

Olfactory Identification and Incidence of Mild Cognitive Impairment in Older Age

Robert S. Wilson, PhD; Julie A. Schneider, MD; Steven E. Arnold, MD; Yuxiao Tang, PhD; Patricia A. Boyle, PhD; David A. Bennett, MD

Context: Mild cognitive impairment (MCI) is often a precursor to Alzheimer disease, but knowledge about factors that predict its development is limited.

Objective: To test the hypothesis that impaired odor identification is related to increased risk of incident MCI.

Design: Longitudinal cohort study.

Setting: Academic research.

Participants: Subjects were 589 community-dwelling older persons without cognitive impairment at study baseline, at which time odor identification was assessed using the 12-item Brief Smell Identification Test (mean \pm SD score, 9.3 ± 1.9).

Main Outcome Measures: Incidence of MCI and rate of decline in cognitive function.

Results: During annual observation of up to 5 years, 177 subjects developed MCI. In a proportional hazards model

adjusted for age, sex, and education, odor identification score predicted development of MCI (relative risk, 1.15; 95% confidence interval, 1.07-1.23), with risk increased by 50% in persons with below-average (score of 8 [25th percentile]) compared with above-average (score of 11 [75th percentile]) odor identification scores. Results were not substantially changed in subsequent analyses that controlled for level of cognitive function or disability, presence of stroke, or smoking status at baseline or that required MCI to persist for at least 1 year. Impaired odor identification was also associated with a lower level of global cognition at baseline and with more rapid decline in episodic memory, semantic memory, and perceptual speed.

Conclusion: Among older persons without manifest cognitive impairment, difficulty in identifying odors predicts subsequent development of MCI.

Arch Gen Psychiatry. 2007;64(7):802-808

Author Affiliations: Rush Alzheimer's Disease Center (Drs Wilson, Schneider, Boyle, and Bennett), Rush Institute for Healthy Aging (Dr Tang), and Departments of Neurological Sciences (Drs Wilson, Schneider, and Bennett), Behavioral Sciences (Drs Wilson and Boyle), Pathology (Dr Schneider), and Internal Medicine (Dr Tang), Rush University Medical Center, Chicago, Illinois; and Center for Neurobiology and Behavior, University of Pennsylvania, Philadelphia (Dr Arnold).

MILD COGNITIVE IMPAIRMENT (MCI) is increasingly recognized as a precursor to Alzheimer disease (AD), but there have been few prospective studies¹⁻⁶ of the transition from normal cognition to MCI, so knowledge of its antecedents is limited. In the present study, we tested the hypothesis that impaired ability to identify odors is associated with increased incidence of MCI. The hypothesis is based on 2 lines of evidence. First, impaired odor identification has been associated with more rapid cognitive decline⁷⁻¹⁰ and with the transition from MCI to AD.^{11,12} Second, in earlier clinicopathological analyses of this cohort, odor identification had a robust association with neurofibrillary tangles in the entorhinal cortex and CA1 region of the hippocampus,¹³ components of the central olfactory system that are thought to be among the first sites of AD pathologic changes.¹⁴⁻¹⁷ Therefore, we reasoned that difficulty in identifying odors might precede the development of cognitive impairment.

To test this hypothesis, we used data from the Rush Memory and Aging Project,¹⁸ a longitudinal clinicopathological study of risk factors for common chronic conditions of older age. We assessed odor identification using a standard test in persons without cognitive impairment who had annual clinical evaluations thereafter. In analyses, we tested the association of odor identification score with risk of developing MCI. Because of the lack of secure agreement on how best to diagnose MCI, we also tested the relation of odor identification to cognitive decline, a continuous outcome that underlies the transition from normal cognition to MCI.

METHODS

PARTICIPANTS

All subjects were from the Rush Memory and Aging Project. The study began in 1997 and is ongoing.¹⁸ Participants agreed to annual clinical evaluations and to brain donation at death. The study was approved by the Institutional Review Board of Rush University Medical Center, Chicago, Illinois.

Persons in the greater Chicago metropolitan area were recruited from several settings, including retirement communities, subsidized housing facilities, local churches, and social service agencies. Following a presentation about the project, attendees rated their interest in participation. Those expressing interest were subsequently contacted by project staff members, who discussed the study in further detail and obtained informed consent.

At the time of enrollment, each participant underwent a uniform clinical evaluation that was repeated annually thereafter. It included a medical history, neurological examination, and detailed cognitive function testing. Clinical classification of dementia and MCI was accomplished in 2 steps, blinded to all previously collected data, following procedures developed in other longitudinal cohort studies^{19,20} before their implementation here.²¹ First, a neuropsychologist rated impairment in 5 cognitive domains (orientation, attention, memory, language, and perception) based on review of all cognitive test results and information about education, effort, and sensory and motor deficits. To help maintain consistency in the ratings, the neuropsychologist was given provisional ratings of each domain based on educationally adjusted cutoff scores on 11 tests that are discussed in an earlier study.¹⁹ Second, an experienced clinician rendered diagnostic judgments based on an in-person evaluation of the participant and a review of all available data from that evaluation, including the neuropsychologist's ratings.²² The dementia criteria were based on the guidelines proposed by the joint working group of the National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association²³ and require a history of cognitive decline and evidence of impairment in at least 2 cognitive domains, 1 of which must be memory, to meet the criteria for AD. Persons were classified as having MCI if they were rated as having cognitive impairment by the neuropsychologist yet did not meet the criteria for dementia. Although there are no consensus criteria for MCI, these criteria are similar to those proposed by others,²⁴ and in this cohort and in the Religious Orders Study,²⁵ they have been validated clinically (in the form of associations with subsequent cognitive decline and risk of dementia and death^{19,21}) and pathologically (in the form of associations with the pathologic hallmarks of late-life dementia^{26,27}). Mild cognitive impairment was classified as amnesic if episodic memory was impaired, as previously reported.²⁸

Of 976 subjects who had completed the baseline clinical evaluation at the time of these analyses, we excluded 44 persons who met the criteria for dementia and 238 persons with MCI. This left 694 subjects without cognitive impairment; 11 died before the first follow-up evaluation, and 54 had not been in the study long enough to be followed up. Of the remaining 629 persons, follow-up data were available on 589 (93.6%), with 2 complete annual evaluations in 140 subjects, 3 in 144 subjects, 4 in 189 subjects, 5 in 74 subjects, and 6 in 42 subjects. Overall, 95.2% of annual follow-up evaluations were completed by survivors, with the differential number of evaluations per individual reflecting rolling admission to the study and differential survival. They had a mean \pm SD age at baseline of 79.9 \pm 6.8 years, a mean \pm SD of 14.6 \pm 3.0 years of schooling, and a mean \pm SD score of 28.5 \pm 1.6 on the Mini-Mental State Examination. Seventy-seven percent were women, 91.0% were of white and non-Hispanic race/ethnicity, 9.7% required assistance with at least 1 physical activity of daily living (eg, dressing and toileting) on the 6-item scale by Katz et al,²⁹ and 46.9% needed help with at least 1 instrumental activity of daily living (eg, using the telephone and taking medications) on an 8-item modified version of the scale of the Older Americans Resources and Services project.³⁰ Clinical stroke, classified on the basis of the findings of the medical history and neurological examination,¹⁸ was present in 10.5%.

ASSESSMENT OF ODOR IDENTIFICATION

The ability to identify familiar odors was assessed at baseline using the 12-item Brief Smell Identification Test.^{31,32} On each item, a microcapsule containing a familiar odor was scratched with a pencil and was placed under the nose of the participant, who attempted to match the smell with 1 of 4 alternatives. The score was the number of correct choices. As in previous research,^{10,13} we allowed a maximum of 2 missing responses, with a score of 0.25 assigned to each missing item. Performance on the Brief Smell Identification Test has been shown to have adequate temporal stability, with a test-retest correlation of 0.71 in a study³¹; performance has been associated with risk of AD¹² and rate of cognitive decline^{7,9,10} in prospective studies and with a genetic risk factor for AD,³¹ level of AD pathologic features,¹³ and presence of Parkinson disease³³ in cross-sectional studies. Nevertheless, its temporal stability³¹ and predictive validity^{12,31} are reduced compared with the 40-item University of Pennsylvania Smell Identification Test,³⁴ from which it was developed.

ASSESSMENT OF COGNITIVE FUNCTION

A battery of 21 cognitive tests was administered at each annual evaluation in an approximately 1-hour session. The Mini-Mental State Examination was used for descriptive purposes, and Complex Ideational Material was used for diagnostic evaluation. Analyses were based on the remaining 19 tests, which include 7 measures of episodic memory (immediate and delayed recall of the East Boston Story and Story A from Logical Memory and Word List Memory, Word List Recall, and Word List Recognition). Semantic memory was assessed using a 15-item version of the Boston Naming Test, a 15-item reading recognition test, and Verbal Fluency. There were 3 measures of working memory (Digit Span Forward, Digit Span Backward, and Digit Ordering). Perceptual speed tests included the oral version of the Symbol Digit Modalities Test, Number Comparison, and 2 measures from a modified Stroop Neuropsychological Screening Test (the number of color names correctly read in 30 seconds minus the number of errors and the number of colors correctly named in 30 seconds minus errors). Visuospatial ability was assessed using a 16-item version of Standard Progressive Matrices and a 15-item version of Judgment of Line Orientation.

To minimize floor and ceiling artifacts and other sources of measurement error, composites of 2 or more tests were used in analyses. We formed a measure of global cognition based on all 19 test results. In addition, based in part on factor analyses of the test results at baseline,^{35,36} we constructed measures of episodic memory (7 tests), semantic memory (3 tests), working memory (3 tests), perceptual speed (4 tests), and visuospatial ability (2 tests). In each case, raw scores were converted to *z* scores, using the baseline mean and SD in the cohort, and the *z* scores of component tests were averaged to yield the composite. Detailed information on the individual test results and on the derivation of these composite scores is contained in previous publications.^{35,36}

DATA ANALYSIS

All analyses controlled for age, sex, and education. Cox proportional hazards models³⁷ were used to test the relation of olfactory score to risk of incident MCI. The first model included the olfactory score. In separate analyses, we added terms to control for semantic memory, global cognitive score, perceptual speed score, Katz scale score, instrumental activities score, stroke, and smoking status. We repeated the original analysis using

Table 1. Descriptive Information on Subjects Who Developed Incident Mild Cognitive Impairment (MCI) vs Those Who Did Not^a

Characteristic	Incident MCI (n = 177)	No Cognitive Impairment (n = 412)	P Value
Age, y	81.7 ± 6.7	79.2 ± 6.8	<.001
Educational achievement, y	14.8 ± 3.1	14.5 ± 3.0	.36
Female sex	71.2	79.6	.03
Test scores			
Odor identification	8.8 ± 2.2	9.5 ± 1.8	<.001
Semantic memory	-0.09 ± 0.69	0.35 ± 0.52	<.001
Global cognition	0.10 ± 0.41	0.41 ± 0.40	<.001
Dependent in physical ADLs	13.0	8.3	.08
Dependent in instrumental ADLs	54.8	43.6	.01
Stroke	13.6	9.2	.12
Smoking history			
Current	5.1	3.6	.42
Former	35.6	34.7	.84

Abbreviation: ADLs, activities of daily living.

^aData are given as mean ± SD or as percentage.

persistent MCI (ie, present on consecutive evaluations) instead of first occurrence of MCI as the outcome. We also constructed a model using an indicator for the persistent subtype of MCI and a term for the interaction of the indicator with olfactory score and then conducted an identical analysis using amnesic MCI subtype. We tested the assumption about the proportionality of the hazard function by examining graphs of Schoenfeld residuals and by performing additional analyses using time-dependent versions of model terms, and we found that it was adequately met.

Mixed-effects models³⁸ were used to test the relation of olfactory score to baseline level and rate of change in cognitive function. An advantage of this approach is that the baseline level of cognition and rate of change are explicitly modeled as sources of random variability, with each individual path assumed to follow the mean path of the group (conditional on covariates) except for random effects that cause baseline level to be higher or lower and rate of change to be faster or slower. Each model included terms for time (in years since baseline) and time squared to allow for nonlinear change in cognitive function (which has been previously observed in this cohort³⁹) and for olfactory score and the interaction of olfactory score with time (and random effects for baseline level of cognition and time). The term for olfactory score indicates the association of the score with the level of cognition at baseline, and the interaction tests the relation of olfactory score to rate of change in cognition. We validated these models by examining plots of residuals against predictors (to test the linearity assumption) and by using contour plots and the Shapiro-Wilk test (to assess normality of errors and random effects). Further information on the application of these models to longitudinal cognitive data is provided in an earlier publication using similar data from a separate cohort.⁴⁰

We examined the relation of olfactory score to change in instrumental activities of daily living using a generalized estimating equation model.⁴¹ Because of the skewed distribution of the instrumental activities scale, we used a log-link function with a Poisson error structure.

Programming was performed using SAS software (SAS Institute, Cary, North Carolina)⁴²: PROC PHREG procedures for

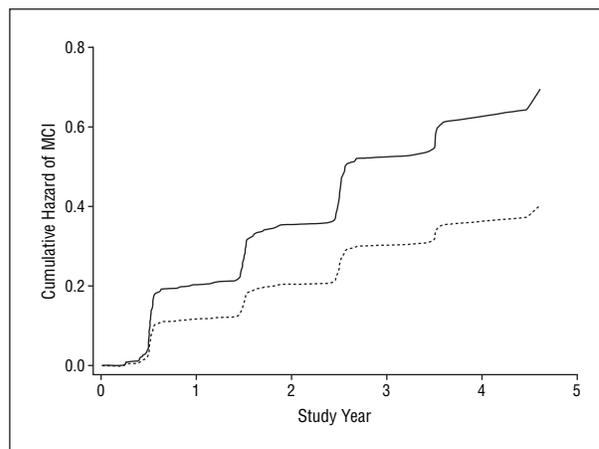


Figure 1. Cumulative risk of developing mild cognitive impairment (MCI) in typical participants with below-average (solid line [25th percentile]) or above-average (dotted line [75th percentile]) odor identification scores.

proportional hazards models, PROC MIXED procedures for mixed-effects models, and GENMOD procedures for the generalized estimating equation model.

RESULTS

Scores on the Brief Smell Identification Test ranged from 1 to 12 (mean ± SD score, 9.3 ± 1.9), with higher scores indicating better odor identification. Performance was inversely related to age ($r = -0.16$, $P < .001$) and was unrelated to education ($r = 0.02$, $P = .65$). Women (mean score, 9.4) performed slightly better than men (mean score, 8.9) ($t_{176} = 2.1$, $P = .04$).

ODOR IDENTIFICATION AND INCIDENT MCI

Of 589 subjects without cognitive impairment at baseline, 177 subjects (30.1%) developed MCI during the follow-up period. Those who developed MCI were older and more apt to be men than those who did not develop impaired cognition, and they had lower levels of odor identification and cognitive function (**Table 1**).

We examined the relation of odor identification score to risk of initial occurrence of MCI in a proportional hazards model that controlled for age, sex, and education. In this analysis, risk of MCI increased as the odor identification score decreased (relative risk [RR], 1.15; 95% confidence interval [CI], 1.07-1.23). **Figure 1**, which is based on this analysis, shows this association: a person with below-average test performance (score of 8 [solid line, 25th percentile]) was 50% more likely to develop MCI than a person with above-average test performance (score of 11 [dotted line, 75th percentile]).

Because odor identification involves linking an odorant to a verbal label,⁴³ thereby engaging semantic memory,⁴⁴ we repeated the analysis using a term for score on a composite measure of semantic memory at the time of smell assessment. The association of odor identification with incidence of MCI was not substantially changed in this analysis (RR, 1.14; 95% CI, 1.06-1.22) or after controlling for global cognition (RR, 1.12; 95% CI, 1.04-1.20 [composite of 19 individual tests]). We also con-

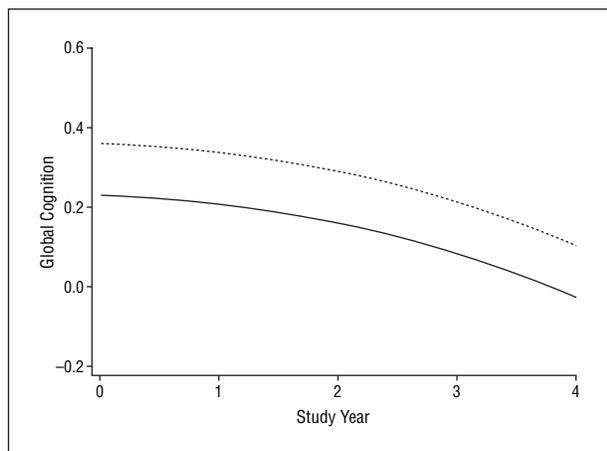


Figure 2. Predicted paths of global cognitive decline in typical participants with below-average (solid line [25th percentile]) or above-average (dotted line [75th percentile]) odor identification scores.

considered the possibility that results were affected by subtle deficits in executive thinking or in functional competence, but results were comparable after controlling for a composite measure of perceptual speed, which included tests of executive functioning (RR, 1.13; 95% CI, 1.05-1.21) or physical (RR, 1.14; 95% CI, 1.06-1.22 [Katz scale]) or instrumental (RR, 1.12; 95% CI, 1.05-1.20 [modified version of Older Americans Resources and Services project scale]) activities of daily living.

Cigarette smoking and stroke have been associated with impaired olfactory function.⁴⁵ Therefore, we repeated the analysis using a term for clinically diagnosed stroke (present in 10.5% at baseline) and using indicators contrasting current (4.1%) and past (35.0%) smokers with those who never smoked. In this analysis, odor identification continued to be related to risk of MCI (RR, 1.14; 95% CI, 1.07-1.22).

Mild cognitive impairment does not always progress to dementia or even persist, with large numbers of persons reverting back to normal cognitive performance.^{46,47} Of 177 persons with incident MCI, 73 had MCI or dementia at their next evaluation or had died. We constructed a proportional hazards model to test the association of olfactory score with risk of this definition of persistent MCI. In this analysis, risk decreased by about 16% for a 1-point increase in odor identification test score (RR, 1.16; 95% CI, 1.05-1.28), which is almost identical to that in the original analysis. In subsequent analyses, the association of odor identification with MCI did not depend on MCI meeting the criteria for persistent or amnesic (present in 54.2%) subtype (data not shown).

ODOR IDENTIFICATION AND COGNITIVE DECLINE

Because development of MCI involves cognitive decline, assessing change in cognitive function in persons initially free of MCI or dementia provides a complementary approach to investigating risk factors for MCI that does not depend on how MCI or its incidence is defined. Accordingly, we constructed a mixed-effects model to characterize change in cognitive function in those with-

Table 2. Relation of Odor Identification to Baseline Level of and Rate of Decline in Different Domains of Cognition^a

Cognitive Outcome and Model Term	Estimate, Mean ± SE	P Value
Episodic memory		
Odor identification	0.038 ± 0.009	<.001
Odor × -time	0.009 ± 0.004	.02
Semantic memory		
Odor identification	0.044 ± 0.011	<.001
Odor × -time	0.007 ± 0.003	.03
Working memory		
Odor identification	0.051 ± 0.014	<.001
Odor × -time	0.001 ± 0.004	.69
Perceptual speed		
Odor identification	0.060 ± 0.013	<.001
Odor × -time	0.009 ± 0.004	.03
Visuospatial ability		
Odor identification	0.031 ± 0.012	.01
Odor × -time	0.004 ± 0.004	.35

^aEstimated from mixed-effects models adjusted for age, sex, and education.

out baseline cognitive impairment and to test the hypothesis that difficulty in identifying odors is related to more rapid cognitive decline in this subgroup. The model included terms for time and time squared (to allow for a gradually accelerating course of cognitive decline), for odor identification and its interaction with time, and for the potentially confounding effects of age, sex, and education. In this analysis, odor identification was positively related to baseline level of global cognition (mean ± SE estimate, 0.043 ± 0.008; $P < .001$). With this baseline effect accounted for, lower olfactory score was associated with more rapid linear decline in global cognition (mean ± SE estimate, 0.006 ± 0.003; $P = .03$), as hypothesized.

To illustrate this result, we plotted the predicted paths of change in cognitive function for participants with below-average (score of 8 [solid line, 25th percentile]) and above-average (score of 11 [dotted line, 75th percentile]) olfactory test performances (**Figure 2**). Difficulty in identifying odors was associated with a lower initial level of cognition and with a more rapid rate of decline.

To see if odor identification was associated with decline in some forms of cognition but not in others, we repeated the analysis using specific measures of cognition in place of the global measure (**Table 2**). In these analyses, difficulty in identifying odors was associated with lower function at baseline in all cognitive domains and with more rapid decline in episodic memory, semantic memory, and perceptual speed but not in working memory or visuospatial ability.

We also examined whether odor identification was associated with increasing dependence in instrumental activities of daily living, a common consequence of cognitive decline. A lower odor identification score was associated with more dependence in instrumental activities at baseline (mean ± SE estimate, -0.095 ± 0.025 ; $P < .001$) but not with a change in dependence over time (mean ± SE estimate, 0.004 ± 0.006 ; $P = .48$).

ODOR IDENTIFICATION AND THE TRANSITION FROM MCI TO AD

Because odor identification has also been reported to predict the transition from MCI to AD,^{11,12} we examined this issue in persons diagnosed as having MCI at baseline (and excluded from all analyses to this point). Follow-up data were available on 183 subjects with MCI at baseline, and 53 of these subsequently developed AD. In a proportional hazards model, risk of AD increased by about 18% for a 1-point increase in odor identification test score (RR, 1.18; 95% CI, 1.07-1.30).

COMMENT

We assessed the ability to identify familiar odors in a group of almost 600 older persons without evidence of cognitive impairment at study onset. During annual follow-up evaluations for up to 5 years, about 30% of the group developed MCI, and the risk of developing MCI was increased by 50% in those with mild difficulty in identifying odors at baseline compared with persons with preserved odor identification. The results indicate that olfactory dysfunction can precede cognitive impairment in AD.

As already noted, impaired olfactory identification has been associated with the risk of AD in persons with MCI^{11,12} (also shown in this study) and with a more rapid rate of cognitive decline in older persons initially free of dementia.⁷⁻¹⁰ The present findings build on this research by showing that difficulty in identifying odors predicts not only the transition from MCI to AD but also the transition from normal cognition to MCI. This latter finding is important: by the time persons meet the criteria for MCI, they are already exhibiting the primary clinical manifestation of AD, accelerated cognitive decline,^{19,21} and the neuropathologic hallmarks of the disease,^{24,48-50} consistent with the idea that MCI is a prodromal stage of AD. As treatments are developed to prevent AD or to delay its onset, it may be important to intervene before this prodromal period begins and before cognitive systems are manifestly dysfunctional. The results of this and other prospective studies¹⁻⁶ suggest it may be possible to identify subsets of older subjects without cognitive impairment who are at increased risk for developing MCI and AD.

The neurobiological bases of age-associated olfactory dysfunction are uncertain. Odor information from the olfactory bulb is transmitted via the olfactory tract to primary olfactory cortical areas (eg, piriform cortex, cortical nuclei of the amygdala, and entorhinal cortex) and to subcortical areas (eg, ventral striatum and ventromedial hypothalamus), which project to secondary olfactory regions such as hippocampus and orbitofrontal cortex. In a previous study¹³ of this cohort, odor identification was related to the density of tau-immunoreactive tangles in areas within this central olfactory system (ie, entorhinal cortex and hippocampus) but not outside of it, implicating the accumulation of neurofibrillary pathologic features within central olfactory pathways in age-related olfactory impairment. Neuropathological^{14,15} and neuroradiological^{16,17} evidence suggests that medial temporal lobe structures, par-

ticularly the entorhinal cortex and hippocampus, are affected early in the course of AD. In the model of disease progression by Braak and Braak,¹⁵ for example, neurofibrillary tangles are confined to the entorhinal cortex in the initial transentorhinal period. Although this period is hypothesized to be clinically silent, accumulating entorhinal tangles would be expected to impair olfactory processing at some point, with further dysfunction occurring as more of the limbic system is affected (and prodromal clinical signs appear) in the subsequent limbic stage of the model.

Impaired olfaction is seen in age-related disorders not involving neurofibrillary pathologic features, most notably Parkinson disease,^{33,51} suggesting that factors other than tangles are involved in age-related olfactory dysfunction. Olfactory regions are early sites of Lewy body pathologic findings in Parkinson disease,⁵² and Lewy bodies have been associated with impaired olfaction in dementia.^{53,54} Another consideration is that neurogenesis in the olfactory bulb persists throughout life. Animal studies show that bulbar neurogenesis is associated with the efficiency of olfactory processing,^{55,56} regulated in part by a dopaminergic nigro-subventricular circuit,⁵⁷ and greatly reduced in aged individuals.^{55,58} Little is known about bulbar neurogenesis in humans,⁵⁹ although it seems to be reduced in Parkinson disease⁶⁰ and may have relevance to olfaction in older age. Further clinicopathological and clinicoradiological research on age-related olfactory dysfunction is needed.

The lack of a consensus definition of MCI and the transitory nature of the condition complicate research on its incidence. The incidence of MCI in this cohort was higher than that in previous reports,³⁻⁵ likely in part because participants are older, which substantially increases MCI risk.^{1,4,5} When we shifted from a less restrictive (ie, first occurrence of cognitive impairment) to a more restrictive (ie, occurrences on consecutive evaluations) definition of incidence, the estimated rate was reduced by more than half, but the association of odor identification with risk was essentially unchanged. Furthermore, because those diagnosing MCI at each evaluation were blinded to data from all previous evaluations, we were able to use analyses of change in cognitive function as a means of testing the validity of results obtained using MCI as the outcome. That impaired odor identification was associated with lower baseline level of cognition and with more rapid cognitive decline accounts for its robust association with MCI incidence and indicates that the association is not likely to be due to how MCI or its incidence was operationalized in this study.

The use of change in cognitive function instead of MCI as an outcome not only substitutes a continuous measure for a dichotomous one and avoids the definitional problems accompanying MCI but also provides an opportunity to examine whether the relation of odor identification to loss of cognition varies across functional domains. The association was most pronounced in episodic memory, the clinical hallmark of AD, and in the domains of semantic memory and perceptual speed, which include measures of executive function. This finding is consistent with previous research among older persons without dementia,⁸⁻¹⁰ possibly reflecting the accumulation of AD pathologic features in regions of the medial

temporal lobe and prefrontal cortex involved in olfactory and cognitive processing.

This study has several limitations. The findings are based on a selected group of older persons. Therefore, it will be important to establish whether they generalize to more diverse cohorts and to defined populations. It also remains to be seen whether results can be replicated using different definitions of MCI. Psychometric differences between the cognitive domain measures may have contributed to the differential association of olfactory score with change in those measures. We assessed olfactory function using a short form of an established test, which may have led us to underestimate the association of olfaction with MCI. Finally, results are based exclusively on olfactory identification, as has been the case for most prospective studies⁷⁻¹² of subjects initially free of dementia. Findings from cross-sectional studies of persons with AD^{61,62} or at risk for it^{62,63} suggest that other forms of olfactory processing (eg, odor detection or memory) are affected by the disease, but the extent to which these can be dissociated from impaired olfactory identification^{64,65} and contribute to prediction of MCI is uncertain.

In conclusion, a brief test of odor identification, previously associated with tangle density in the entorhinal cortex and hippocampus,¹³ predicted cognitive decline and incidence of MCI in older subjects without evidence of cognitive impairment at study onset. The findings suggest that olfactory dysfunction can be an early manifestation of AD, possibly a marker of transentorhinal AD in Braak terminology, and that olfactory assessment may be useful for early disease identification.

Submitted for Publication: August 16, 2006; final revision received November 13, 2006; accepted November 13, 2006.

Correspondence: Robert S. Wilson, PhD, Rush Alzheimer's Disease Center, Rush University Medical Center, 600 S Paulina, Ste 1038, Chicago, IL 60612 (rwilson@rush.edu).

Author Contributions: Dr Wilson had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

Funding/Support: This study was supported by grants R01 AG17917, R01 AG022018, R01 AG024480, and K23 AG23040 from the National Institute on Aging and by the Illinois Department of Public Health.

Role of the Sponsor: The sponsors had no role in the design or conduct of the study; in the collection, management, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

Additional Contributions: We thank the many Illinois residents for participating in the Rush Memory and Aging Project; Traci Colvin, MPH, and Tracy Hagman for coordinating the study; Zhaotai Cui, MS, for statistical programming; George Dombrowski, MS, and Greg Klein for data management; and Valerie J. Young for preparing the manuscript.

REFERENCES

1. Kryscio RJ, Schmitt FA, Salazar JC, Mendiondo MS, Markesbery WR. Risk factors for transitions from normal to mild cognitive impairment and dementia. *Neurology*. 2006;66(6):828-832.
2. Verghese J, LeValley A, Derby C, Kulansky G, Katz M, Hall C, Buschke H, Lipton RB. Leisure activities and the risk of amnesic mild cognitive impairment in the elderly. *Neurology*. 2006;66(6):821-827.
3. Lopez OL, Jagust WJ, Dulberg C, Becker JT, DeKosky ST, Fitzpatrick A, Breitner J, Lyketsos C, Jones B, Kawas C, Carlson M, Kuller LH. Risk factors for mild cognitive in the Cardiovascular Health Study Cognition Study: part 2. *Arch Neurol*. 2003;60(10):1394-1399.
4. Tervo S, Kivipelto M, Hanninen T, Vanhanen M, Hallikainen M, Mannermaa A, Soininen H. Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. *Dement Geriatr Cogn Disord*. 2004;17(3):196-203.
5. Solfrizzi V, Panza F, Colacicco AM, D'Introno A, Capurso C, Torres F, Grigoletto F, Maggi S, Del Parigi A, Reiman EM, Caselli RJ, Scafato E, Farchi G, Capurso A; Italian Longitudinal Study on Aging Working Group. Vascular risk factors, incidence of MCI, and rates of progression to dementia. *Neurology*. 2004;63(10):1882-1891.
6. Geda YE, Knopman DS, Mrazek DA, Jicha GA, Smith GE, Negash S, Boeve BF, Ivnik RJ, Petersen RC, Pankratz VS, Rocca WA. Depression, apolipoprotein E genotype, and the incidence of mild cognitive impairment. *Arch Neurol*. 2006;63(3):435-440.
7. Graves AB, Bowen JD, Rajaram L, McCormick WC, McCurry SM, Schellenberg GD, Larson EB. Impaired olfaction as a marker for cognitive decline: interaction with apolipoprotein E ϵ 4 status. *Neurology*. 1999;53(7):1480-1487.
8. Royall DR, Chiodo LK, Polk MJ, Jaramillo CJ. Severe dysosmia is specifically associated with Alzheimer-like memory deficits in nondemented elderly retirees. *Neuroepidemiology*. 2002;21(2):68-73.
9. Swan GE, Carmelli D. Impaired olfaction predicts cognitive decline in nondemented older adults. *Neuroepidemiology*. 2002;21(2):58-67.
10. Wilson RS, Arnold SE, Tang Y, Bennett DA. Odor identification and decline in different cognitive domains in old age. *Neuroepidemiology*. 2006;26(2):61-67.
11. Devanand DP, Michaels-Marston KS, Liu X, Pelton GH, Padilla M, Marder K, Bell K, Stern Y, Mayeux R. Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *Am J Psychiatry*. 2000;157(9):1399-1405.
12. Tabert MH, Liu X, Doty RL, Serby M, Zamora D, Pelton GH, Marder K, Albers MW, Stern Y, Devanand DP. A 10-item smell identification scale related to risk for Alzheimer's disease. *Ann Neurol*. 2005;58(1):155-160.
13. Wilson RS, Arnold SE, Schneider JA, Tang Y, Bennett DA. The relationship between cerebral Alzheimer's disease pathology and odour identification in old age. *J Neurol Neurosurg Psychiatry*. 2007;78(1):30-35.
14. Hyman BT, Van Hoesen GW, Kromer C, Damasio A. Alzheimer's disease: cell-specific pathology isolates the hippocampal formation. *Science*. 1984;225(4667):1168-1170.
15. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol (Berl)*. 1991;82(4):239-259.
16. Killiany RJ, Hyman BT, Gomez-Isla T, Moss MB, Kikinis R, Jolesz F, Tanzi R, Jones K, Albert MS. MRI measures of entorhinal cortex vs hippocampus in preclinical AD. *Neurology*. 2002;58(8):1188-1196.
17. Kesslak JP, Nalcioglu O, Cotman CW. Quantification of magnetic resonance scans for hippocampal and parahippocampal atrophy in Alzheimer's disease. *Neurology*. 1991;41(1):51-54.
18. Bennett DA, Schneider JA, Buchman AS, Mendes de Leon CF, Bienias JL, Wilson RS. The Rush Memory and Aging Project: study design and baseline characteristics of the study cohort. *Neuroepidemiology*. 2005;25(4):163-175.
19. Bennett DA, Wilson RS, Schneider JA, Evans DA, Beckett LA, Aggarwal NT, Barnes LL, Fox JH, Bach J. Natural history of mild cognitive impairment in older persons. *Neurology*. 2002;59(2):198-205.
20. Evans DA, Bennett DA, Wilson RS, Bienias JL, Morris MC, Scherr PA, Hebert LE, Aggarwal NT, Beckett LA, Joglekar R, Berry-Kravis E, Schneider JA. Incidence of Alzheimer's disease in a biracial urban community: relation to apolipoprotein allele status. *Arch Neurol*. 2003;60(2):185-189.
21. Boyle PA, Wilson RS, Aggarwal NT, Tang Y, Bennett DA. Mild cognitive impairment: risk of Alzheimer's disease and rate of cognitive decline. *Neurology*. 2006;67(3):441-445.
22. Bennett DA, Schneider JA, Aggarwal NT, Arvanitakis Z, Shah RC, Kelly JF, Fox JH, Cochran EJ, Arends D, Treinkman AD, Wilson RS. Decision rules guiding the clinical diagnosis of Alzheimer's disease in two community-based cohort studies compared to standard practice in a clinic-based cohort study. *Neuroepidemiology*. 2006;27(3):169-176.

23. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan E. Clinical diagnosis of Alzheimer's disease: report of the NINCDS/ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34(7):939-944.
24. Tuokko H, Frerichs RJ, Graham J, Rockwell K, Kristjansson B, Fisk J, Bergman H, Kozma A, McDowell I. Five-year follow-up of cognitive impairment with no dementia. *Arch Neurol*. 2003;60(4):577-582.
25. Wilson RS, Bienias JL, Evans DA, Bennett DA. Religious Orders Study: overview and change in cognitive and motor speed. *Aging Neuropsychol Cogn*. 2004;11(2-3):280-303.
26. Bennett DA, Schneider JA, Wilson RS, Bienias JL, Arnold SE. Mild cognitive impairment is related to Alzheimer's disease pathology and cerebral infarctions. *Neurology*. 2005;64(5):834-841.
27. Bennett DA, Schneider JA, Arvanitakis Z, Kelly JF, Aggarwal NT, Shah RC, Wilson RS. Neuropathology of older persons without cognitive impairment. *Neurology*. 2006;66(12):1837-1844.
28. Boyle PA, Wilson RS, Aggarwal NT, Arvanitakis Z, Kelly JF, Bienias JL, Bennett DA. Parkinsonian signs in subjects with mild cognitive impairment. *Neurology*. 2005;65(12):1901-1906.
29. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. *JAMA*. 1963;185:914-923.
30. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*. 1969;9(3):179-186.
31. Doty RL, Marcus A, Lee WW. Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). *Laryngoscope*. 1996;106(3, pt 1):353-356.
32. Doty RL, Frye RE, Agrawal U. Internal consistency reliability of the fractionated and whole University of Pennsylvania Smell Identification Test. *Percept Psychophys*. 1989;45(5):381-384.
33. Double KL, Rowe DB, Hayes M, Chan DKY, Blackie J, Corbett A, Joffe R, Fung VS, Morris J, Halliday GM. Identifying the pattern of olfactory deficits in Parkinson's disease using the Brief Smell Identification Test. *Arch Neurol*. 2003;60(4):545-549.
34. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav*. 1984;32(3):489-502.
35. Wilson R, Barnes LL, Bennett DA. Assessment of lifetime participation in cognitively stimulating activities. *J Clin Exp Neuropsychol*. 2003;25(5):634-642.
36. Wilson RS, Barnes LL, Krueger KR, Hoganson G, Bienias JL, Bennett DA. Early and late life cognitive activity and cognitive systems in old age. *J Int Neuropsychol Soc*. 2005;11(4):400-407.
37. Cox DR. Regression models and life tables (with discussion). *J R Soc Stat B*. 1972;74:187-220.
38. Laird NM, Ware JH. Random-effects models for longitudinal data. *Biometrics*. 1982;38(4):963-974.
39. Wilson RS, Krueger KR, Arnold SE, Schneider JA, Kelly JF, Barnes LL, Tang Y, Bennett DA. Loneliness and risk of Alzheimer disease. *Arch Gen Psychiatry*. 2007;64(2):234-240.
40. Wilson RS, Beckett LA, Barnes LL, Schneider JA, Bach J, Evans DA, Bennett DA. Individual differences in rates of change in cognitive abilities of older persons. *Psychol Aging*. 2002;17(2):179-193.
41. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42(1):121-130.
42. SAS Institute Inc. *SAS OnlineDoc 9.1.3*. Cary, NC: SAS Institute Inc; 2004.
43. Zelano C, Sobel N. Humans as an animal model for systems-level organization of olfaction. *Neuron*. 2005;48(3):431-454.
44. Finkel D, Pedersen NL, Larsson M. Olfactory functioning and cognitive abilities: a twin study. *J Gerontol B Psychol Sci Soc Sci*. 2001;56(4):P226-P233.
45. Murphy C, Schubert CR, Cruickshanks KJ, Klein BEK, Klein R, Nondahl DM. Prevalence of olfactory impairment in older adults. *JAMA*. 2002;288(18):2307-2312.
46. Ritchie K, Artero S, Touchon J. Classification criteria for mild cognitive impairment: a population-based validation study. *Neurology*. 2001;56(1):37-42.
47. Fisk JD, Merry HR, Rockwood K. Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. *Neurology*. 2003;61(9):1179-1184.
48. Markesbery WR, Schmitt FA, Kryscio RJ, Davis DG, Smith CD, Wekstein DR. Neuropathologic substrate of mild cognitive impairment. *Arch Neurol*. 2006;63(1):38-46.
49. Petersen RC, Parisi JE, Dickson DW, Johnson KA, Knopman DS, Boeve BF, Jicha GA, Ivnik RJ, Smith GE, Tangalos EG, Braak H, Kokmen E. Neuropathologic features of amnesic mild cognitive impairment. *Arch Neurol*. 2006;63(5):665-672.
50. Guillozet AL, Weintraub S, Mash DC, Mesulam MM. Neurofibrillary tangles, amyloid, and memory in aging and mild cognitive impairment. *Arch Neurol*. 2003;60(5):729-736.
51. Ponsen MM, Stoffers D, Booij J, van Eck-Smit BL, Wolters ECh, Berendse HW. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. *Ann Neurol*. 2004;56(2):173-181.
52. Del Tredici K, Rub U, De Vos RAI, Bohl JRE, Braak H. Where does Parkinson's disease pathology begin in the brain? *J Neuropathol Exp Neurol*. 2002;61(5):413-426.
53. Olichney JM, Murphy C, Hofstetter CR, Foster K, Hansen LA, Thal LJ, Katzman R. Anosmia is very common in the Lewy body variant of Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2005;76(10):1342-1347.
54. McShane RH, Nagy Z, Esiri MM, King E, Joachim C, Sullivan N, Smith AD. Anosmia in dementia is associated with Lewy bodies rather than Alzheimer's disease pathology. *J Neurol Neurosurg Psychiatry*. 2001;70(6):739-743.
55. Enwere E, Shingo T, Gregg C, Fujikawa H, Ohta S, Weiss S. Aging results in reduced epidermal growth factor receptor signaling, diminished olfactory neurogenesis, and deficits in fine olfactory discrimination. *J Neurosci*. 2004;24(38):8354-8365.
56. Rochefort C, Gheusi G, Vincent JD, Lledo PM. Enriched odor exposure increases the number of newborn neurons in the adult olfactory bulb and improves odor memory. *J Neurosci*. 2002;22(7):2679-2689.
57. Freundlieb N, Francois C, Tande D, Oertel WH, Hirsch EC, Höglinger GU. Dopaminergic substantia nigra neurons project topographically organized to the subventricular zone and stimulate precursor cell proliferation in aged primates. *J Neurosci*. 2006;26(8):2321-2325.
58. Mirich JM, Williams NC, Berlau DJ, Brunjes PC. Comparative study of aging in the mouse olfactory bulb. *J Comp Neurol*. 2002;454(4):361-372.
59. Bédard A, Parent A. Evidence of newly generated neurons in the human olfactory bulb. *Brain Res Dev Brain Res*. 2004;151(1-2):159-168.
60. Höglinger GU, Rizk P, Muriel MP, Duyckaerts C, Oertel WH, Caille I, Hirsch EC. Dopamine depletion impairs precursor cell proliferation in Parkinson's disease. *Nat Neurosci*. 2004;7(7):726-735.
61. Doty RL, Reyes PF, Gregor T. Presence of both odor identification and detection deficits in Alzheimer's disease. *Brain Res Bull*. 1987;18(5):597-600.
62. Gilbert PE, Murphy C. The effect of the ApoE ε4 allele on recognition memory for olfactory and visual stimuli in patients with pathologically confirmed Alzheimer's disease, probable Alzheimer's disease, and healthy elderly controls. *J Clin Exp Neuropsychol*. 2004;26(6):779-794.
63. Bacon AW, Bondi MW, Salmon DP, Murphy C. Very early changes in olfactory functioning due to Alzheimer's disease and the role of apolipoprotein E in olfaction. *Ann N Y Acad Sci*. 1998;855:723-731.
64. Meshulam RI, Moberg PJ, Mahr RN, Doty RL. Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's disease. *Arch Neurol*. 1998;55(1):84-90.
65. Doty RL, Smith R, McKeown DA, Raj J. Tests of human olfactory function: principal components analysis suggests that most measure a common source of variance. *Percept Psychophys*. 1994;56(6):701-707.