

Pathology-Informed Polygenic Scores Identify Distinct Genetic Contributors to Alzheimer's and Non-Alzheimer's Dementia Across Ancestries

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INTRODUCTION

- ☐ Dementia is clinically and biologically heterogeneous and may reflect Alzheimer disease, vascular, mixed, or other neurodegenerative pathologies.
- ☐ Plasma P-tau217 is a blood-based biomarker closely associated with Alzheimer disease pathology.
- ☐ Combining plasma P-tau217 status with cognitive status allows classification of:
 - ❖ P-tau217-negative cognitively unimpaired individuals;
 - ❖ P-tau217-positive cognitively unimpaired individuals with preclinical AD pathology;
 - ❖ P-tau217-positive symptomatic individuals consistent with AD dementia;
 - ❖ P-tau217-negative symptomatic individuals suggestive of non-AD dementia.

□ The genetic contributors to P-tau217-defined AD dementia and P-tau217-negative non-AD dementia remain insufficiently understood. Because adequately powered genome-wide association studies of these biologically defined dementia subtypes are not yet available, pathology-informed polygenic risk scores derived from related diseases and biomarkers may provide a practical alternative for investigating their underlying genetic pathways.

- We investigated whether pathology-informed polygenic risk scores could distinguish AD-related from vascular and other non-AD genetic pathways contributing to dementia and evaluated the biological and functional relevance of these associations through cerebrospinal fluid biomarker and longitudinal cognitive analyses.

METHODS

- ❑ Data were drawn from Wisconsin (WRAP and Wisconsin ADRC), ADNI, HABS-HD, WHICAP, and the EFICA independent and family cohorts. Cohorts were eligible for inclusion if they had an established plasma P-tau217 cutoff selected to optimize the balance between sensitivity and specificity.
- ❑ Analyses were conducted separately among non-Hispanic White (Wisconsin, ADNI, HABS-HD, and WHICAP) and Caribbean Hispanic participants (WHICAP, EFICA independent and family cohorts).
- ❑ Plasma P-tau217 positivity was defined using both sensitivity-based and specificity-based cutoffs. Cognitively unimpaired, P-tau217-negative participants served as the reference group. Symptomatic participants were classified as: P-tau217-positive AD dementia; or P-tau217-negative non-AD dementia.

- Pathology-informed PRS represented AD, Core-1/2 biomarkers, vascular disease, metabolic disease, and other neurodegenerative pathways.

We addressed two primary questions:

- ❑ **Do pathology-specific PRSs capture stable genetic signals associated with distinct dementia phenotypes?**
- ❖ We identified the strongest association between each pathology-specific PRS and each dementia phenotype.
- ❖ Cohort-specific association estimates were combined using meta-analysis.
- ❖ To reduce dependence on a single threshold, a PRS signal was considered stable only if more than half of the tested thresholds showed the same direction of association.

☐ Are these stable PRS associations generalizable across cohorts?

- ❖ We applied a leave-one-cohort-out framework
- ❖ In each iteration, PRSs were trained in all cohorts except the held-out testing cohort.
- ❖ The direction of association in the training cohorts was required to match that observed in the independent held-out cohort.
- ❖ Held-out cohort estimates were combined using meta-analysis to identify stable and generalizable associations.

Secondary analyses

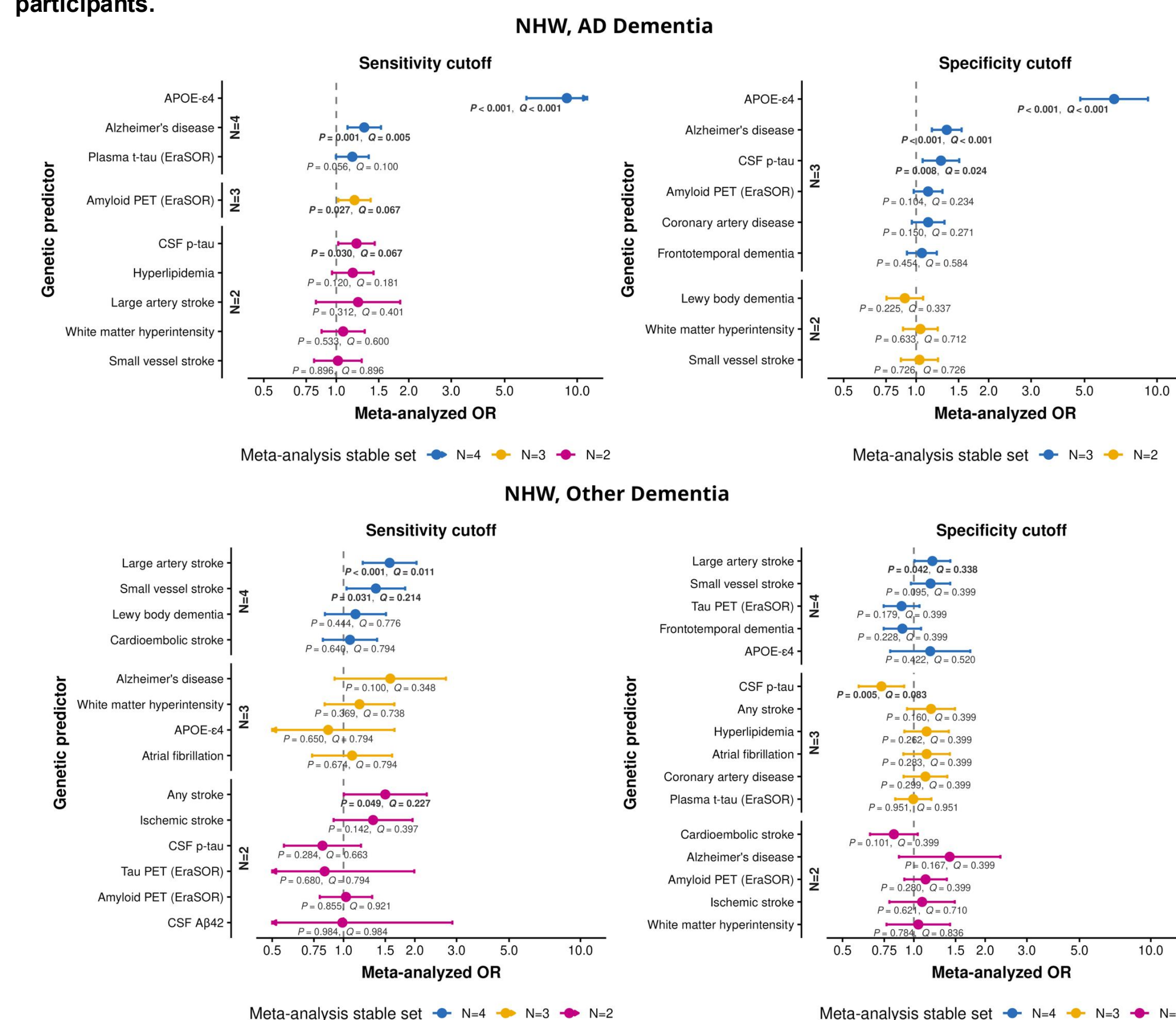
- ☐ We evaluated associations with preclinical AD, cerebrospinal fluid biomarkers, and longitudinal cognitive trajectories.

RESULTS

Table 1. Descriptive Statistics of the Study Sample

Characteristic	Non-Hispanic White					Caribbean Hispanic			
	Overall ¹	ADNI N = 533 ²	HABS-HD N = 922 ²	WHICAP N = 258 ²	Wisconsin N = 1,511 ²	Female ³	EFIGA N = 1,392 ²	FAMILY N = 295 ²	WHICAP N = 505 ²
Age	70.2 (8.4)	75.4 (6.7)	70.1 (8.6)	74.5 (6.6)	67.8 (7.6)	72.6 (8.3)	71.8 (8.1)	70.0 (9.7)	76.4 (6.6)
Education	16.0 (2.5)	16.4 (2.6)	15.7 (2.5)	15.6 (3.3)	16.0 (2.3)	6.5 (5.4)	5.9 (5.4)	8.1 (6.4)	7.6 (4.4)
Sex									
Male	1,286 (39.9%)	290 (54.4%)	401 (43.5%)	104 (40.3%)	491 (32.5%)	696 (31.8%)	456 (32.8%)	95 (32.2%)	145 (28.7%)
Female	1,938 (60.1%)	243 (45.6%)	521 (56.5%)	154 (59.7%)	1,020 (67.5%)	1,496 (68.2%)	936 (67.2%)	200 (67.8%)	360 (71.3%)
<i>APOE-ε4 status</i>									
Carrier	2,048 (63.5%)	293 (55.0%)	646 (70.1%)	192 (74.1%)	917 (60.7%)	1,479 (67.5%)	923 (66.3%)	165 (55.9%)	391 (77.4%)
Non-carrier	1,176 (36.5%)	240 (45.0%)	276 (29.9%)	66 (25.6%)	594 (39.3%)	713 (32.5%)	469 (33.7%)	130 (44.1%)	114 (22.6%)
<i>Dementia status (sensitivity cutoff)</i>									
Healthy control	1,318 (40.9%)	206 (38.6%)	52 (5.6%)	153 (59.3%)	907 (60.0%)	848 (38.5%)	482 (34.6%)	113 (38.3%)	253 (50.1%)
Other dementia	84 (2.6%)	45 (8.4%)	6 (0.7%)	5 (1.9%)	28 (1.9%)	351 (16.0%)	250 (18.0%)	30 (10.2%)	71 (14.1%)
Preclinical	1,409 (43.7%)	119 (22.3%)	709 (76.9%)	93 (36.0%)	488 (32.3%)	491 (22.4%)	313 (22.5%)	75 (25.4%)	103 (20.4%)
AD dementia	143 (12.8%)	163 (30.6%)	155 (16.8%)	7 (2.7%)	88 (5.8%)	502 (22.9%)	347 (24.9%)	77 (26.1%)	78 (15.4%)
<i>Dementia status (specificity cutoff)</i>									
Healthy control	2,016 (62.5%)	280 (52.5%)	334 (36.2%)	214 (82.8%)	1,168 (76.8%)	1,106 (51.4%)	706 (50.7%)	161 (54.6%)	319 (63.2%)
Other dementia	172 (5.3%)	180 (35.0%)	41 (4.4%)	9 (3.5%)	42 (2.8%)	573 (26.1%)	409 (29.0%)	51 (17.3%)	113 (22.4%)
Preclinical	711 (22.1%)	45 (8.4%)	427 (46.3%)	32 (12.4%)	207 (13.7%)	153 (7.0%)	89 (6.4%)	27 (9.2%)	37 (7.3%)
AD dementia	325 (10.1%)	128 (24.0%)	120 (13.0%)	3 (1.2%)	74 (4.9%)	280 (12.8%)	188 (13.5%)	56 (19.0%)	36 (7.1%)
¹ Mean (SD); n (%)									

Figure 1. Leave-one-cohort-out meta-analysis of associations between pathology-specific polygenic risk scores and Alzheimer disease dementia and other dementia among non-Hispanic White (NHW) participants.



Figures 1 and 2. Leave-one-cohort-out meta-analysis of associations between pathology-specific polygenic risk scores and Alzheimer disease dementia and other dementia among non-Hispanic White and Caribbean Hispanic participants, respectively. Polygenic risk scores were constructed using the clumping-and-thresholding approach. In each leave-one-cohort-out iteration, PRSs were trained in all cohorts except the cohort designated for testing and were subsequently evaluated in the independent held-out cohort. A pathology-specific PRS was considered stable and included in the meta-analysis only if more than half of the tested PRS thresholds showed evidence of association in the training cohorts and that direction was also consistent with the association observed in the held-out testing cohort. Finally, the effect meta-analysis was used to combine cohort-specific association estimates. All PRS association models were adjusted for age, sex, education, and the first five genetic principal components.

Figure 3. Associations of the best-performing pathology-specific polygenic risk scores identified through the leave-one-cohort-out analyses as most strongly associated with Alzheimer disease dementia and other dementia with longitudinal cognitive trajectories among non-Hispanic White participants in the ADNI and Wisconsin cohorts. Analyses were conducted in both the full sample and the subgroup of individuals who were cognitively unimpaired. Longitudinal associations were estimated using linear mixed-effects models with repeated cognitive measurements and were adjusted for age, sex, education, practice effects, and the first five genetic principal components.

RESULTS

Figure 2. Leave-one-cohort-out meta-analysis of associations between pathology-specific polygenic risk scores and Alzheimer disease dementia and other dementia among Caribbean Hispanic (CH) participants.

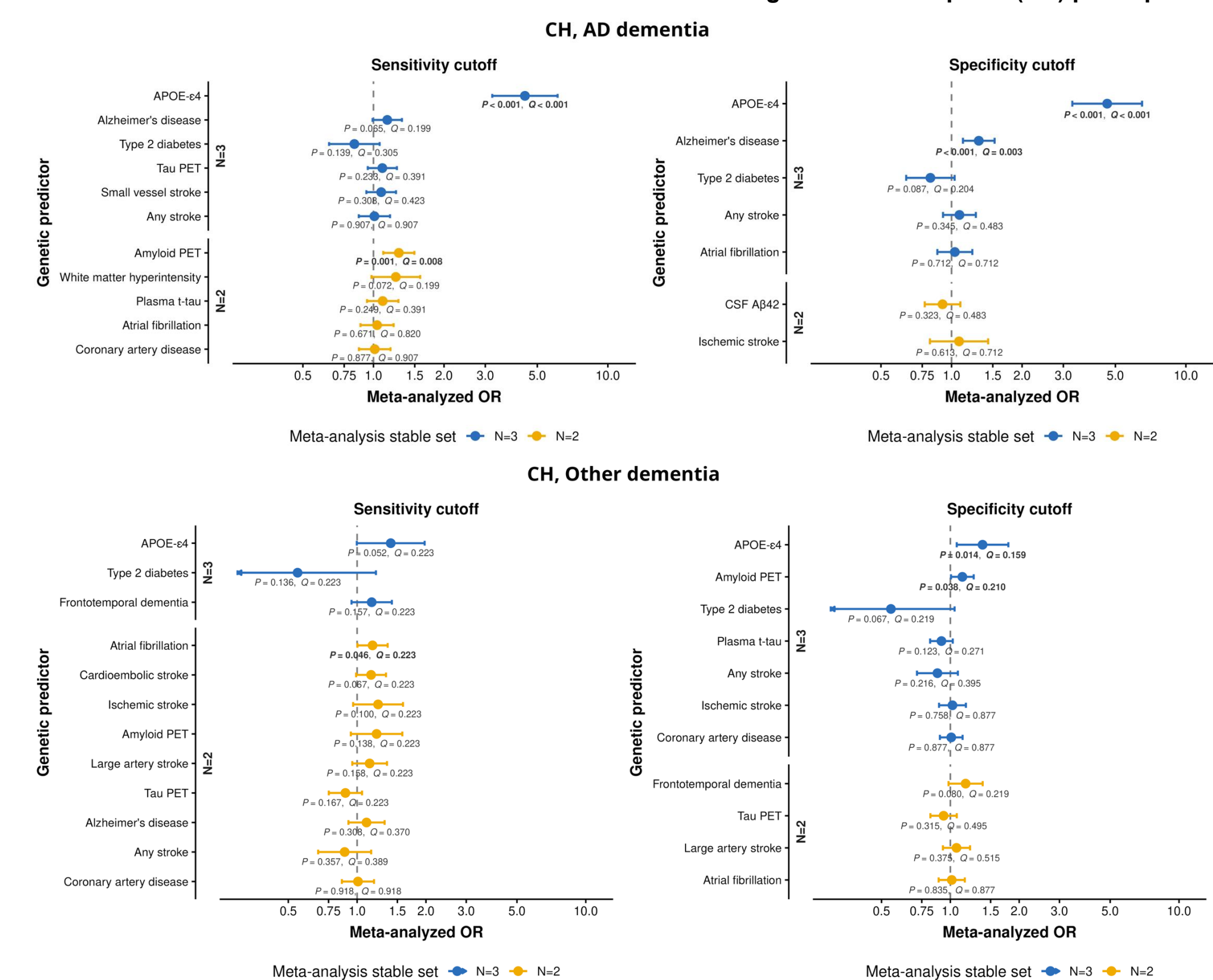
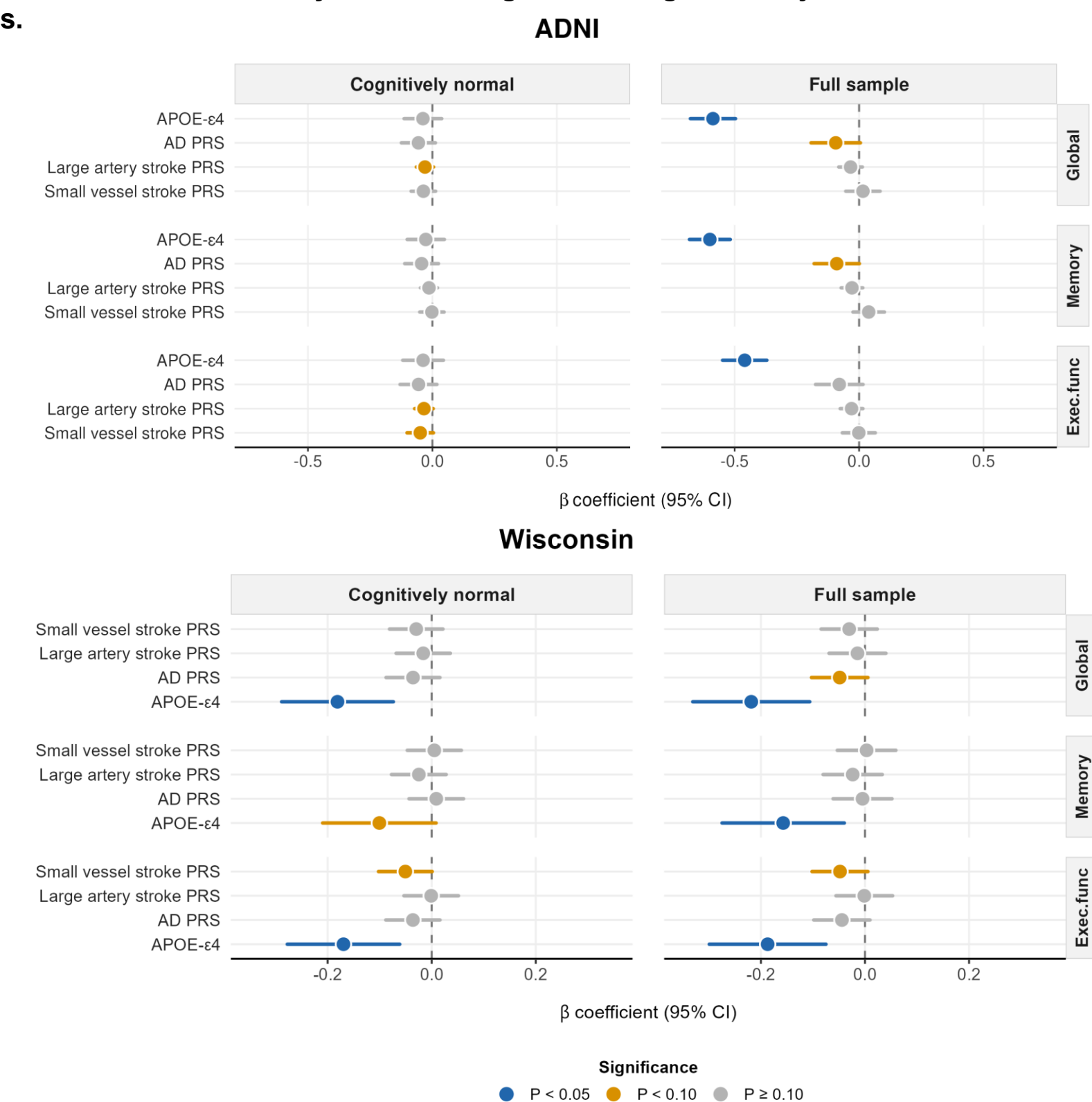


Figure 3. Associations of the best-performing pathology-specific polygenic risk scores identified through the leave-one-cohort-out analyses with longitudinal cognitive trajectories in the ADNI and Wisconsin cohorts.



RESULTS

Figure 4. Associations of the best-performing pathology-specific polygenic risk scores identified through the leave-one-cohort-out analyses with longitudinal trajectories of cerebrospinal fluid biomarkers in the ADNI and Wisconsin cohorts.

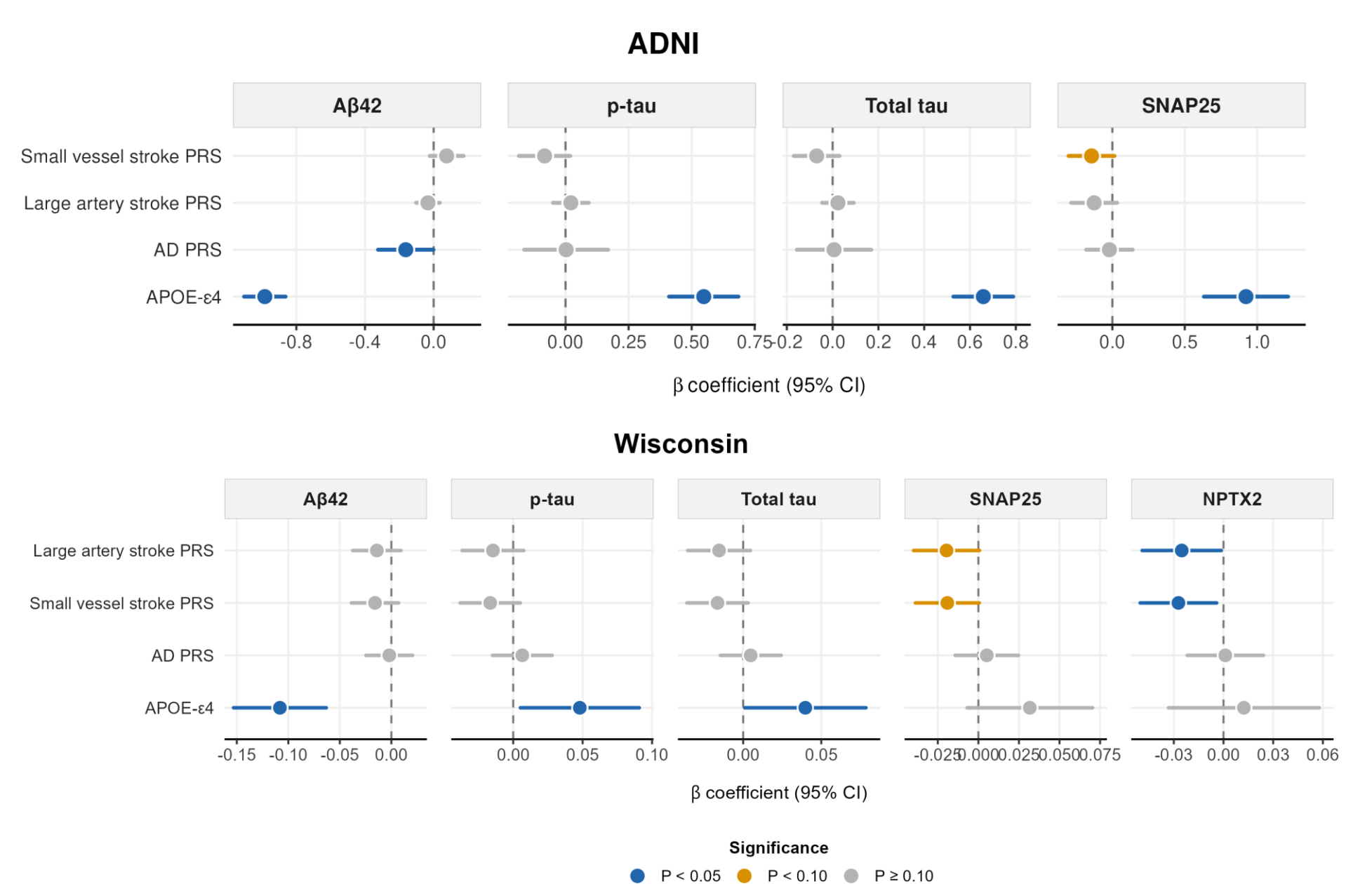


Figure 4. Associations of the best-performing pathology-specific polygenic risk scores identified through the leave-one-cohort-out analyses as most strongly associated with Alzheimer disease dementia and other dementia with longitudinal cerebrospinal fluid biomarker trajectories among non-Hispanic White participants in the ADNI and Wisconsin cohorts. Analyses were restricted to participants with available cerebrospinal fluid measurements. Longitudinal associations were estimated using linear mixed-effects models with repeated biomarker measurements and were adjusted for age, sex, education and the first five genetic principal components.

CONCLUSION

- ❑ **AD- and Core-1 biomarker-related genetic liability was more strongly associated with P-tau217-positive AD dementia.**
- ❑ **Stroke-related genetic liability, particularly large-artery and small-vessel stroke PRS, was more strongly associated with P-tau217-negative non-AD dementia.**
- ❑ **Biomarker findings supported distinct biological pathways:**
- ❖ ***APOE*- ϵ 4 and AD-related PRSs were associated with amyloid- and tau-related CSF biomarkers;**
- ❖ **Stroke-related PRS were associated with synaptic and vascular biomarkers, including *SNAP-25* and *NPTX2*.**
- ❑ Cognitive findings provided additional functional validation, with stroke-related PRS showing stronger associations with executive and other non-memory domains.
- ❑ Similar overall patterns were observed across non-Hispanic White and Caribbean Hispanic participants.
- ❑ Integrating genetic, biomarker, and cognitive information may improve etiologic classification, risk stratification, and clinical trial enrichment for AD-related versus vascular or non-AD dementia pathways.

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