Odor identification as a biomarker of preclinical AD in older adults at risk

ABSTRACT

Objective: To assess odor identification (OI) as an indicator of presymptomatic Alzheimer disease (AD) pathogenesis in cognitively normal aging individuals at increased risk of AD dementia.

Methods: In 274 members of the PREVENT-AD cohort of healthy aging persons with a parental or multiple-sibling history of AD dementia, we assessed the cross-sectional association of OI with potential indicators of presymptomatic AD. Some 101 participants donated CSF, thus enabling assessment of AD pathology with the biomarkers total tau (t-tau), phospho-tau (P_181-tau), and their ratios with β-amyloid (Aβ_1-42). Adjusted analyses considered age, cognition, APOE ε4 status, education, and sex as covariates. We measured OI using the University of Pennsylvania Smell Identification Test and cognitive performance using the Repeatable Battery for Assessment of Neuropsychological Status. Standard kits provided assays of the AD biomarkers. Analyses used robust-fit linear regression models.

Results: Reduced OI was associated with lower cognitive score and older age, as well as increased ratios of CSF t-tau and P_181-tau to Aβ_1-42 (all p < 0.02). However, the observed associations of OI with age and cognition were unapparent in adjusted models that restricted observations to CSF donors and included AD biomarkers. OI showed little association with CSF Aβ_1-42 alone except in APOE ε4 carriers having lowest-quartile Aβ_1-42 levels.

Conclusions: These findings from healthy high-risk older individuals suggest that OI reflects degree of preclinical AD pathology, while its relationships with age and cognition result from the association of these latter variables with such pathology. Diminished OI may be a practical and affordable biomarker of AD pathology.

GLOSSARY

Aβ = β-amyloid; AD = Alzheimer disease; INTREPAD = Impact of Naproxen Treatment on Presymptomatic Alzheimer’s Disease; OI = odor identification; P_181-tau = phospho-tau; PREVENT-AD = Presymptomatic Evaluation of Experimental or Novel Treatments for Alzheimer’s Disease; RBANS = Repeatable Battery for Assessment of Neuropsychological Status; t-tau = total tau; UPSIT = University of Pennsylvania Smell Identification Test.

Prevention of Alzheimer disease (AD) dementia can be accomplished by retarding the progression of the disease in its presymptomatic stages, thus postponing the onset of clinical symptoms. Hence, research on the identification and development of AD preventives can be aided by quantitative measures of disease progression before symptom onset. Such presymptomatic disease progress may be revealed by subtle cognitive changes, various MRI or PET imaging techniques, or AD biomarkers in the CSF. These measures are generally inconvenient, and more accessible markers of preclinical AD pathology are needed.

Because rhinencephalic brain regions are especially vulnerable to AD pathology, a candidate marker for this purpose may be odor identification (OI), i.e., the ability to identify and name specific odorants. Like cognition, OI is known to be impaired in both aging and...
In longitudinal studies, reduced OI performance predicts faster cognitive decline in elderly controls and persons with mild cognitive impairment or AD dementia.5,8–10,15–17 Finally, an important study of cognitively healthy persons showed that reduced OI ability predicted postmortem AD pathology.6

We therefore sought to evaluate OI as a measure of presymptomatic AD pathogenesis. In a study of aging asymptomatic individuals at risk of AD dementia, we investigated the association between OI and recognized in vivo AD biomarkers such as CSF total tau (t-tau) and phospho-tau (P181-tau) and their ratio with Alzheimer β-amyloid (Aβ1–42). We hypothesized that degree of impairment in OI would predict biomarker evidence of AD neuropathology.

METHODS The PREVENT-AD cohort. We investigated cross-sectional baseline measures from 274 participants in a cohort of cognitively unimpaired individuals assembled for Presymptomatic Evaluation of Experimental or Novel Treatments for Alzheimer’s Disease (PREVENT-AD).1 PREVENT-AD enrollees had a parent or multiple siblings with a history of AD-like dementia. They were ≥60 years of age, except that individuals 55 to 59 years old were eligible if their current age was within 15 years of dementia onset in their youngest-affected relative. In general, persons with a first-degree family history have an elevated risk of AD.1,2 We first screened their cognitive state using the Montreal Cognitive Assessment19 and the Clinical Dementia Rating scale.20 Individuals with questionable Impact of Naproxen Treatment on Presymptomatic Alzheimer Disease (INTREPAD), a placebo-controlled, biomarker-endpoint prevention trial of the nonsteroidal anti-inflammatory drug naproxen in 184 participants. We obtained CSF data from a subset of 101 volunteers from that trial.

We assessed OI abilities using the Odor Identification.

Methods of assessment. Review of health and neurocognitive status. Participants were evaluated while accompanied by an informant. Assessments included a health history and review of systems, a standardized neurologic examination, and a cognitive examination with version A of the Repeatable Battery for Assessment of Neuropsychological Status (RBANS).21 The RBANS is available in both English and Canadian French. It measures 5 domains of cognitive performance. Participants also underwent phlebotomy for routine laboratory tests and banking of plasma and a multimodal MRI/MRI scan session.

CSF collection. INTREPAD volunteers’ lumbar punctures were performed in the morning after an overnight fast. CSF was collected with the Sponture 24-gaugeatraumatic needle. The time of collection was recorded. All procedures followed recommendations of the BiomarkAPD project in the EU Joint Programme in Neurodegeneration.22 Briefly, CSF was centrifuged at 3,000 RPM (2,000g) at room temperature to precipitate cells and other insoluble material. Within 4 hours of collection, CSF samples were frozen and stored in 0.4-mL aliquots at −80°C in 500μL polypropylene cryotubes. The samples went through only one freeze-thaw cycle. We assayed CSF t-tau, P181-tau, and Aβ1–42 levels using the Innogenetik/Fujirebio (previously Innomrogenics, Ghent, Belgium) ELISA kit, again following Joint Programme in Neurodegeneration–specified procedures. This technology is based on specific fluorescent antibody labeling. We used the biomarker ratios CSF t-tau/Aβ1–42 and P181-tau/Aβ1–42 to indicate disease state.

APOE genotyping. DNA was extracted automatically from buffy coat samples with the QiiaSymphony DNA mini kit (Qiagen, Toronto, ON, Canada). APOE genotype was determined with the PyroMark Q96 pyrosequencer (Qiagen). The DNA was amplified using reverse transcriptase–PCR, forward primers 5’-ACGGCTGTCCAAGGAGCTG-3’ (rs429358) and 5’-CTTCGGGATGCGCGATGAC-3’ (rs7412), and reverse biotinylated primers 5’-CACCTGCCGGCGTACTG-3’ (rs429358) and 5’-CCCAGGCCCTGTCACGTCG-3’ (rs7412). The DNA was sequenced with these primers: 5’-CGGACATGGAGGAGCTG-3’ (rs429358) and 5’-CGATGACGCTGCGAG-3’ (rs7412).

Odor identification. We assessed OI abilities using the 40-item University of Pennsylvania Smell Identification Test (UPSIT).23 This test includes a simple scratch-and-sniff booklet along with multiple-choice response forms for OI. The UPSIT has been validated in people 5 to 85 years of age and shows a test-retest reliability of r = 0.92 to 0.95.24,25 In score is computed as the sum of the correct responses of a maximum possible 40. Both francophone and anglophone participants were presented with odors from the US version of the UPSIT. The francophone test used an in-house French translation. In a leave-one-out analysis, we assessed the reliability of the UPSIT in the PREVENT-AD cohort among an initial sample of 159 participants, obtaining a Cronbach α of 0.821, which suggests high internal consistency.

Data analyses. To avoid left skewness and a leptokurtic distribution, we transformed the raw OI scores to an UPSIT error score of log10 (41 − raw UPSIT score), as described by Moberg et al.26 Higher transformed scores thus represented greater deficit in OI. We used a Kruskal-Wallis test to compare scores in APOE e4 carriers and noncarriers. To assess the main effects on OI of various indicators of interest, we first examined bivariate relationships using simple linear regression. To examine the effect of each predictor variable in full perspective, we then constructed multivariable models, iteratively adding measures individually or in combination. Both the bivariate and multivariable analyses used robust-fit linear regression with a tuning constant of 1.205 to down-weight outliers. The latter general linear model analyses considered, in various combinations, age, sex, years of education, APOE e4 carrier status, RBANS total score (global cognition), and the CSF t-tau/Aβ1–42 ratio.
Table 1  Demographics of INTREPAD participants

<table>
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<th>Demographics</th>
<th>INTREPAD participants with LP</th>
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<th>INTREPAD participants no LP</th>
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<th>All INTREPAD participants</th>
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<td>P181-tau, pg/mL</td>
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<td>44</td>
<td>114</td>
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<td>t-tau/Aβ1-42</td>
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Abbreviations: Aβ  = β-amyloid; INTREPAD = Impact of Naproxen Treatment on Presymptomatic Alzheimer’s Disease; LP = lumbar puncture; Max, maximum; Min, minimum; MoCA = Montreal Cognitive Assessment; P181-tau = phospho-tau; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; t-tau = total tau; UPSIT = University of Pennsylvania Smell Identification Test.

χ² test for categorical variables and Kruskal-Wallis test for continuous variables.

*Participants did not consent to genotyping.

bThree RBANS reports of individuals who underwent the LP were lost.

cOne person did not consent, and some data were excluded (see Methods).
sometimes substituted as specified below by other CSF indicators of AD pathogenesis. Adjusting for age, sex, years of education, and APOE ε4 carrier status enabled us to compare our work to other highly cited findings. We verified the absence of collinearity in the multivariable models by investigating the variance inflation factor and tolerance. To test our primary hypothesis, we explored the relationships between OI and CSF AD biomarkers, seeking identifiable subgroups and examining interaction terms of interest.

Two sensitivity analyses assessed the effects of potential confounders on olfactory function. For both analyses, we grouped available data on brain injury, TIA, and stroke into a binary categorical variable called brain health. A second binary variable grouped nasal polyps, nasal surgeries, deviated septum, and history of a broken nose. A third such variable identified participants with a history of asthma, and a fourth identified current smokers of any substance. A final potential confounder characterized participants with any of the foregoing conditions (past or present) mentioned only at the time of olfactory testing. The first sensitivity analysis added all 5 of these potential confounders as covariates in the analytic framework of model 7. The other was a version of model 7 that excluded data from all participants with a positive rating on any of the 5 potential confounding variables.

RESULTS Of the 274 PREVENT-AD participants who met inclusion and exclusion criteria, 1 individual who consented for a lumbar puncture did not consent to the OI test. RBANS test results were lost for 4 participants. We excluded data from 8 participants who had incomplete test scores or nasal congestion on the day of testing. The analytic sample then comprised 265 PREVENT-AD participants, including 100 INTREPAD lumbar puncture volunteers who had complete CSF biomarker and OI data. The participant pool included predominantly francophone and female individuals who were well educated. As expected, their proportion of APOE ε4 carriers was higher than population norms (table 1). The INTREPAD participants from whom we

![Figure 1 Robust-fit linear regression models of UPSIT error score vs CSF biomarkers of AD](image-url)
collected CSF were slightly younger than other INTREPAD participants and had a higher proportion of francophone individuals and slightly lower Montreal Cognitive Assessment scores. The CSF donors appeared demographically similar to the entire PREVENT-AD group of 274 PREVENT-AD enrollees (table 1 and table e-1 at Neurology.org).

In bivariate modeling, the UPSIT error score was higher in older participants (n = 265, β = 0.0134, p = 2.24 × 10⁻³; figure e-1) and in participants with lower RBANS total score (n = 261, β = -0.00666, p = 1.28 × 10⁻³; figure e-1). However, because we were interested especially in the CSF AD biomarker data, we also evaluated models restricted to the 100 participants who had both OI and CSF data. In the reduced sample, the statistical association with older age was seen only at a trend level (β = 6.79 × 10⁻³, p = 0.095; figure e-2), but the association of reduced OI with decreased cognition remained robust (β = -4.76 × 10⁻³, p = 0.011; figure e-2). Similar unadjusted analyses showed strong association between higher UPSIT error score and increased values of CSF t-tau/Aβ₁-42 (β = 0.286, p = 4.94 × 10⁻³), P₁₈₁-tau/Aβ₁-42 (β = 1.77, p = 0.0165), and CSF t-tau levels (β = 3.61 × 10⁻³, p = 0.0257; figure 1). There was a weaker but still suggestive relationship between increased UPSIT error score and elevated CSF P₁₈₁-tau (β = 2.10 × 10⁻³, p = 0.0724) but no relationship with Aβ₁-42 alone (β = -7.01 × 10⁻³, p = 0.359).

We observed no group difference in OI between APOE ε4 carriers and noncarriers (n = 262, p = 0.271). A similar result was observed in the reduced sample of 100 participants with CSF (p = 0.7129).
However, previously observed correlations between UPSIT error score and several CSF markers of AD pathology were now apparent only in e4 carriers. In contrast to unstratified samples, the carriers showed an association between higher UPSIT error scores and reduced levels of Aβ_{1-42} (n = 33, β = −3.76 × 10^{-4}, p = 0.00841). In keeping with previously noted findings, UPSIT error score was associated in the e4 carriers with higher t-tau/Aβ_{1-42} (β = 0.352, p = 0.0158) and P_{181-tau}/Aβ_{1-42} (β = 2.416, p = 0.0270), but a comparable association appeared only at a trend level for t-tau (β = 4.68 × 10^{-4}, p = 0.0914) and not at all for P_{181-tau} (β = 2.76 × 10^{-3}, p = 0.204; figure 2). In addition, we saw that individuals with lowest CSF Aβ_{1-42} levels appeared to have a higher proportion of APOE e4 carriers (supplemental materials).

The multiple linear regression models assessed the relationships between OI and age, cognition, and CSF biomarkers added sequentially in models adjusted for sex, education, and APOE e4 carrier status. Multivariable models from the full PREVENT-AD dataset (without CSF variables) showed strong associations of UPSIT error score with age and diminished cognition, either alone or in combination (table e-2). Table 2 shows comparable analyses in the reduced sample, now including CSF data. Models 1, 2, and 3 in table 2 (supplemental materials) indicate no association of UPSIT error score with age, a trend with cognitive score (p = 0.06), but a strong association with CSF t-tau/Aβ_{1-42} (p = 0.003). Model 4 suggests that the trend association with cognition was unapparent after adjustment for age (p = 0.145). Model 5 confirms the absence (in adjusted models) of any association between OI and age, and it shows the absence of a material effect of age adjustment on the association of OI with CSF t-tau/Aβ_{1-42}.

Model 6 indicates that any association of OI with cognition became unapparent after the inclusion of CSF t-tau/Aβ_{1-42} (RBANS, p = 0.151; CSF t-tau/ Aβ_{1-42}, p = 0.004). Model 7, which includes all the described variables, made these findings clearer by suggesting that OI was predicted by its relationship with CSF t-tau/Aβ_{1-42} (p = 0.005) regardless of age, cognition, APOE e4 status, sex, or education (figure e-3). This last model explained 19.7% of the variance in OI score (F_{7,90} = 3.68, p < 0.00258). Both sensitivity analysis variants of model 7 produced nearly identical results (in the first analysis, F_{12,85} = 2.47, p < 0.00993; in the second, F_{7,83} = 2.59, p < 0.0236). The latter reduced model still explained 15.9% of the variance in OI score. Other similar multiple linear regression analyses (not shown) essentially reproduced the findings of model 7, substituting t-tau or P_{181-tau} alone or the ratio of P_{181-tau}/Aβ_{1-42} as independent CSF biomarker predictors.

DISCUSSION We investigated relationships of performance in OI with global cognitive scores, established AD risk factors, and several CSF biomarkers known to predict subsequent dementia. Our main finding was that a decrease in OI was associated with increasing CSF biomarker evidence of AD pathology. This association survived adjustment not only for sex, educational attainment, APOE e4 carrier status, and potential brain and olfactory health history confounders but also for age or cognitive score. The relationships of OI performance with age and cognitive ability recapitulate earlier findings.11,12 In the present sample, however, the relationship of OI with cognitive performance appears to be spurious because it represents the conjoint (confounded) relationship of both variables with the CSF biomarkers. We suggest that the relationship between OI and age (observed in
ological health issues. They chose to exclude participants with such issues. In addition, the earlier research was characterized by intervals ranging up to 5 years between tests of OI and PET scans, whereas our work consistently tested OI within 3 months of CSF collection. A recent study demonstrated that OI deficits are more readily detected in patients with acute brain trauma when olfactory testing is performed within days of injury.33 Recent PET studies of olfactory sensory neurons in lesioned, aging, or AD-like animal models further support this point.34

Limitations of this study include its high proportion of women and participants’ level of educational attainment, attributes that are common in aging volunteer cohorts. Although we attempted to control for these factors in multivariable models, participants who volunteered for lumbar punctures may be an even more select population, an important concern because these 100 participants produced our most informative findings. Because our results come from cross-sectional observations only, it remains unknown whether altered biomarker levels represent a process of ongoing change and, if so, the rate at which such change is accumulating. Longitudinal studies for this purpose are now in progress, as are studies assessing the physical accumulation of amyloid and tau with specific PET tracers.

Lastly, we acknowledge that our failure to observe a relationship between OI and age in the restricted sample may result from the limited sample size of the CSF donor participant pool. Generally, age is reported to be the strongest known predictor of impaired OI35,36 and the best known predictor of AD dementia. However, at least some of this age-related loss in olfactory function may relate to factors unrelated to AD pathogenesis (e.g., deterioration of nasal epithelium or calcification of the cribriform plate36).

While impaired OI may in fact help identify persons who could for various reasons eventually have cognitive impairment, we strongly urge that our present cross-sectional results not be regarded as rationale for clinical use of olfactory testing as an AD diagnostic. We suggest, however, that OI may serve for research purposes as a simple and inexpensive indicator of evolving AD pathology. Indeed, we are exploring its use as a biomarker in clinical trials among asymptomatic persons at risk of later dementia symptoms. In this and other ways, OI may add valuably to the measures available for AD prevention research.

AUTHOR CONTRIBUTIONS
Marie-Elyse Lafaille-Magnan: study concept and design, data collection (RBANS and UPSIT), statistical analysis, data interpretation, drafting/revising the manuscript. Anne Labonté, BSc, John Breitner: study concept and design, data interpretation, drafting/revising the manuscript. Pierre Etienne and Pedro Rosa-Neto: study concept and design, revising the manuscript. Jennifer Tremblay-Mercier and Joanne Frenette: study concept and design.

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conducted the CSF biomarker analyses. Cécile Madjar, MSc, directed data management, and Doris Des and Louise Thiboux did the genotyping. Cynthia Picaud, PhD, helped write the descriptions of laboratory methods. Tanya Lee, Melissa Appleby, Laura Mahur, Galina Pogossova, Renuka Giles, and Karen Wan collected cognitive and olfaction data. All are with the Centre for Studies on Prevention of AD, Douglas Mental Health University Institute. Thomas Beaudy, BSc (McGill Centre for Studies in Aging, Douglas Mental Health University Institute; Perform Centre, Concordia University), helped edit the manuscript. Tharick Ali Pascoal, MD, Marina Tedeshi Duaa, MD, and Laksakan Cheewakriengkrai, MD (McGill Centre for Studies in Aging and Centre for Studies on Prevention of AD, Douglas Mental Health University Institute), collected the CSF. Katarina Dedovic, PhD (Canadian Institutes for Health Research, Ottawa), provided valuable advice, as did Miranda Tuwaal, MSc, Angela Tam, MSc, Christina Karazian, Pierre-Francois Meyer, MSc, and Melissa Savard, MSc (all at the Centre for Studies on Prevention of AD, Douglas Mental Health University Institute). Special thanks go to Marianne Dufour, administrative assistant, and to Ginette Mayrand, Joanne Frenette, MSc, Isabelle Vallée, Rana El-Khoury, and Fabiola Ferdinand, all nurses who met with participants, as well as the entire PREVENT-AD Research Group (https://prevent.ioris.ca/acknowledgements. php?date=2017-1-26). The authors acknowledge the generosity and commitment of all research participant volunteers for this work.

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DISCLOSURE
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