

Olfactory Deficits in Patients With Mild Cognitive Impairment Predict Alzheimer's Disease at Follow-Up

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Objective: This study evaluated the predictive utility of olfactory identification deficits in patients with mild cognitive impairment for follow-up diagnosis of probable Alzheimer's disease.

Method: Ninety outpatients with mild cognitive impairment were examined at 6-month intervals. Matched healthy comparison subjects (N=45) were examined annually. The University of Pennsylvania Smell Identification Test was given at baseline.

Results: Olfaction scores were lower in patients with mild cognitive impairment than in healthy comparison subjects. Seventy-seven patients were followed up; 19 were diagnosed with Alzheimer's disease by 2 years. Patients with low olfaction scores (≤ 34 of 40), and patients with low olfaction scores who reported no subjective problems smelling, were more likely to develop Alzheimer's disease than other patients. In a Cox proportional hazards

model adjusted for age, sex, modified Mini-Mental State score, and education, low olfaction scores did not predict time until development of Alzheimer's disease, but low olfaction scores accompanied by lack of awareness of olfactory deficits predicted time to development of Alzheimer's disease. This effect remained when attention or memory measures replaced modified Mini-Mental State score in the model. In patients with high Mini-Mental State scores (≥ 27 of 30), low olfaction with lack of awareness remained a significant predictor of Alzheimer's disease. Olfaction scores of 30–35 showed moderate to strong sensitivity and specificity for diagnosis of Alzheimer's disease at follow-up.

Conclusions: In patients with mild cognitive impairment, olfactory identification deficits, particularly with lack of awareness of olfactory deficits, may have clinical utility as an early diagnostic marker for Alzheimer's disease.

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Early in the course of Alzheimer's disease, degeneration occurs in the entorhinal-hippocampal-subicular complex, and the neurons of the olfactory epithelium show numerous neurofibrillary tangles (1). Studies of olfactory tasks have consistently shown olfactory identification (discrimination among odors) deficits in patients with Alzheimer's disease in relation to comparison subjects (2–5). There is some evidence that the severity of olfactory dysfunction increases with age (6) and severity of dementia (3, 7, 8). Impaired olfactory detection has been observed in first-degree relatives of patients with Alzheimer's disease (9). The association between olfactory dysfunction and Alzheimer's disease shows moderate specificity against common neurologic and psychiatric disorders (10). Deficits in olfactory identification are not consistently seen in patients with Huntington's disease (11) or depression (12), but mild deficits have been observed in the Parkinson's dementia complex of Guam (11) and in amyotrophic lateral sclerosis (13), whereas the findings for Parkinson's disease are equivocal (14).

There is limited information on olfactory identification test performance in patients with mild cognitive impairment, defined broadly as fitting into the category between being "normal" and having "dementia." Nordin and Mur-

phy (5) have shown that compared to 16 normal comparison subjects, 16 patients with "questionable" Alzheimer's disease had significantly higher thresholds for odor but not for taste, performed significantly worse on tests of recognition memory for odors and visual stimuli, and tended to be less familiar with odors but not visual stimuli.

Early detection of Alzheimer's disease has clinical and potential therapeutic application in patients with mild cognitive impairment, some of whom progress to Alzheimer's disease, while others do not (15). Lack of awareness of cognitive deficits is common in Alzheimer's disease and may occur at the mild cognitive impairment stage, before the diagnosis of Alzheimer's disease is made (16). Similarly, lack of awareness of olfactory identification deficits may occur in patients with mild cognitive impairment, which, to our knowledge, has not been studied previously. We hypothesized that olfactory identification deficits, particularly when accompanied by lack of awareness of olfactory deficits, characterize patients with mild cognitive impairment who subsequently develop Alzheimer's disease. We report initial findings to test these hypotheses in a study of patients with mild cognitive impairment (and normal comparison subjects) followed systematically in a clinical setting.

Method

Subjects

Outpatients with mild cognitive impairment who were seen at a memory disorders center were recruited for a prospective study that examined putative early diagnostic markers of Alzheimer's disease. The research protocol was approved by the institutional review boards of the New York State Psychiatric Institute and Columbia Presbyterian Medical Center, and written informed consent was obtained from each patient. Patients were examined at 6-month intervals. Normal comparison subjects, who were matched to the patients with mild cognitive impairment on age, sex, and years of education, were examined annually.

For patients, inclusion criteria were age ≥ 40 years, intellectual impairment for ≥ 6 months and ≤ 10 years, and the diagnosis of "not demented" (score=0) or "questionably demented" (score=0.5) on the Clinical Dementia Rating scale (17). Patients had a minimum modified Mini-Mental State score of ≥ 40 of 57 (equivalent to Mini-Mental State score of ≥ 22 [18, 19]), with the caveat that primarily Spanish-speaking patients with ≤ 5 years of education were included if they had a modified Mini-Mental State score of ≥ 35 . The following deficits on neuropsychological testing served as screening guidelines: impairment in memory, as evidenced by recall of fewer than three of three objects after 5 minutes on the modified Mini-Mental State (18), a delayed recall score of more than one standard deviation below norms in the six-trial Selective Reminding Test (20), or impaired intellectual performance, as evidenced by a WAIS-R performance IQ ≥ 10 points below the WAIS-R verbal IQ. These neuropsychological criteria served only as screening guidelines; the final determination for study inclusion was based on a consensus diagnosis by expert raters.

Exclusion criteria were a diagnosis of dementia, schizophrenia, schizoaffective disorder, or primary major affective disorder that clearly preceded the onset of cognitive impairment; ECT within the past 6 months; current or recent (past 6 months) history of alcohol or substance dependence (per DSM-IV criteria); clinical or historical evidence of stroke (cortical stroke or an infarct ≥ 2 cm in diameter on any magnetic resonance imaging [MRI] slice; periventricular hyperintensities and small subcortical lacunae or infarcts did not lead to exclusion); cognitive impairment rated as entirely caused by concomitant medications; and the presence of major neurologic illness (e.g., Parkinson's disease or amyotrophic lateral sclerosis). These inclusion and exclusion criteria defined a relatively broad group of patients between "normal" and "with dementia" and were similar to those used in other studies of mild cognitive impairment (21, 22).

Procedures

At the initial evaluation, a study physician (neurologist or psychiatrist) obtained a detailed medical history and conducted general physical, neurological, and psychiatric examinations. Laboratory tests included a CBC with differential and measures of serum electrolytes, liver and renal function, thyroid function, VDRL, serum B₁₂ and folate levels, and an MRI scan of the brain. A trained neuropsychology technician administered the following tests: the WAIS-R, the Wechsler Memory Scale (23), the Selective Reminding Test (24), the Rosen Drawing Test (25), the Controlled Oral Word Association Test (26), the category naming test from the Boston Diagnostic Aphasia Evaluation (27), the Boston Naming Test (28), the Benton Visual Retention Test (29), and the Target Finding Test (30) (shape and letter cancellation tasks). A senior neuropsychologist (Y.S.) reviewed the test results, and a diagnostic impression and report were completed for each patient.

A team of neurologists, psychiatrists, and neuropsychologists, including the evaluating physician, reviewed all the available in-

formation and reached a provisional diagnosis. Subsequently, two authors who were also expert clinical raters (D.P.D. and Y.S.) used this information and additional data (e.g., the patient's report or behavior during testing procedures) to make independent diagnoses, followed by a consensus research diagnosis. This consensus diagnosis, made by the two raters, determined study inclusion or exclusion.

At annual follow-ups, a similar set of evaluations was conducted. Only the information obtained from those visits was available, from which the two raters independently made diagnoses. If the diagnosis changed from the previous evaluation, a review of the entire medical and research record was conducted to confirm the change. A diagnosis of dementia was made on the basis of DSM-IV criteria, and the diagnosis of possible or probable Alzheimer's disease was made on the basis of criteria from the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (31). For the diagnoses of both cognitive impairment and dementia, the most likely etiology (or etiologies) was identified. The consensus diagnosis made by the two expert raters was the primary outcome variable. There was diagnostic agreement in 95.5% of the cases for the two expert raters' independent diagnosis of dementia versus no dementia.

At baseline evaluation, with the use of a rating on a 4-point scale for lack of awareness of cognitive impairment (32), 16 of the 19 patients who developed Alzheimer's disease on follow-up scored 1 (fully aware of cognitive impairment), and three patients scored 2 (mild lack of awareness of cognitive impairment). This near-universal high level of awareness of cognitive impairment was likely due to inherent bias resulting from the study group, which comprised patients with mild cognitive impairment who brought themselves to a memory disorders clinic for evaluation; hence, this variable was not analyzed as a predictor of Alzheimer's disease at follow-up.

At initial evaluation donepezil had been taken by one patient, vitamin E or ginkgo biloba by 10 patients, and estrogen by seven patients. The use of these putative cognitive enhancers was analyzed as a dichotomous variable (present or absent). At follow-up one patient had taken donepezil, three to nine patients had taken vitamin E or ginkgo biloba, and three to eight patients had taken estrogen at various times.

For patients with mild cognitive impairment and comparison subjects, apolipoprotein E genotyping was conducted by means of standard methods in which DNA was amplified by the polymerase chain reaction (33). Genotypes were determined while researchers were blind to subject status (patient or comparison) by the sizes of DNA fragments present and viewed and photographed under ultraviolet light after staining with 0.5 μ g of ethidium bromide.

Test of Olfaction

Strong psychometric properties have been demonstrated for the University of Pennsylvania Smell Identification Test (34), a scratch-and-sniff test that takes 10–15 minutes to administer. Each of 40 common odorants is embedded in a microcapsule on a separate page, and the subject has to select one of four written multiple-choice alternatives for each odorant (total score range=0–40). At the initial evaluation a trained research coordinator administered the University of Pennsylvania Smell Identification Test to patients with mild cognitive impairment and comparison subjects, presenting stimuli to both nostrils simultaneously. The total score obtained for each subject was used in statistical analyses. In the University of Pennsylvania Smell Identification Test, introductory questions requested a smoking history, and the derived smoking variables (current or past smoking history) were also evaluated.

Statistical Analyses

Two-tailed t tests or chi-square analyses were conducted to compare the demographic and clinical features and olfaction scores of patients with mild cognitive impairment and normal comparison subjects. Two-tailed t tests or chi-square analyses were also conducted to evaluate the association between patients with and without the follow-up diagnosis of dementia and baseline age, sex, modified Mini-Mental State score, years of education, and olfaction scores. The initial question on the University of Pennsylvania Smell Identification Test states, "Do you suffer from smell problems?" Possible answers are "yes" or "no." Patients with mild cognitive impairment who had low baseline olfaction scores (≤ 34 ; cutoff point was the median score of patients with mild cognitive impairment who did not develop Alzheimer's disease by follow-up) accompanied by the report of no problems smelling were classified into one group and the remainder of the patients made up the other group. This dichotomous classification variable, "low olfaction plus lack of awareness," was analyzed in addition to total olfaction score on the University of Pennsylvania Smell Identification Test.

Because of varying lengths of follow-up, survival analysis was the main statistical method employed. A Kaplan-Meier nonparametric survival function was calculated. A global test for proportions was used to check the assumptions of the Cox proportional hazards model, which was used to assess the relative risk of incident Alzheimer's disease. The timing variable was the time from the initial visit to the first follow-up, during which a diagnosis of Alzheimer's disease was made. In addition to the two olfaction measures, age, sex, modified Mini-Mental State score, and years of education were included as variables in these analyses. The choice of these covariates was based on their association with the outcome of Alzheimer's disease in this clinical group, which was consistent with the literature (21, 22). To evaluate prediction of Alzheimer's disease in the intermediate term, logistic regression analyses were conducted with the same covariates after restricting the group with mild cognitive impairment to patients who had completed the 2-year follow-up (or developed Alzheimer's disease before that time); the binary outcome was the indication of developing Alzheimer's disease within 2 years of the baseline evaluation. Sensitivity and specificity for the follow-up diagnosis of Alzheimer's disease were calculated for both low olfaction and the low olfaction plus lack of awareness variable across a range of scores (27–37) on the University of Pennsylvania Smell Identification Test for the group followed up at 2 years.

Results

Baseline Demographic and Clinical Features

The study clinical group comprised 90 patients with mild cognitive impairment (47 women, 52.2%) and 45 normal comparison subjects (24 women, 53.3%). At the initial evaluation patients with mild cognitive impairment had a mean age of 66.7 years ($SD=10.7$) and a mean of 15.0 years of education ($SD=3.9$). For normal comparison subjects, the mean age was 64.0 years ($SD=10.0$), and the mean number of years of education was 15.6 ($SD=2.6$). The mean modified Mini-Mental State score (range=0–57) was significantly lower in patients (mean=51.3, $SD=4.4$) than in comparison subjects (mean 55.0, $SD=1.5$) ($t=4.9$, $df=133$, $p<0.001$), as was the mean Mini-Mental State score (patients: 27.4, $SD=2.1$; comparison subjects: 29.4, $SD=0.8$) ($t=4.5$, $df=133$, $p<0.001$). In the 90 patients with mild cognitive impairment, the clinical dementia rating was 0

(no dementia) in 38.9% ($N=35$) and 0.5 (questionable dementia) in 61.1% ($N=55$).

Olfaction at Initial Evaluation

The mean baseline olfaction total score was significantly lower in patients with mild cognitive impairment (31.0, $SD=7.4$) than in normal comparison subjects (35.2, $SD=3.9$) ($t=3.6$, $df=133$, $p<0.001$). In patients, baseline olfaction scores correlated inversely with age (Pearson's $r=-0.44$, $df=88$, $p<0.001$), positively with baseline modified Mini-Mental State score ($r=0.37$, $df=88$, $p<0.001$), and positively with years of education ($r=0.27$, $df=88$, $p<0.02$) but not with sex, duration of cognitive impairment, score on the Blessed Functional Activity Scale (35), or current or past smoking history. In normal comparison subjects, the mean baseline olfaction score showed no significant associations with age, sex, years of education, current or past smoking history, or modified Mini-Mental State score.

Follow-Up Evaluation

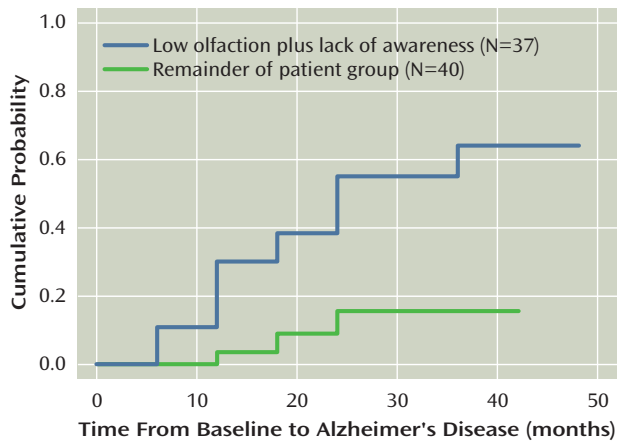
In the 77 patients with mild cognitive impairment who were followed up (13 recently recruited patients had not yet returned for follow-up), the mean duration of follow-up was 20 months ($SD=12$). Of these 77 patients, all 19 who met the consensus diagnostic criteria for dementia also met the criteria for probable Alzheimer's disease (31). The patients who used putative cognitive enhancers were not significantly less likely to develop Alzheimer's disease than the remainder of the clinical group.

Prediction of Alzheimer's Disease at Follow-Up

Women were more likely than men to receive a final diagnosis of Alzheimer's disease ($\chi^2=4.8$, $df=1$, $p<0.05$). Age ($t=3.2$, $df=75$, $p<0.01$), fewer years of education ($t=2.4$, $df=75$, $p<0.05$), low baseline modified Mini-Mental State scores ($t=3.1$, $df=75$, $p<0.01$), and low baseline olfaction scores ($t=3.4$, $df=75$, $p<0.001$) were each associated with the diagnosis of Alzheimer's disease at follow-up. Family history of dementia and baseline scores on the Blessed Functional Activity Scale and the 17-item Hamilton Depression Rating Scale were not associated with a final diagnosis of Alzheimer's disease. Sixteen of 64 patients who reported no problems smelling, compared to three of 13 patients who reported problems smelling, had developed Alzheimer's disease by follow-up (n.s.).

Low olfaction scores (≤ 34) predicted the diagnosis of Alzheimer's disease at follow-up (19 of 47 with low olfaction scores developed Alzheimer's disease compared to zero of 30 with high olfaction scores) ($\chi^2=16.1$, $df=1$, $p<0.001$); all 19 patients with mild cognitive impairment who developed Alzheimer's disease had low olfaction scores. Low olfaction scores accompanied by subjective report of no problems smelling were present in 16 of 19 patients who met the criteria for Alzheimer's disease at follow-up compared to 21 of 58 who did not meet (or had not yet met) the criteria for Alzheimer's disease at follow-up ($\chi^2=13.2$, $df=1$, $p<0.001$). When we examined cutoff points

FIGURE 1. Kaplan-Meier Survival Curve of Probability of Developing Alzheimer's Disease Over 4 Years in Subjects With Mild Cognitive Impairment at Baseline, by Presence or Absence of Baseline Olfactory Deficit Plus Lack of Awareness of Deficit



for “low olfaction score” across the 30–36 (≤ 30 to ≤ 36) scoring range, low olfaction plus lack of awareness remained a significant predictor of Alzheimer's disease ($\chi^2=8.9-13.2$, $df=1$, $p<0.01-0.001$). Fourteen of 19 who developed Alzheimer's disease had low olfaction plus lack of awareness at a cutoff point of ≤ 33 , 16 of 19 who developed Alzheimer's disease had low olfaction plus lack of awareness at a cutoff point of ≤ 35 (or ≤ 34 ; cutoff used in the analyses), and 16 of 19 who developed Alzheimer's disease had low olfaction plus lack of awareness at a cutoff point of ≤ 36 . Among patients with mild cognitive impairment, only three (3.9%) of 77 reported problems smelling but scored ≥ 35 on the olfaction test.

The Kaplan-Meier survival curve for patients with low olfaction plus lack of awareness, compared to that for the remainder of the patient group, is presented in Figure 1. In a Cox proportional hazards model, olfaction scores alone predicted time to develop Alzheimer's disease ($\chi^2=8.8$, $df=1$, $p<0.005$), but subjective reports of problems smelling analyzed alone were not predictive of Alzheimer's disease. In Cox analyses, low olfaction scores (or olfaction scores dichotomized as ≤ 34 versus >34) were not significantly predictive when age (n.s.), sex (n.s.), modified Mini-Mental State score (n.s.), and years of education (n.s.) were entered into the same model. Low olfaction plus lack of awareness was a significant predictor (relative risk=7.3, 95% confidence interval [CI]=1.7–23.1, $p<0.01$) of time to develop Alzheimer's disease when age (n.s.), sex (n.s.), modified Mini-Mental State score (n.s.), and years of education (n.s.) were also included in the Cox model. This effect remained when, instead of modified Mini-Mental State score, the attention (Target Finding Test letter cancellation task) or memory (Selective Reminding Test total recall task) measures were included in this model with low olfaction plus lack of awareness (attention: relative risk=10.7, 95% CI=2.5–41.0, $p<0.005$; and memory: relative

risk=4.7, 95% CI=1.2–18.2, $p<0.05$). Low olfaction plus lack of awareness remained a significant predictor of time until the development of Alzheimer's disease (relative risk=7.3, 95% CI=1.8–42.7, $p<0.01$), even after entering age (n.s.), sex (n.s.), and all three neuropsychological measures (modified Mini-Mental State score [n.s.], attention measure [$p<0.02$], and memory measure [n.s.]) into the same Cox model.

For each olfaction score in the 31–36 range, the low olfaction plus lack of awareness variable remained a significant predictor of time to develop Alzheimer's disease in Cox analyses that included age, sex, years of education, and modified Mini-Mental State score as covariates. For an olfaction score of ≤ 30 , the values for low olfaction plus lack of awareness were not significant.

Additional Cox analyses were conducted separately in the subgroup with high baseline Mini-Mental State scores (≥ 27 of 30, $N=52$); low olfaction plus lack of awareness remained a significant predictor of time until the development of Alzheimer's disease (relative risk=10.8, 95% CI=1.1–105.0, $p<0.05$) when age, sex, years of education, and baseline Mini-Mental State score were included in the model. In this subgroup with high scores on the Mini-Mental State, eight of nine patients who met the criteria for Alzheimer's disease had baseline low olfaction plus lack of awareness ratings compared to 15 of 43 who did not meet (or had not yet met) the criteria for Alzheimer's disease ($\chi^2=8.8$, $df=1$, $p<0.01$). The nine patients with high Mini-Mental State scores who were diagnosed with Alzheimer's disease at the 2-year follow-up had significantly lower baseline olfaction scores (mean=27.1, $SD=5.9$) than the 43 patients who were not diagnosed with Alzheimer's disease at the 2-year follow-up (mean=34.1, $SD=4.6$) ($t=3.8$, $df=51$, $p<0.001$).

To evaluate clinically relevant prediction in the intermediate term, further analyses were conducted by restricting the clinical group with mild cognitive impairment to the patients who had completed 2 years of follow-up ($N=36$) or had already developed Alzheimer's disease by 2 years ($N=4$). In this subsample of 40 patients with mild cognitive impairment (18 who had and 22 who had not developed Alzheimer's disease), baseline olfaction scores were lower in those who had developed Alzheimer's disease (mean=26.3, $SD=7.7$) than in those who had not (mean=31.5, $SD=7.4$) ($t=2.1$, $df=38$, $p<0.05$). Fifteen of 18 patients who met the criteria for Alzheimer's disease at the 2-year follow-up had low olfaction plus lack of awareness at baseline compared to nine of 22 who had not met (or have not yet met) the criteria for Alzheimer's disease ($\chi^2=7.4$, $df=1$, $p<0.01$). In survival analyses that evaluated the outcome of Alzheimer's disease at the 2-year follow-up, low baseline olfaction scores (or olfaction scores dichotomized as ≤ 34 versus >34) did not predict Alzheimer's disease when age, sex, modified Mini-Mental State score, and years of education were also included in the model. However, low olfaction plus lack of awareness at baseline was a significant predic-

tor of Alzheimer's disease (relative risk=6.4, 95% CI=1.5–26.8, $p<0.01$) when age, sex, modified Mini-Mental State score, and years of education were also included in the model. Similarly, for patients who had completed the 2-year follow-up, logistic regression analyses revealed that low olfaction plus lack of awareness at baseline was a significant predictor of Alzheimer's disease (odds ratio=13.1, 95% CI=1.6–116.0, $p<0.05$) when age, sex, modified Mini-Mental State score, and years of education were also included in the model.

For this subgroup followed up at 2 years, baseline olfaction total scores of ≤ 34 led to 100% sensitivity and 45.5% specificity for the diagnosis of Alzheimer's disease, including a progressive decrease in sensitivity and an increase in specificity with lower olfaction scores (Table 1). Comparable figures were obtained for the low olfaction plus lack of awareness variable by using a wide range of cutoff points for "low olfaction score" (Table 1). For both olfaction variables, the optimal tradeoff between sensitivity and specificity appeared to be in the 30–35 scoring range.

The apolipoprotein E genotype was evaluated in 77 patients with mild cognitive impairment. Only 11 (14.3%) of the 77 patients with mild cognitive impairment had the apolipoprotein E $\epsilon 4$ allele (hetero- or homozygous), and four of these 11 patients had developed Alzheimer's disease. There was no association between the presence of the $\epsilon 4$ allele and either of the olfaction measures or the outcome of Alzheimer's disease, but the small number of patients with the $\epsilon 4$ allele precluded meaningful statistical analyses.

Discussion

In this clinical group of patients with mild cognitive impairment, low olfactory identification test scores at baseline predicted the diagnosis of Alzheimer's disease at follow-up. Subjective reports of no problems smelling were not predictive of the development of Alzheimer's disease because most patients who reported no problems smelling actually scored well (≥ 35 of 40) on the olfaction test (like most of the general population). However, 16 of 19 patients who reported no problems smelling yet scored low on the olfaction test had developed Alzheimer's disease by the 2-year follow-up. This effect remained significant in Cox survival analyses after controlling for age, sex, years of education, and cognitive scores (on the modified Mini-Mental State and attention or memory measures), indicating that the results could not be explained by lack of attention or poor memory. Similar findings were obtained by using logistic regression analyses for the subgroup followed up at 2 years. Although low olfaction score alone predicted time to develop Alzheimer's disease, it did not predict time to develop Alzheimer's disease in Cox analyses that controlled for age, sex, years of education, and modified Mini-Mental State score, indicating overlapping variance in prediction (baseline olfaction score cor-

TABLE 1. Sensitivity and Specificity of Olfaction and Olfaction Plus Lack of Awareness of Olfactory Deficit in Predicting Alzheimer's Disease at 2-Year Follow-Up^a in 40 Patients With Mild Baseline Cognitive Impairment^b

Cutoff for Olfaction Score (range=0–40)	Baseline Olfaction Score		Olfaction Score Plus Lack of Awareness of Olfactory Deficit	
	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)
<27	44.4	81.8	27.8	86.4
<28	44.4	81.8	27.8	86.4
<29	44.4	77.3	27.8	81.8
<30	55.6	77.3	38.9	81.8
<31	55.6	72.7	38.9	81.8
<32	61.1	68.2	44.4	77.2
<33	77.8	59.1	61.1	72.7
<34	88.9	50.0	72.2	63.6
<35	100.0	45.5	83.3	59.1
<36	100.0	36.4	83.3	54.5
<37	100.0	18.1	83.3	36.4

^a Four patients had not yet been followed up for the full 2 years but had already developed Alzheimer's disease.

^b Olfaction was measured with the University of Pennsylvania Smell Identification Test. The test's first question, "Do you suffer from smell problems?," was used to determine awareness of olfactory problems. Subjects who answered "no" and had olfaction scores ≤ 34 were considered to lack awareness of the olfactory deficit.

related significantly with age [inverse], education, and modified Mini-Mental State score). The results suggest that low olfaction plus lack of awareness may not have the same degree of overlapping variance with these demographic and clinical factors and, hence, may contribute uniquely to the prediction of time to develop Alzheimer's disease.

In patients with high baseline scores on the Mini-Mental State (≥ 27 of 30), low olfaction plus lack of awareness remained a significant predictor of Alzheimer's disease in Cox analyses that controlled for demographic and clinical factors. This suggests the possible predictive utility of olfactory deficits in patients with minimal cognitive deficits, who are often difficult to diagnose and in whom prognosis is unclear. For the 2-year prediction of Alzheimer's disease, both the low olfaction and low olfaction plus lack of awareness variables showed high sensitivity for scores of ≤ 35 , with high specificity for scores of ≤ 30 . Scores above or below the 30–35 range led to relatively low sensitivity or specificity (Table 1), suggesting that University of Pennsylvania Smell Identification Test scores in the 30–35 range may be useful in patients with mild cognitive impairment as a potential predictor of Alzheimer's disease. In cross-sectional studies that compared patients with Alzheimer's disease to comparison subjects and first-degree relatives of Alzheimer's patients to comparison subjects, cutoff scores of 27 and 30 on the University of Pennsylvania Smell Identification Test showed the best discrimination, respectively (7, 9). Olfaction scores are known to decrease with increasing severity of the disease (7), so it is not surprising that the cutoff scores for the University of Pennsylvania Smell Identification Test showing the best prediction of Alzheimer's disease in our study of mild cognitive

impairment were higher than those in studies of patients with Alzheimer's disease.

In our study group, sample data were used to derive the optimal cutoff scores (≤ 34), as was done in studies of patients with Alzheimer's disease (7, 9). Given this limitation and the paucity of other data on the use of the University of Pennsylvania Smell Identification Test in predicting Alzheimer's disease in patients with mild cognitive impairment, our findings require independent replication before specific cutoff scores on the University of Pennsylvania Smell Identification Test can be recommended for use in clinical practice. Also, linking low olfaction scores with the symptom of lack of awareness of the olfactory deficit to create a dichotomous variable has not been done before, to our knowledge, in studies of mild cognitive impairment or Alzheimer's disease, further emphasizing the need for independent replication.

One consequence of the follow-up being limited to date is that these analyses absorb considerable error because many current patients with mild cognitive impairment but without Alzheimer's disease at the 2-year follow-up will develop Alzheimer's disease after longer follow-up intervals. The use of survival analyses only partly addressed this limitation, which precludes being definitive about the prediction of long-term outcomes. Another limitation of the study was the use of a single "yes" or "no" item for subjective reports of problems smelling. Future research should evaluate in greater depth this subjective symptom, which, to our knowledge, has not previously been evaluated in patients with mild cognitive impairment.

We found that patients with mild cognitive impairment scored lower than matched normal comparison subjects on the University of Pennsylvania Smell Identification Test. This result is consistent with findings from other studies that compared patients with mild cognitive impairment (5) and patients in the early stages of Alzheimer's disease (2–4) to normal comparison subjects. The findings with the low olfaction plus lack of awareness variable are also consistent with results from a study that reported lack of awareness of loss of smell in 74% of the patients with Alzheimer's disease compared to only 8% of the patients with sinusitis (36). Other studies have shown that unlike olfaction deficits, deficits in other sensory modalities, including taste, do not distinguish patients with Alzheimer's disease from normal comparison subjects (3, 5).

From a theoretical perspective, lack of awareness of the olfactory deficit can be considered a type of anosognosia. In the patients with mild cognitive impairment who subsequently met the criteria for Alzheimer's disease, anosognosia was in the domain of lack of awareness of the olfactory deficit and not in the domain of lack of awareness of the cognitive deficit; the latter was a likely artifact of the fact that this was a clinical group with mild cognitive impairment that was evaluated for cognitive complaints. Anosognosia, broadly defined, is thought to be mediated primarily by the parietal lobe (37), although the frontal

lobe may also be involved (38). In Anton's syndrome, unawareness of the visual deficit is due to damage to the visual association cortex, which is in close proximity to the primary visual cortex (39). Using this analogy, we speculate that awareness of the loss of the sense of smell, for which the brain center remains unidentified, may be localized to medial-temporal lobe structures that are known to be affected early in Alzheimer's disease and are associated with olfactory detection deficits (10). This could explain why low olfaction scores accompanied by a lack of awareness of the olfactory deficit in patients with mild cognitive impairment strongly predicted Alzheimer's disease at follow-up.

In patients with Alzheimer's disease, both a sensory deficit and a higher-level deficit in the cortical perception and integration of an olfactory stimulus may occur (10). The findings of deficits in both olfactory detection and the awareness of olfactory deficits suggest that deficits at both the sensory level and the level of higher-order processing for olfaction occur at the stage of mild cognitive impairment in patients who eventually meet the clinical diagnostic criteria for Alzheimer's disease. The strength of our findings suggests potential clinical utility for olfactory deficits, particularly the variable for low olfaction plus lack of awareness, as an early diagnostic marker of Alzheimer's disease. Longer follow-up periods and independent replication in larger clinical groups are needed to establish clinical utility.

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dropout, at which point the data for that subject are censored from the analysis. This method also demonstrated a significant interaction (Cox proportional hazards regression model, $\chi^2=7.56$, $df=1$, $p=0.006$); similar data patterns were obtained. Thus, all three analyses—intent to treat, completer, and survival—demonstrate a significant interaction of gender and treatment, which underscores the strength of our findings.

Dr. Quitkin et al. note that other studies have not shown differences in response rates between SSRIs and tricyclic antidepressants in depressed men, although no references are given. They also raise the possibility that our findings were due to a type I error. To our knowledge, this is the first large published study to compare rates of response to SSRIs and tricyclic antidepressants by gender. As men typically constitute a minority of the participants in studies of depression, it is conceivable that earlier studies may not have had adequate power to detect such modest, albeit important, differences. Although few researchers have examined sex differences in response rates, the results of several studies have supported our findings (1–3; unpublished report by Yonkers et al., 1996; unpublished report by Baca et al., 2000). Such consistencies across studies mitigate the likelihood of a coincidental finding or a type I error.

We believe that the possibility of differential treatment response rates by gender warrants serious investigation. One of the major points of our article was the importance of analyzing data by both gender and menopausal status, and not assuming there are no differences in response or tolerability that are related to these factors.

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Olfactory Deficit in Alzheimer's Disease?

TO THE EDITOR: D.P. Devanand, M.D., and colleagues (1) reported that a deficit in identifying odors, as measured by the Pennsylvania Smell Identification Test, predicted later development of Alzheimer's disease in subjects who were unaware of their olfactory deficit. However, it remains unclear whether the observed deficit was a result of an impairment in olfactory discrimination or of a more general semantic categorization impairment (naming odors or recognizing their names). The few studies of olfactory evoked potentials in Alzheimer's dis-

ease have contradictory results. In the study by Sakuma et al. (2) of patients with Alzheimer's disease, olfactory evoked potentials had fewer components despite the patients' having no olfactory dysfunction. By contrast, Hawkes and Shephard (3) found that scores on the Pennsylvania Smell Identification Test were abnormal in eight patients with Alzheimer's disease, although olfactory evoked potentials were normal in the four who could be tested.

Dr. Devanand et al. found that olfactory difficulties, along with the lack of awareness of olfactory dysfunction, together predicted development of Alzheimer's disease. Sixteen of their 19 patients who developed Alzheimer's disease were aware of their declining cognitive function but reported having no problem identifying smells. However, explicit and implicit categorization is disrupted in patients with Alzheimer's disease. Patients with Alzheimer's disease are impaired in learning prototype categories (4) and in recognizing semantic categories (5). The Pennsylvania Smell Identification Test requires patients to recognize and select the name of the previously smelled odor from a list, which requires semantic categorization. Thus, impaired categorization could contribute to impairment on the Pennsylvania Smell Identification Test.

Because the prevalence of Alzheimer's disease is 3% in individuals above age 40 in the population, the study by Dr. Devanand et al. is potentially of great significance; it could lead to the development of an easy, inexpensive olfaction/categorization screening test for Alzheimer's disease. If impaired categorization is responsible for the findings of impaired odor identification in patients with Alzheimer's disease, several other tests of categorization could be suggested for screening. On the other hand, if the olfactory impairment is found to be specific to Alzheimer's disease, the use of the Pennsylvania Smell Identification Test and other olfactory measurements will be necessary. Further studies using complex behavioral, psychophysiological, and electrophysiological measures of olfaction could solve this problem.

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TO THE EDITOR: I read with great interest the article by Dr. Devanand et al. Although this is a fascinating and important study that is in general accordance with another recent pro-

spective study (1), there are several errors that should be pointed out.

First, the authors stated that deficits in olfactory identification are not consistently seen in patients with Huntington's disease. In fact, olfactory loss is common in patients with Huntington's disease once the clinical signs of the disorder are manifest. For example, in one study (2), 25 of 25 Huntington's disease patients exhibited Pennsylvania Smell Identification Test scores below those of matched comparison subjects and at-risk asymptomatic relatives. This is nearly equivalent to the finding reported by my colleagues and me in 1987 (3) that 23 of 25 patients with early-stage Alzheimer's disease who were capable of psychophysical testing scored below matched normal comparison subjects on the Pennsylvania Smell Identification Test. In accordance with the general thesis of Dr. Devanand et al., we found in this early study that only two of 34 patients with Alzheimer's disease were aware of their deficit.

Second, the authors stated that the findings relative to olfactory losses for Parkinson's disease are "equivocal." In fact, the prevalence and magnitude of olfactory losses of patients with Parkinson's disease are indistinguishable from those seen in early-stage Alzheimer's disease, both in terms of scores on the Pennsylvania Smell Identification Test and threshold values (4, 5).

Dr. Devanand et al., as well as others, have asked whether many older patients with olfactory losses and marginal cognitive impairment already have Alzheimer's disease that has not progressed clinically to the point at which it can meet the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association. If so, then a redefinition of the operational criteria for establishing the presence of Alzheimer's disease at its earliest stages may be in the offing, perhaps incorporating criteria determined from both olfactory tests and magnetic resonance imaging (MRI) (6).

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TO THE EDITOR: The report by Dr. Devanand and colleagues confirmed prior work (1, 2) but confused some terms and

concepts. The authors cited evidence (2) that "impaired olfactory detection has been observed in first-degree relatives of patients with Alzheimer's disease" (p. 1399). In fact, the study to which they referred demonstrated significantly reduced olfactory *identification* scores, not odor *detection* scores, in these relatives. A prior study (1) noted impaired odor identification at the earliest phase of Alzheimer's disease but intact detection until at least moderate disease progression. This means that a patient with early Alzheimer's disease or someone who has preclinical Alzheimer's disease (is at risk) may have an impaired ability to choose the correct name of an odorant but can smell the presence of that odor as well as any age-matched comparison subject. Because these patients can detect odors normally, they probably report no problem smelling. Thus, their negative response to the question about problems smelling does not relate to their reduced ability to name odorants; this cannot, then, be considered anosognosia.

The authors also supported their findings by noting a prior report of the lack of awareness of loss of smell in 74% of patients with Alzheimer's disease compared to 8% of subjects with sinusitis (3). The latter ailment affects peripheral portions of the olfactory system, leading to diminished detection, which is likely to be perceived as loss of smell. Alzheimer's disease patients, however, have damaged medial temporal lobes, leading to poor identification but no change in detection. In summary, the study by Dr. Devanand et al. mixed the "aromas" of apples and oranges.

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Dr. Devanand and Colleagues Reply

TO THE EDITOR: Drs. Nagy and Loveland propose that the olfactory identification deficit in Alzheimer's disease is a result of a general semantic categorization impairment (trouble naming odors or recognizing their names) and is not due to an olfactory memory deficit. However, evidence from a number of studies has clearly shown that the deficit in olfactory identification in Alzheimer's disease is largely the result of impairment in olfactory memory. In an elegant series of experiments, Larsson et al. (1) showed that patients with mild Alzheimer's disease performed worse than matched healthy comparison subjects on four types of olfactory identification tasks, one of which involved the matching of specific smells to which the subject had been previously exposed without requiring him or her to name the smell. In our study of mild cognitive impairment, olfactory identification deficits accompanied by lack of awareness of these deficits predicted conversion to Alzheimer's disease in Cox analyses (relative risk=5.91, 95% confidence interval=1.5-23.7, $p < 0.02$), even af-

ter control for age, sex, education, and modified Mini-Mental State Examination (MMSE) and Boston Naming Test scores (data for attentional and memory measures but not the Boston Naming Test were presented in the article). This finding supports the view that the olfactory deficit in Alzheimer's disease is not caused solely by a deficit in naming or semantic categorization. We agree with these authors' view that olfactory evoked potentials are probably not likely to prove useful for potential clinical application in making the early diagnosis of Alzheimer's disease.

We agree with Dr. Doty's point that olfactory identification deficits are not specific to Alzheimer's disease but are also present in Huntington's disease and Parkinson's disease. A critical point by Dr. Doty is that in an earlier study only two of 34 Alzheimer's disease patients were aware of their olfactory deficit. These data provide independent confirmatory evidence to support some of our main findings. Finally, the suggestion that operational diagnostic criteria for Alzheimer's disease should include MRI and olfactory criteria is intriguing, but more research to establish sensitivity, specificity, and positive and negative predictive value for these putative early diagnostic markers is necessary before such a step can be taken.

We thank Dr. Serby for pointing out that the word "detection" was erroneously used instead of "identification" in the reference in our article to family members of patients with Alzheimer's disease. However, throughout the rest of our article, there was repeated mention of the fact that the deficit in Alzheimer's disease is in the identification and not in the detection of odors, as has been established in the literature.

In our study, low olfaction scores in mild cognitive impairment predicted Alzheimer's disease during follow-up, and low olfaction scores accompanied by lack of awareness of the olfactory deficit added unique variance to the prediction of Alzheimer's disease after control for age, gender, education, and MMSE score. To assess awareness of difficulty in smelling, we used the Pennsylvania Smell Identification Test item that asks whether the subject has any problems smelling. We agree with Dr. Serby that this standard question in the Pennsylvania Smell Identification Test is ambiguous and that the subject can interpret it to mean problems in detecting or identifying smells or both. Future research on this issue should separate these two components to avoid potential ambiguity for subjects answering questions about their ability to smell.

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Anxiety in Major Depression

TO THE EDITOR: In their study, Giovanni P.A. Placidi, M.D., et al. (1) made an impressive effort to deconvolute the complex relationships among suicide attempts, panic disorder, and anxiety-related variables in the context of major depression. They

found no greater risk of suicide attempts in depressed patients with comorbid panic disorder and suggested that anxiety may actually play a role in preventing suicide attempts. They effectively articulated the serious implications this finding might have for the treatment of comorbid anxiety and depression.

Several issues need to be considered before conclusions can be drawn regarding the exact relationship between comorbid anxiety and suicide attempts. Community-based studies have shown a greater level of past suicide attempts in subjects with comorbid disorders (2, 3). The apparent discordance among studies might easily be accounted for by sample differences, but the question remains: which sample is more representative of the patients in the typical psychiatric care setting? In addition, numerous investigations, including longitudinal studies (see reference 4 for a review), have suggested that panic disorder is associated with a greater risk of suicide in depressed patients.

The authors stated that, in a logistic regression model, "panic disorder and anxiety measures together, with adjustment for aggression, were significant predictors of attempter status" (p. 1615), with greater anxiety associated with a lower likelihood of suicide attempts. The details of the multivariate analysis used to reach those conclusions were not made clear. Not all of the unadjusted Hamilton Anxiety Rating Scale and Brief Psychiatric Rating Scale anxiety scores were significantly associated with attempter status, and it is unclear which anxiety scores were included in the model. This is particularly important given the likely distinct etiologies of cognitive and somatic anxiety. Moreover, it would be advantageous to know the quantitative relationships between the anxiety scores and attempter status and how those relationships might translate into clinically observable phenomena. It is particularly surprising that the Beck Depression Inventory score was not considered in the multivariate analyses given that the differences between the attempters and nonattempters in the Beck Depression Inventory scores were more significant than differences in any of the Hamilton anxiety scale scores.

It is intrinsically difficult to draw conclusions about suicidality from cross-sectional studies; however, this study demonstrated the value of measuring quantitative anxiety-related traits in assessing suicidal behavior. It is hoped that the investigators will consider such variables in the design of future longitudinal studies.

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