

Neuropsychiatric symptoms, amyloid pathology, and sex-specific associations in older people

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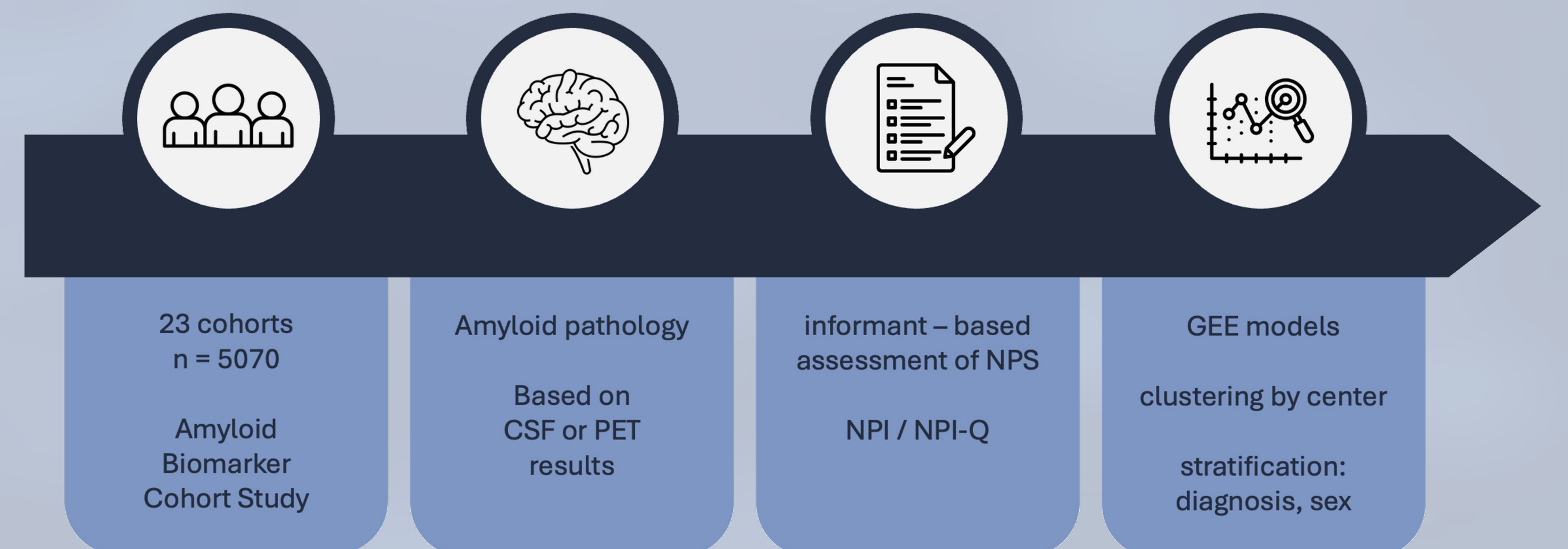
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Background

Neuropsychiatric symptoms (NPS) are common in older people and may represent early manifestations of neurodegenerative diseases, particularly Alzheimer's disease (AD).

We aimed to investigate the associations between NPS and amyloid pathology across the AD continuum, considering sex differences, in the Amyloid Biomarker Study, a large-scale multi-cohort data pooling initiative.

Methods



Results

Demographics

	total n = 5070	NC n = 1982	MCI n = 2352	dementia n = 736
Demographic data				
female, n (%)	2466 (48.6)	1052 (53.1)	1070 (45.5)	344 (46.7)
age, mean ± s.d.	70.5 ± 9.0	69.1 ± 9.8	70.7 ± 8.3	73.3 ± 8.2
education years, mean ± s.d.	13.8 ± 4.2	14.9 ± 3.8	13.1 ± 4.3	13.1 ± 4.5
Biological data, n (%)				
Amyloid status positive	2561 (50.5)	591 (29.8)	1364 (58.0)	606 (82.3)
APOE ε4 carrier	1594 (43.0)	447 (31.4)	821 (46.5)	326 (62.7)
Other				
MMSE, mean ± s.d.	27.3 ± 2.9	28.9 ± 1.2	27.0 ± 2.4	22.5 ± 3.4
NPI, n (%)	2810 (55.9)	1076 (55.4)	1394 (59.3)	340 (46.2)
NPI-Q, n (%)	2221 (44.1)	867 (44.6))	958 (40.7)	396 (53.8)
CSF, n (%)	3807 (75.1)	1378 (69.5)	1926 (81.9)	503 (68.3)
PET, n (%)	1263 (24.9)	604 (30.5)	426 (18.1)	233 (31.7)

Table 1 Cohort characteristics

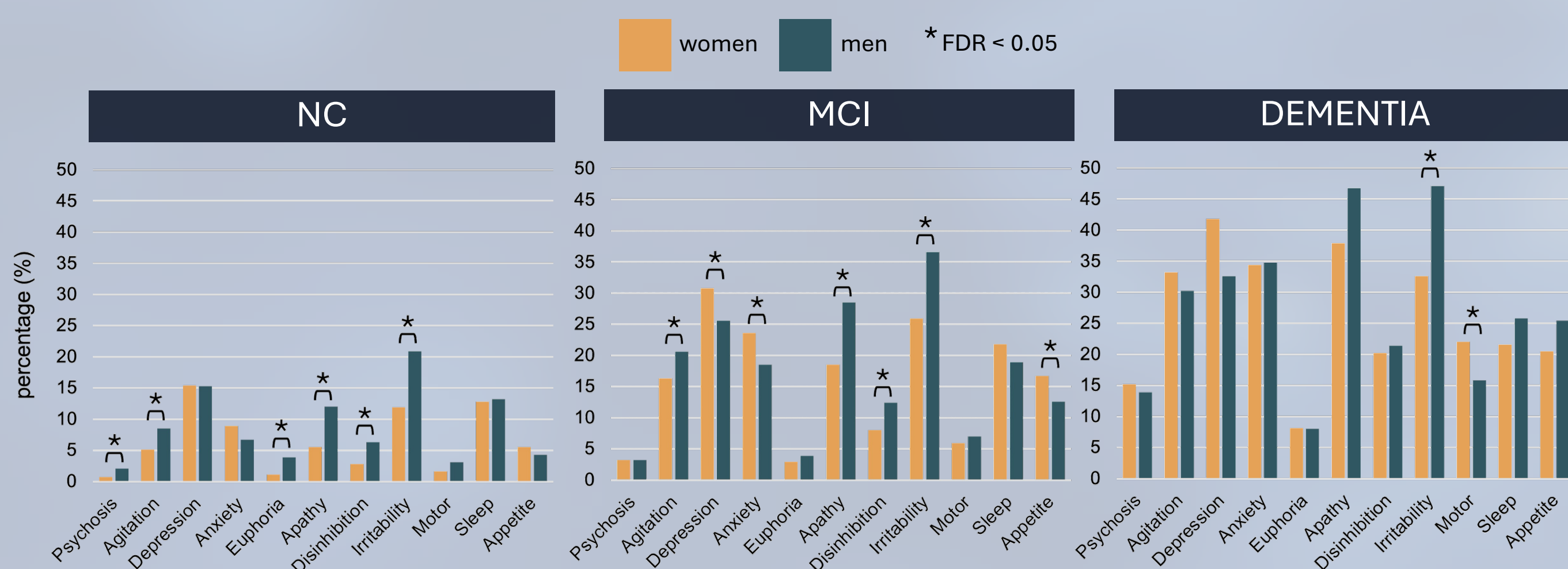


Fig. 1 Sex-specific frequency of NPS across disease stages

INTERACTION EFFECT OF APOE ε4 STATUS

The APOE ε4 carrier status modified the association between NPS and amyloid pathology only in MCI (p = 0.003), but not in NC and dementia. Stratified analyses showed no association within either carriers or non-carriers, suggesting effect heterogeneity rather than a true subgroup-specific relationship.

Associations of NPS with amyloid pathology

	NC				MCI				Dementia			
	OR	low	high	p	OR	low	high	p	OR	low	high	p
All participants												
NPS presence	0.97	0.84	1.15	.748	1.10	0.77	1.57	.615	0.62	0.37	1.02	.058
NPS severity	1.00	0.97	1.04	.932	1.01	0.97	1.05	.718	0.96	0.93	0.99	.017
Women												
NPS presence	0.85	0.72	1.02	.081	1.03	0.68	1.57	.888	0.52	0.26	1.06	.071
NPS severity	0.98	0.92	1.04	.470	1.02	0.96	1.09	.512	0.95	0.9	1	.035
Men												
NPS presence	1.13	0.89	1.44	.310	1.15	0.81	1.63	.439	0.77	0.34	1.72	.052
NPS severity	1.03	0.99	1.06	.134	1	0.97	1.03	.984	0.98	0.94	1.01	.131

Table 2 Associations between the presence and severity of NPS with amyloid pathology in the whole cohort and stratified for sex. ORs with 95% CI and P values across the disease stages (NC, MCI, and dementia) are shown.

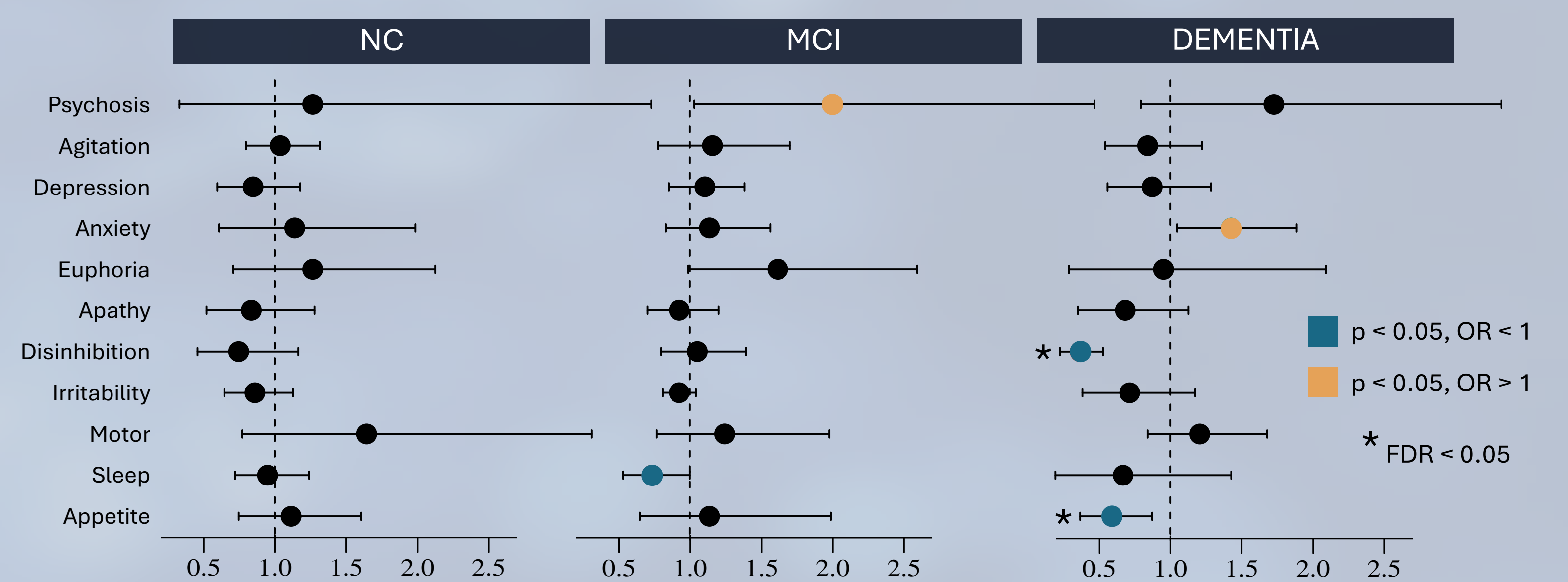


Fig. 2 Associations between individual NPS with amyloid pathology. ORs with 95% CI and P values across the disease stages (NC, MCI, and dementia) are shown.

NC	MCI	AD		NC	MCI	AD	
1.24	1.63	0.97	psychosis	1.26	2.27	2.45	higher OR lower OR
0.79	1.27	0.85	agitation	1.30	1.06	0.96	
0.90	1.15	0.83	depression	0.95	1.06	0.99	
0.80	1.26	1.19	anxiety	1.73	1.02	1.32	
0.54	1.40	0.86	euphoria	1.50	1.69	0.95	
0.65	0.90	0.60	apathy	1.05	0.96	1.00	
0.26	1.04	0.44	disinhibition	1.28	1.06	0.75	
0.96	0.90	0.93	irritability	0.83	0.95	0.75	
1.37	0.98	1.23	motor	1.76	1.43	1.06	
0.85	0.87	0.38	sleep	1.07	0.64	1.37	
1.00	0.97	1.01	appetite	1.27	1.31	0.58	
WOMEN				MEN			

Fig. 3 Associations between individual NPS with amyloid pathology, stratified for sex. ORs are shown and colored according to their P values.

Conclusion

This large multi-cohort study shows that the associations of NPS with amyloid pathology are strongly dependent on both the clinical disease stage and sex. These results have implication for the understanding of the pathogenesis of NPS in older adults and for the development of more personalized diagnostic and therapeutic approaches.

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