

Odor Identification as an Early Marker of Medial Temporal Lobe Pathology and Cognitive Decline in Preclinical Alzheimer’s Disease

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Background

- Cost-effective, noninvasive screening methods for preclinical Alzheimer’s disease (AD) and other neurocognitive disorders remain an unmet need. The olfactory neural circuits develop AD pathological changes prior to symptom onset^{1,2}.

Objective

- We aimed to (1) compare olfactory function between CN individuals with (CN A+) and without (CN A-) amyloid pathology; (2) assess whether olfactory scores are associated with tau burden and the morphometry of MTL regions; and (3) assess the predictive value of odor identification on longitudinal conversion to MCI. We analyzed data from the PREVENT-AD and UCLouvain cohorts, which combine neuropsychological testing, standardized olfactory measures, structural MRI, and tau PET imaging.

Participants

Table 1. Participant characteristics and medial temporal lobe biomarkers.							
	PREVENT-AD			UCLouvain			
Mean (SD)	CN A-	CN A+	p	CN A-	CN A+	MCI A+	p
Demographics							
n	159	58		23	20	16	
Age (y)	65.43 (5.07)	66.91 (5.46)	.056	69.65 (6.42)	72.95 (7.41)	70.74 (8.25)	.321
Sex (%F)	71.7	67.2	.614	39.1	55.0	50.0	.576
Education	15.64 (3.44)	14.91 (3.02)	.152	2.87 (0.46)	2.90 (0.45)	2.44 (0.81)	.018 (b,c)
Cognition							
MMSE	28.94 (1.14)	28.49 (1.56)	.161	29.22 (0.90)	28.68 (0.95)	26.06 (2.59)	<.001 (a,b,c)
Olfaction							
UPSIT identification	34.82 (4.68)	32.72 (6.49)	.008				
SS Identification				11.83 (2.53)	10.20 (3.44)	9.69 (3.57)	.134
SS Discrimination				10.30 (2.96)	10.40 (2.85)	8.19 (3.43)	.095
SS Threshold				6.34 (3.22)	5.45 (2.99)	5.88 (3.81)	.773
Morphometry							
Amygdala volume (mm³)	3368.69 (359.77)	3304.91 (415.12)	.750	3141.94 (449.05)	2987.77 (454.17)	2813.36 (469.95)	.090 (b)
Hippocampal volume (mm³)	7947.39 (812.27)	7705.58 (977.59)	.277	6757.31 (905.85)	5920.69 (802.30)	6162.35 (726.88)	.009 (a,b)
Entorhinal thickness (mm)	2.98 (0.20)	2.87 (0.29)	.030	3.21 (0.23)	2.96 (0.28)	2.93 (0.30)	.009 (a,b)
Parahippocampal thickness (mm)	2.66 (0.20)	2.65 (0.20)	.999	2.72 (0.20)	2.59 (0.26)	2.44 (0.22)	.003 (b,c)
eTIV (mm³)	1532569.66 (142313.04)	1540542.38 (138703.37)	.859	1455062.37 (235913.96)	1452491.87 (180418.35)	1540163.92 (189902.91)	.530
Tau-PET SUVR							
Amygdala tau-PET SUVR	1.24 (0.11)	1.35 (0.20)	<.001	0.68 (0.13)	1.06 (0.66)	1.96 (0.91)	<.001 (a,b)
Entorhinal tau-PET SUVR	1.04 (0.09)	1.16 (0.18)	<.001	0.85 (0.18)	1.38 (0.64)	2.24 (0.93)	<.001 (a,b,c)
Hippocampal tau-PET SUVR	1.28 (0.11)	1.32 (0.19)	.089	0.76 (0.11)	1.00 (0.28)	1.35 (0.44)	<.001 (a,b)
Parahippocampal tau-PET SUVR	1.06 (0.08)	1.12 (0.14)	<.001	0.82 (0.11)	1.22 (0.43)	1.92 (0.92)	<.001 (a,b,c)

Note. Values are mean (SD), unless otherwise indicated; sex is reported as % female. PREVENT-AD p values compare CN A- and CN A+ groups. UCLouvain p values compare CN A-, CN A+, and MCI+ groups. Pairwise symbols for UCLouvain: a = CN A- vs CN A+; b = CN A- vs MCI+; c = CN A+ vs MCI+.

- Amyloid positivity (A+) was defined as a Centiloid value >20.
- Tau positivity (T+) was defined using a temporal meta-ROI flortaucipir SUVR threshold of 1.36 in PREVENT-AD and a physician-rated Braak-like stage >0 in UCLouvain.

Olfactory assessment

- In PREVENT-AD, the University of Pennsylvania Smell Test (UPSIT) was used to measure odor identification.
- In UCLouvain, the Sniffin’ Sticks test battery was used to assess olfactory detection threshold, discrimination of odors, and odor identification.



Neuroimaging

We used FreeSurfer’s recon-all pipeline to extract regional volumes and cortical thickness measurements from T1-weighted MRI images.

From both cohort datasets, we extracted SUVR and morphometric measures (grey matter volume (GMV) and cortical thickness) for the amygdala and hippocampus (GMV) and for the entorhinal cortex and parahippocampal gyrus (cortical thickness). These MTL ROIs are known to be involved in the primary and secondary olfactory areas. Bilateral ROI values were computed by averaging left and right SUVR and cortical thickness values, and by summing left and right GMV.



Lower odor identification in preclinical AD (CN A+)

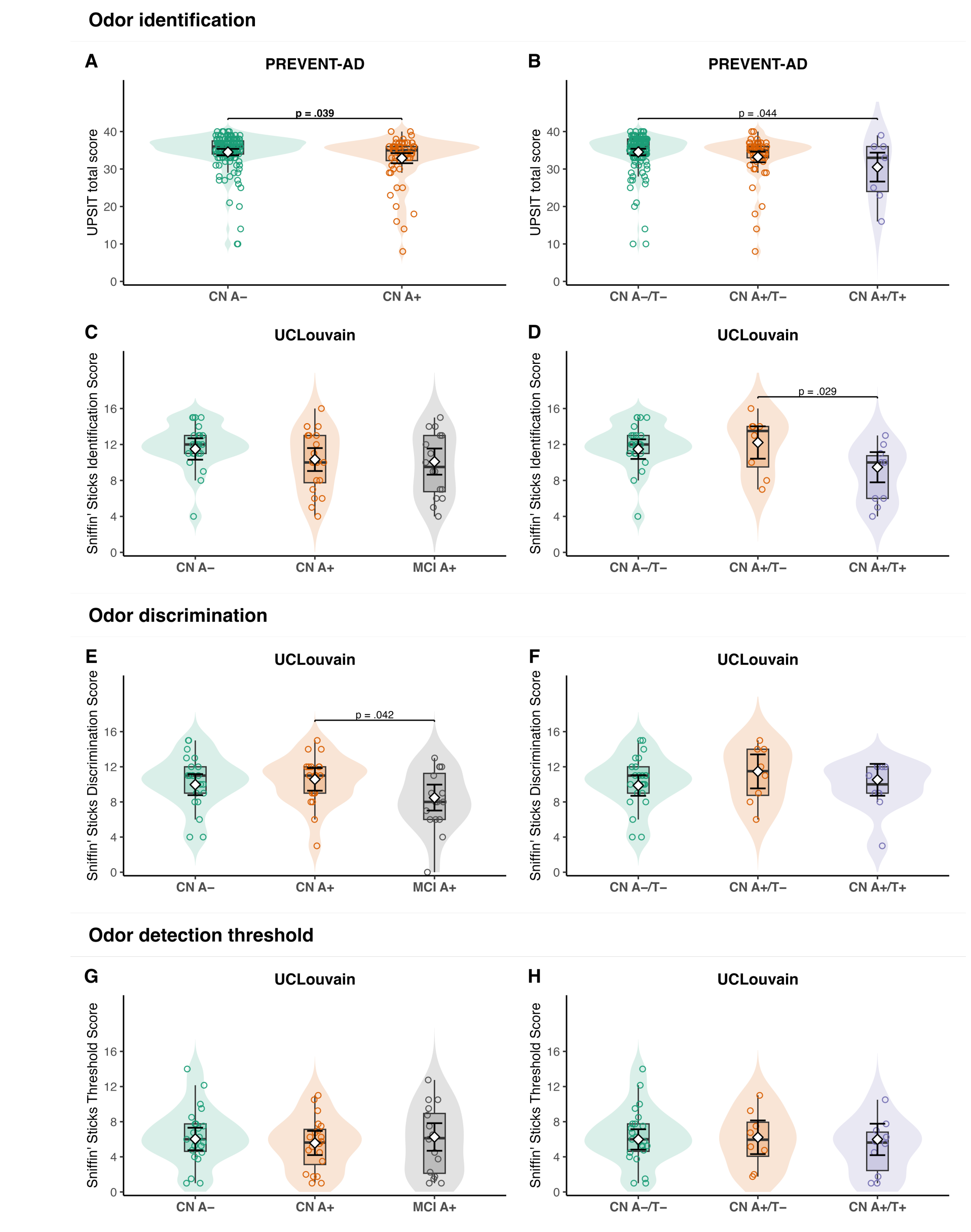


Figure 1. Group differences in olfactory performance across amyloid and tau biomarker groups in PREVENT-AD and UCLouvain. Violin plots show the distribution of olfactory scores across groups, with boxplots indicating medians and interquartile ranges. Open circles represent individual participant scores, and diamonds indicate covariate-adjusted estimated marginal means with 95% confidence intervals from ANCOVA models adjusted for age, sex, and education. Bold p-values indicate contrasts that survived FDR correction.

Odor identification correlates with MTL tau-PET MK-6240 and morphometry

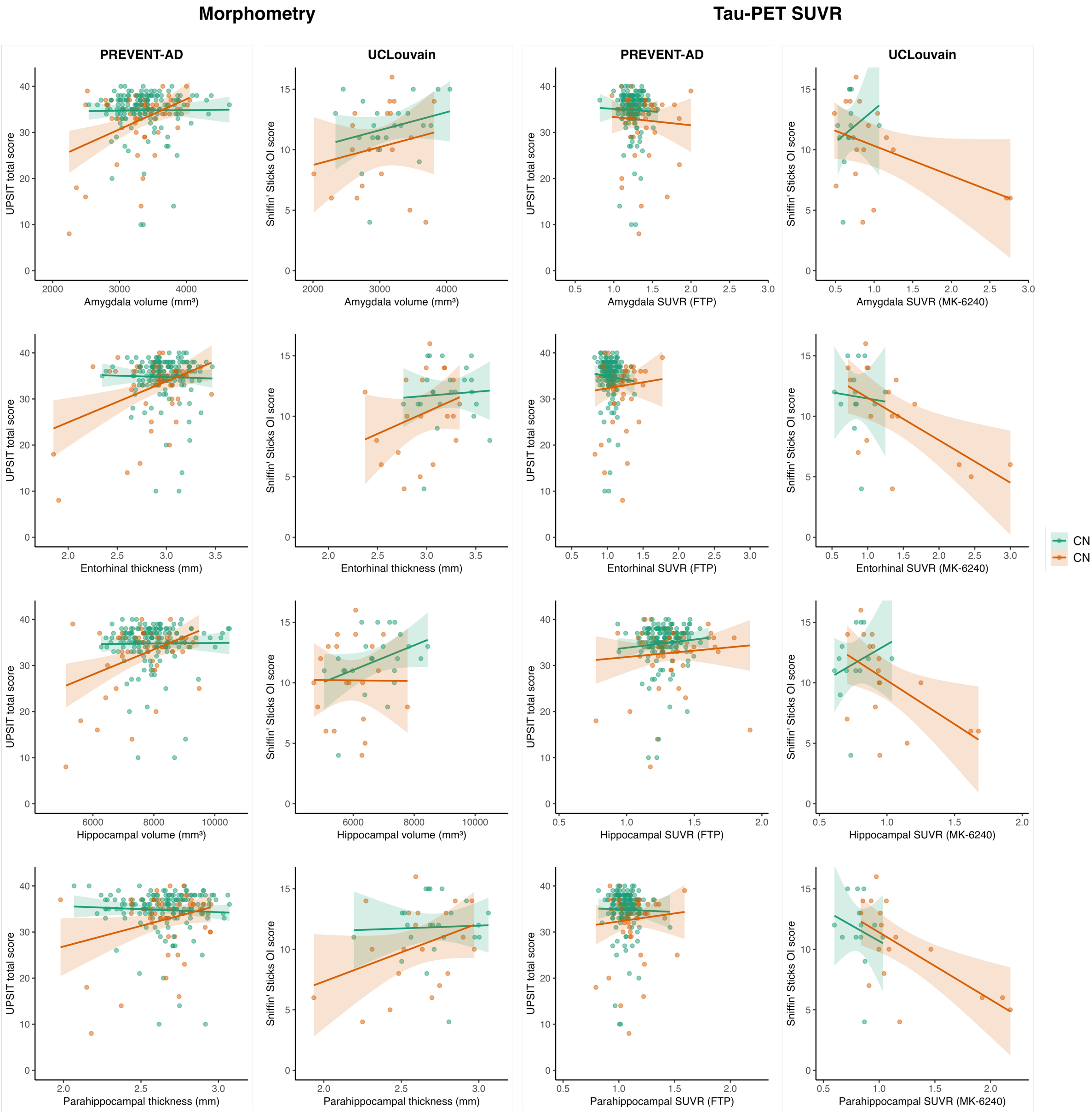


Figure 2. Associations between medial temporal lobe biomarkers and odor identification in the PREVENT-AD and UCLouvain cohorts. In PREVENT-AD, amyloid status modified the association between MTL volume and UPSIT performance ($p < .001$), although most stratified associations were nonsignificant; among CN A+ participants, lower identification scores were associated only with left entorhinal volume, not tau-PET SUVR. In UCLouvain, identification was unrelated to MTL morphometry, but higher MTL tau SUVR was associated with poorer identification among CN A+ participants, with no association among CN A- participants.

Each 1-point lower UPSIT score was associated with a 7% higher risk of MCI conversion in CN A+.

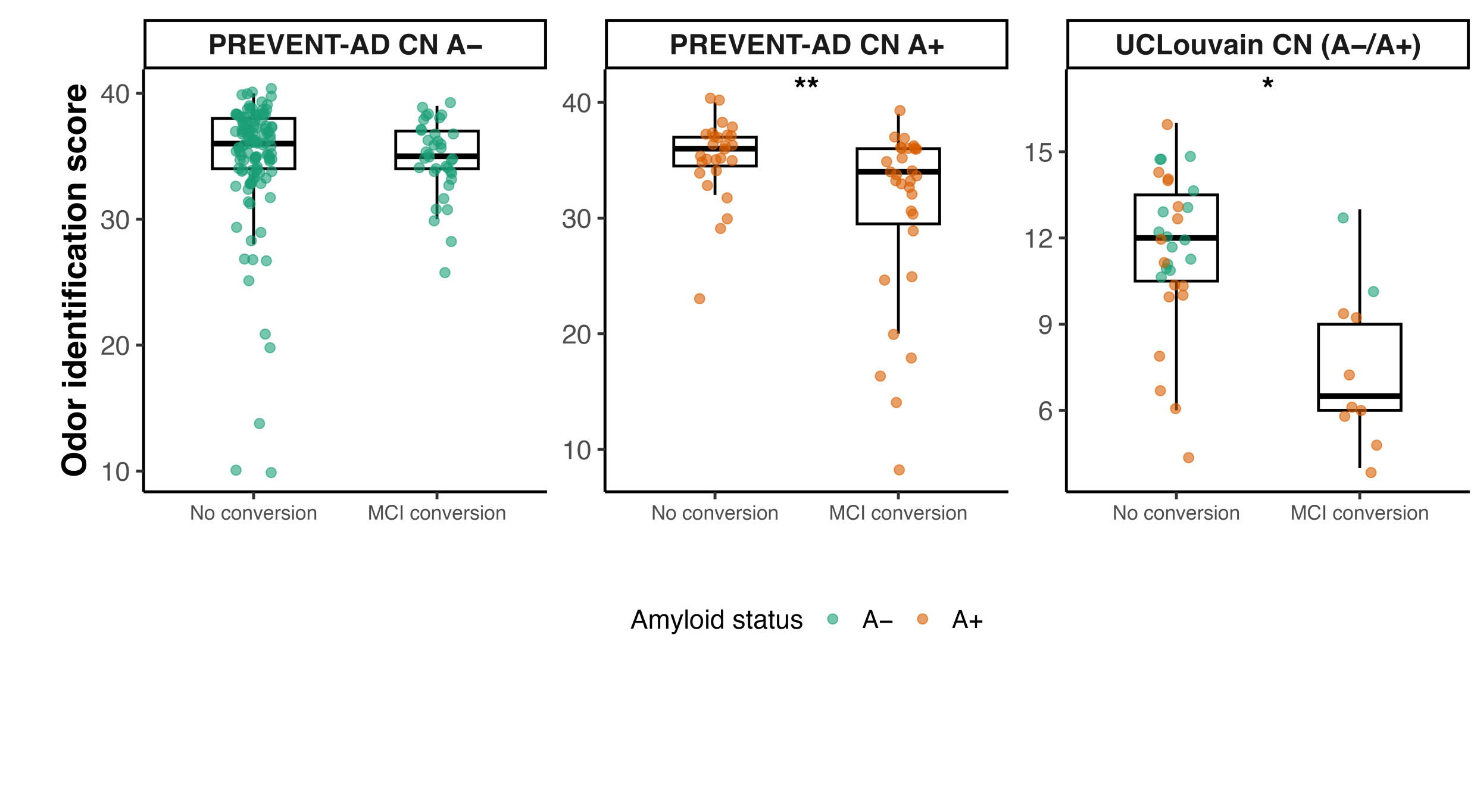


Figure 3. Odor identification performance by incident MCI conversion status. Boxplots show baseline odor identification scores for participants who remained non-converters (CN) and those who converted to MCI during follow-up. Individual points represent participants, with black points indicating A- participants and blue points indicating A+ participants. The central line indicates the median, boxes represent the interquartile range, and whiskers represent the range excluding outliers. Lower scores indicate poorer odor identification. * Statistically significant difference ($p \leq .05$). ** ($p \leq .01$).

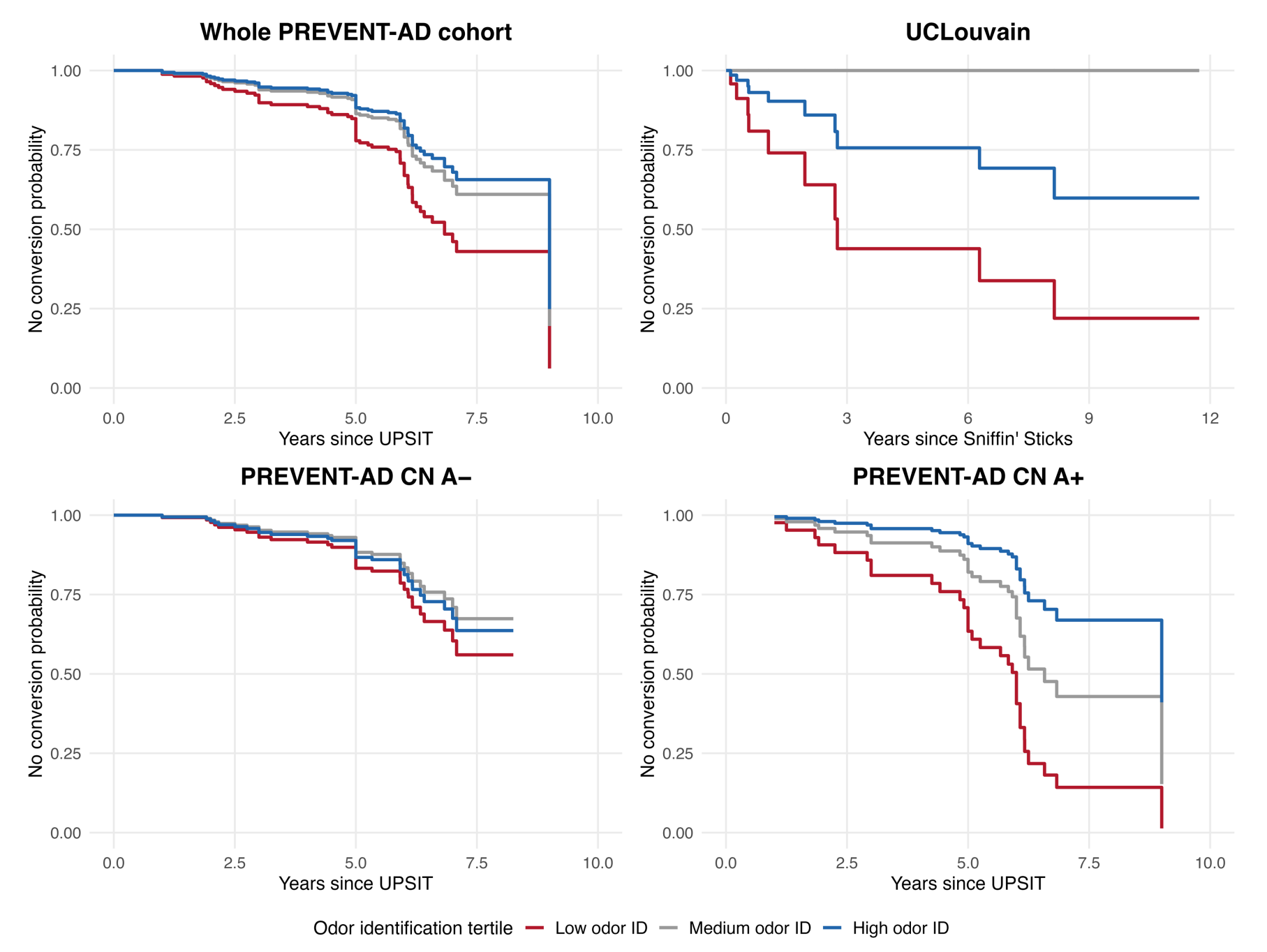
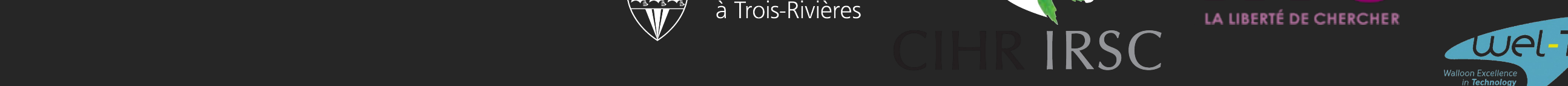


Figure 4. Adjusted survival curves for incident MCI conversion by odor identification performance. Adjusted survival curves for incident MCI conversion by odor identification performance. Curves show model-based MCI conversion-free probability. Odor identification tertiles were used for visualization only; primary statistical inference was based on continuous odor identification scores in adjusted Cox models.

Discussion

- Odor identification decline can be detected in the preclinical stage of AD before overt cognitive impairment and is associated with MTL neuroimaging biomarkers.
- Longitudinal follow-up showed that lower baseline odor identification predicted clinical progression to MCI among CN A+ individuals, with an approximately 7% increased risk for each 1-point decrease in UPSIT score.
- Both cohorts differed in recruitment strategies, olfactory tests, and tau-PET tracers, which may have contributed to cohort-specific findings.

Acknowledgments :



References

- Diez et al. 2024.
- Kovacs et al. 2001.

