -0.23$ vs 0.47), total hippocampus (-0.55 vs -0.00), and right thalamus (-0.72 vs 0.45). Clinical carriers showed marked reductions