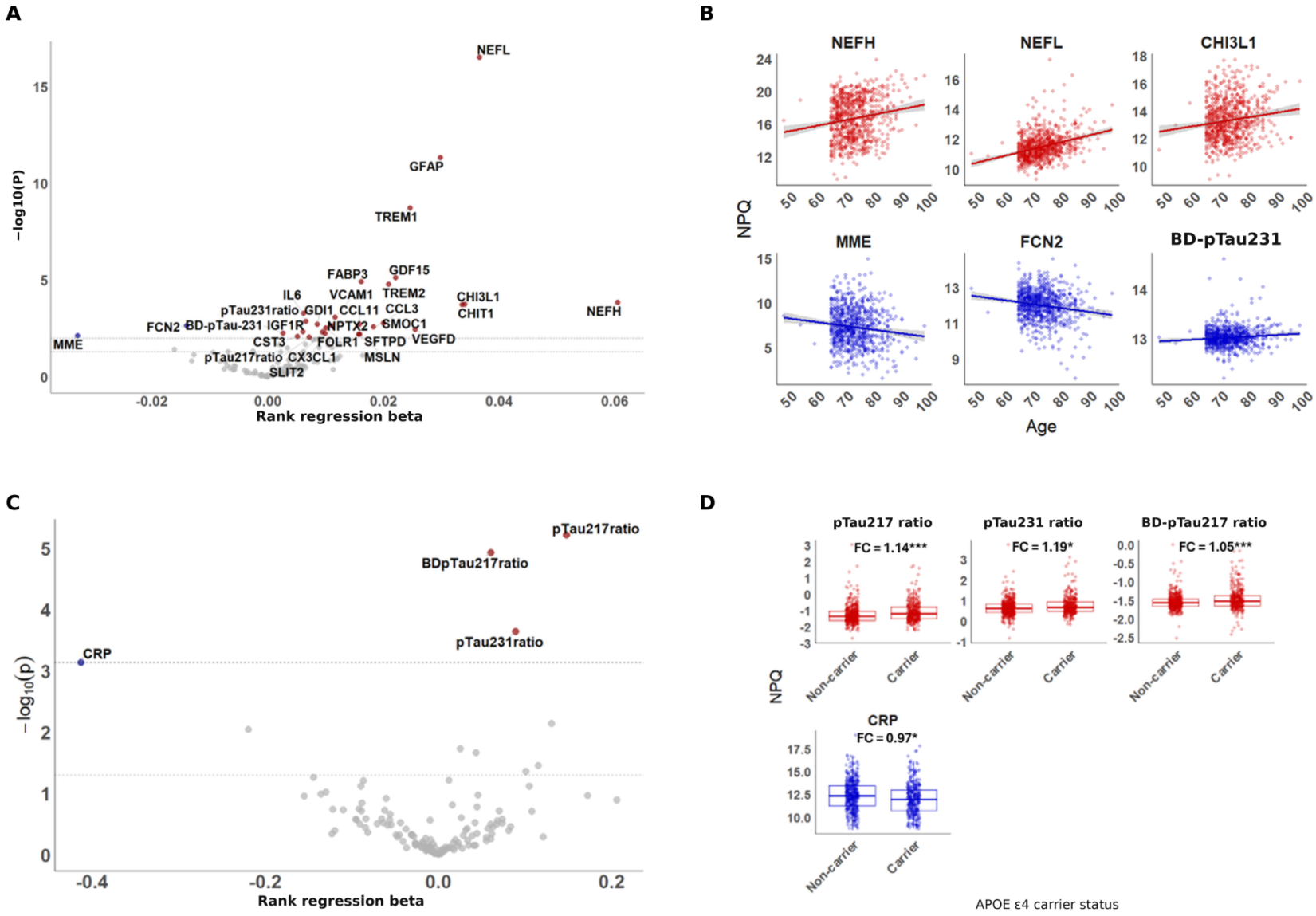
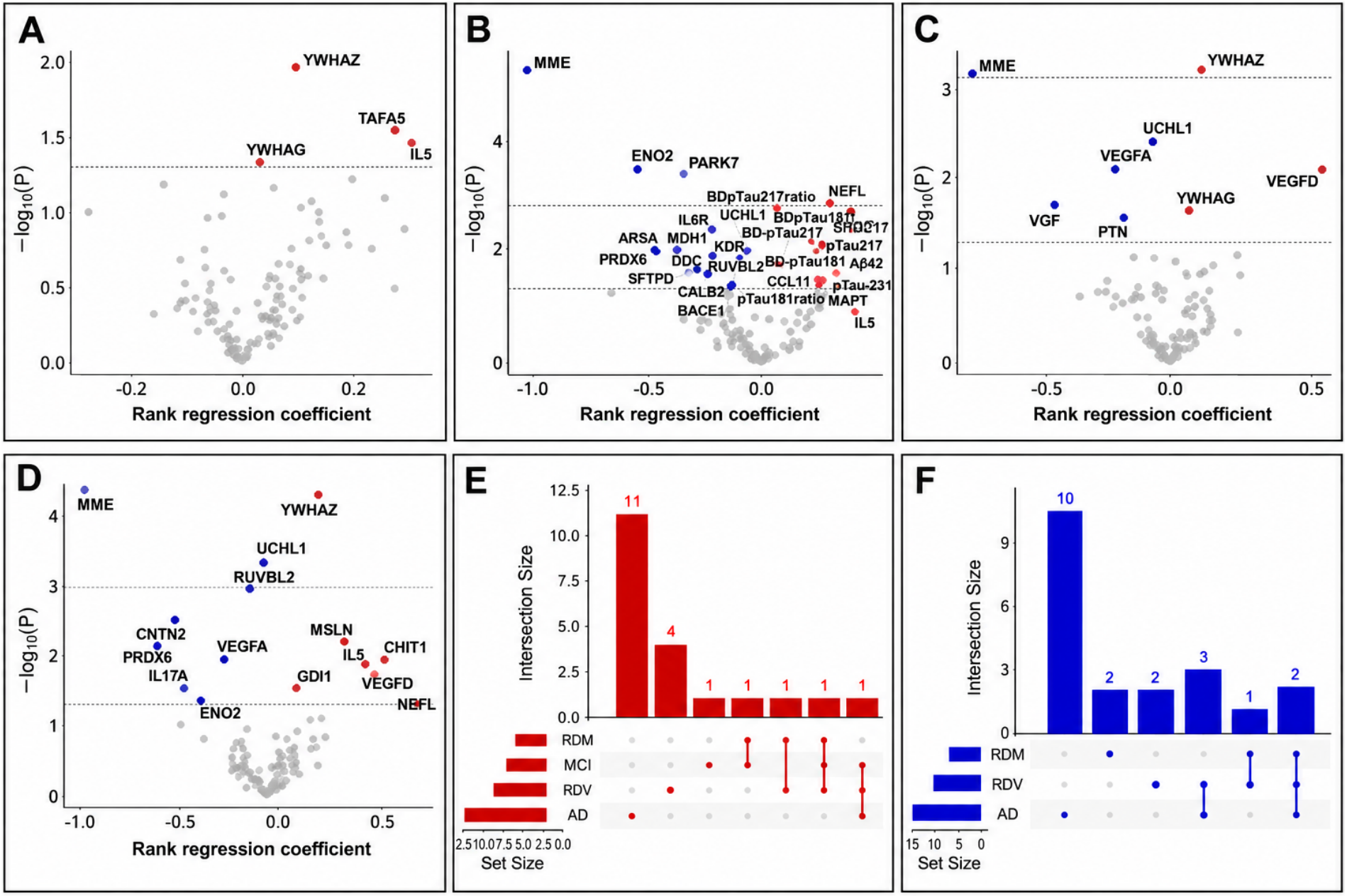
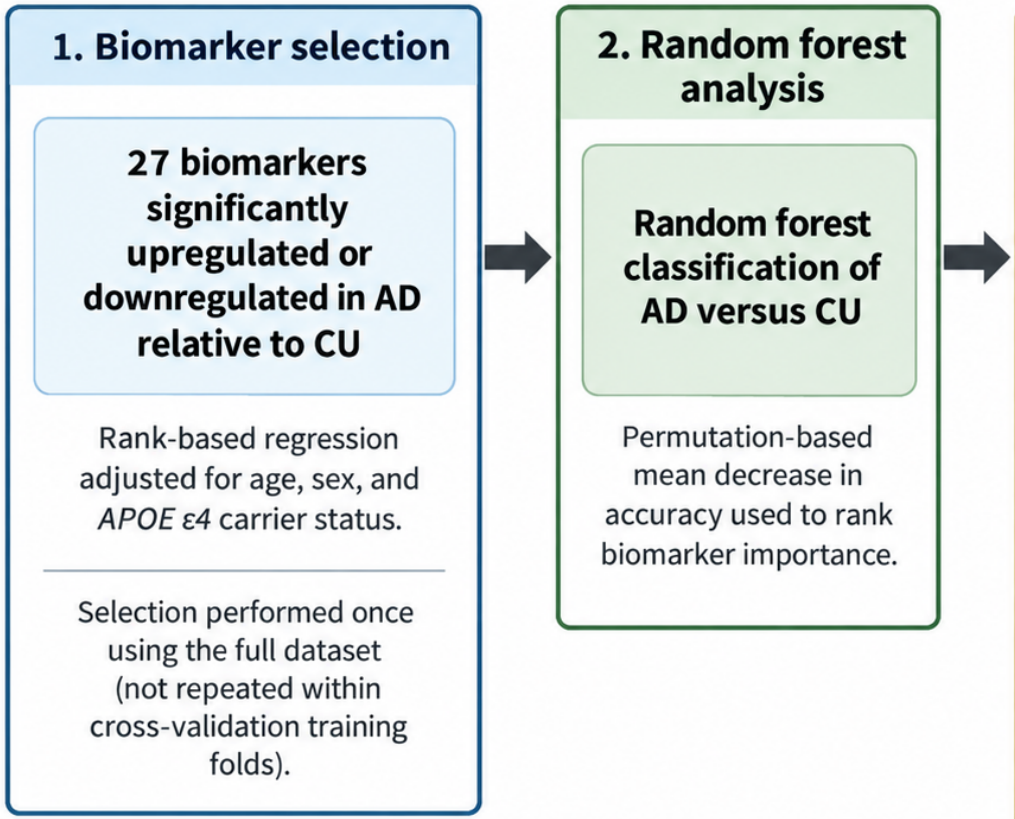


Supplementary Figure 1. Associations of age and APOE ε4 carrier status with biomarker expression. a, Volcano plot showing regression coefficients and P values for associations between age and biomarker expression. b, Age distributions for the three biomarkers with the largest positive associations (NEFH, NEFL, and CHI3L1) and the three biomarkers with the largest negative associations (MME, FCN2, and BD-pTau231). c, Volcano plot showing regression coefficients and P values for associations between APOE ε4 carrier status and biomarker expression. d, Distributions of pTau217 ratio, pTau231 ratio, BD-pTau217 ratio, and CRP by APOE ε4 carrier status. The dashed lines indicate the false discovery rate-adjusted P < .05 threshold.



Supplementary Figure 2. Biomarker expression by diagnostic group relative to cognitively unimpaired participants. Volcano plots compare a, mild cognitive impairment; b, Alzheimer disease; c, mixed dementia; and d, vascular dementia with the cognitively unimpaired group. Models were adjusted for age, sex, and APOE ε4 carrier status. Dashed lines indicate the false discovery rate-adjusted P < .05 threshold. Labeled biomarkers met the adjusted significance criterion. UpSet plots show biomarkers that were significantly e, upregulated and f, downregulated across diagnostic-group comparisons after false discovery rate correction.



3. Biomarker importance ranking

Rank	Biomarker	Permutation importance (mean decrease in accuracy)
1	SMOC1	0.0107559
2	NEFL	0.00966904
3	MME	0.00964858
4	BD-pTau217 ratio	0.0076929
5	MDH1	0.00567913
6	BD-pTau217	0.00324706
7	CALB2	0.00310099
8	pTau217	0.00231026
9	IL6R	0.00220318
10	UCHL1	0.0021065
11	BD-pTau181 ratio	0.00191696
12	CCL11	0.00171091
13	ENO2	0.00168947
14	PARK7	0.00156219
15	Aβ42	0.00152159
16	BACE1	0.00139396
17	IL5	0.00135855
18	KDR	0.00127592
19	SFTPD	0.00086148
20	RUVBL2	0.00081425
21	ARSA	0.00064295
22	BD-pTau181	0.0006113
23	DDC	0.00059837
24	pTau231	6.5746E-05
25	pTau181 ratio	-0.00016395
26	PRDX6	-0.00027084
27	MAPT	-0.00046597

Supplementary Figure 3. Biomarker selection and importance-ranking workflow. Twenty-seven biomarkers that differed significantly between participants with Alzheimer disease and cognitively unimpaired participants after adjustment for age, sex, and APOE ε4 carrier status were entered into a random forest classification model. Biomarkers were ranked using permutation-based mean decrease in accuracy. Candidate biomarker selection and initial importance ranking were performed using the full dataset before cross-validation.