

## Original Investigation

# Association Between Olfactory Dysfunction and Amnestic Mild Cognitive Impairment and Alzheimer Disease Dementia

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**IMPORTANCE** To increase the opportunity to delay or prevent mild cognitive impairment (MCI) or Alzheimer disease (AD) dementia, markers of early detection are essential. Olfactory impairment may be an important clinical marker and predictor of these conditions and may help identify persons at increased risk.

**OBJECTIVE** To examine associations of impaired olfaction with incident MCI subtypes and progression from MCI subtypes to AD dementia.

**DESIGN, SETTING, AND PARTICIPANTS** Participants enrolled in the population-based, prospective Mayo Clinic Study of Aging between 2004 and 2010 were clinically evaluated at baseline and every 15 months through 2014. Participants (N = 1630) were classified as having normal cognition, MCI (amnestic MCI [aMCI] and nonamnestic MCI [naMCI]), and dementia. We administered the Brief Smell Identification Test (B-SIT) to assess olfactory function.

**MAIN OUTCOMES AND MEASURES** Mild cognitive impairment, AD dementia, and longitudinal change in cognitive performance measures.

**RESULTS** Of the 1630 participants who were cognitively normal at the time of the smell test, 33 died before follow-up and 167 were lost to follow-up. Among the 1430 cognitively normal participants included, the mean (SD) age was 79.5 (5.3) years, 49.4% were men, the mean duration of education was 14.3 years, and 25.4% were APOE ε4 carriers. Over a mean 3.5 years of follow-up, there were 250 incident cases of MCI among 1430 cognitively normal participants. We observed an association between decreasing olfactory identification, as measured by a decrease in the number of correct responses in B-SIT score, and an increased risk of aMCI. Compared with the upper B-SIT quartile (quartile [Q] 4, best scores), hazard ratios (HRs) (95% CI) were 1.12 (0.65-1.92) for Q3 ( $P = .68$ ); 1.95 (1.25-3.03) for Q2 ( $P = .003$ ); and 2.18 (1.36-3.51) for Q1 ( $P = .001$ ) (worst scores;  $P$  for trend  $< .001$ ) after adjustment for sex and education, with age as the time scale. There was no association with naMCI. There were 64 incident dementia cases among 221 prevalent MCI cases. The B-SIT score also predicted progression from aMCI to AD dementia, with a significant dose-response with worsening B-SIT quartiles. Compared with Q4, HR (95% CI) estimates were 3.02 (1.06-8.57) for Q3 ( $P = .04$ ); 3.63 (1.19-11.10) for Q2 ( $P = .02$ ); and 5.20 (1.90-14.20) for Q1 ( $P = .001$ ). After adjusting for key predictors of MCI risk, B-SIT (as a continuous measure) remained a significant predictor of MCI (HR, 1.10 [95% CI, 1.04-1.16];  $P < .001$ ) and improved the model concordance.

**CONCLUSIONS AND RELEVANCE** Olfactory impairment is associated with incident aMCI and progression from aMCI to AD dementia. These findings are consistent with previous studies that have reported associations of olfactory impairment with cognitive impairment in late life and suggest that olfactory tests have potential utility for screening for MCI and MCI that is likely to progress.

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Loss of odor identification has been associated with plaques and tangles in the olfactory bulb, entorhinal cortex, and the cornu ammonis 1 regions of the hippocampus in autopsy studies.<sup>1</sup> Consistent with this, several clinic-based, case-control, cross-sectional, or selected participant studies have demonstrated associations of olfactory loss with cognitive decline, mild cognitive impairment (MCI), or Alzheimer disease (AD) dementia.<sup>2-6</sup> This suggests that impairment in odor identification may be a marker for risk of amnesic MCI (aMCI) due to AD or may predict progression from aMCI to AD dementia. In addition, anosmia has been associated with Lewy bodies, suggesting that impaired olfaction may also be a marker for Lewy body dementia<sup>7</sup> and vascular dementia.<sup>8</sup> There are several longitudinal studies on olfactory impairment and progression from MCI to dementia,<sup>3,9-13</sup> but fewer on the association with MCI.<sup>2,4,5,10</sup> Studies on olfaction and MCI have often been conducted in cross-sectional or clinic-based studies and in studies of small sample size or short duration of follow-up.<sup>4,14-16</sup> Furthermore, to our knowledge, few studies have investigated the associations of olfaction with MCI subtypes or with progression from MCI to AD dementia or non-AD dementia in a large population-based cohort. Thus, we sought to replicate previous findings on the association of olfactory impairment with risk of MCI (and MCI subtypes) and progression from MCI and its subtypes to AD or non-AD dementia in a large, prospective, population-based study.

## Methods

### Study Design and Participants

The Mayo Clinic Study of Aging was established in 2004 to study risk factors for MCI and dementia.<sup>17-19</sup> The initial cohort consisted of Olmsted County, Minnesota, residents aged 70 to 89 years on October 1, 2004, who were randomly selected from an enumeration of the county population using the Rochester Epidemiology Project medical records linkage system. In 2008, we began ongoing recruitment using the same protocols as at baseline. This study includes participants who were enrolled between 2004 and 2010 and were evaluated in person. All protocols were approved by the institutional review boards of the Mayo Clinic and the Olmsted Medical Center, and participants provided written informed consent.

### In-Person Evaluation and Assessment of Cognitive Function

At baseline, each participant and an informant were interviewed using questions about memory (participant), Beck Depression Inventory, Beck Anxiety Inventory, the Clinical Dementia Rating scale,<sup>20</sup> Functional Activities Questionnaire,<sup>21</sup> and Neuropsychiatric Inventory Questionnaire (informant). Participants were evaluated by a physician to obtain a medical history, assess global cognition using the Short Test of Mental Status (STMS),<sup>22</sup> complete a modified Unified Parkinson's Disease Rating Scale,<sup>23</sup> and perform a neurological examination. Participants underwent neuropsychological testing to assess performance in 4 cognitive domains: memory (Auditory Verbal Learning Test Delayed Recall Trial, Wechsler Memory Scale-Revised Logical Memory-II, and Visual

Reproduction-II);<sup>24-26</sup> executive function (Trail Making Test B, Wechsler Adult Intelligence Scale-Revised Digit Symbol Substitution);<sup>27-29</sup> language (Boston Naming Test and category fluency test);<sup>30-32</sup> and visuospatial skills (Wechsler Adult Intelligence Scale-Revised Picture Completion and Block Design).<sup>29</sup> The raw test scores were age adjusted using normative data, summed, and scaled to compute domain z scores.<sup>33</sup>

The data for each participant were reviewed for a diagnosis of MCI (aMCI and naMCI, single and multidomain) as previously defined,<sup>17-19</sup> dementia (including AD dementia),<sup>34,35</sup> or normal cognition.<sup>17,18,33</sup> Participants were followed up at 15-month intervals for incident diagnoses of MCI or dementia, using the same protocols as at baseline.

### Assessment of Olfactory Function

Olfaction was assessed using the Brief Smell Identification Test (B-SIT) version A,<sup>36</sup> which consists of 6 food-related and 6 non-food-related smells (cherry, clove, strawberry, menthol, pineapple, lemon, leather, lilac, smoke, soap, natural gas, and rose). Participants were required to scratch, sniff, and select 1 of 4 possible tests. The B-SIT score was computed as the sum of the correct responses for persons with no more than 2 missing responses. A score of 0.25 was assigned for each missing response.<sup>2,6</sup>

### Statistical Analyses

#### Proportional Hazards Models

Follow-up time was computed from the time of administration of the B-SIT (baseline) to the midpoint between the last assessment as cognitively normal (or MCI) and the date of the incident event MCI (or dementia). Persons who died or were lost to follow-up prior to an event were censored at their last follow-up. The association of B-SIT score with (1) incident MCI and (2) progression from MCI to dementia was examined using Cox proportional hazards models. Olfaction was characterized as the continuous or categorical B-SIT score. Osmia categories were based on B-SIT quartiles for cognitively normal participants—anosmia (score <6), microsmia (men, 6-10 and women, 6-10.25), normosmia (men, 10.25-12 and women, 10.5-12) as previously described<sup>4</sup>—and dichotomized as less than 9 (impaired) vs 9 or greater.<sup>3</sup> The basic models were adjusted for sex and education, with age as the time scale. Potential confounding by type 2 diabetes mellitus, hypertension, stroke, apolipoprotein E (APOE) ε4 allele, self-reported alcohol problem and ever-smoking, baseline cognitive domain scores, and STMS was examined in separate models, but there was no confounding by these covariates and the data are not reported. Interaction of the B-SIT score with sex and with each of the covariates listed here was examined.

We determined whether B-SIT score is associated with MCI and improves model fit for MCI after adjusting for predictors of MCI included in a risk score for MCI developed in our cohort.<sup>37</sup> For each participant, we computed a risk score from a basic risk prediction model using variables obtainable in the outpatient setting (education, subjective memory symptoms, alcohol problems, stroke, diabetes mellitus, atrial fibrillation, smoking, dyslipidemia or hypertension in midlife, maximum adult body mass index, and marital status); the basic

Table 1. Characteristics of Cognitively Normal Participants by B-SIT Score Quartiles at Baseline

Characteristics	Mean (SD)					P Value for Trend <sup>a</sup>
	All (N = 1430)	Q1 (n = 298)	Q2 (n = 409)	Q3 (n = 294)	Q4 (n = 429)	
Smell score, range	1-12	0-7.5	8-9	9.25-10.5	11-12	
Male, No. (%)	706 (49.4)	181 (60.7)	215 (52.6)	139 (47.3)	171 (39.9)	<.001
Age, y	79.5 (5.3)	81.3 (5.4)	80.1 (5.3)	78.9 (5.2)	78.0 (4.8)	<.001
Education, y	14.3 (2.8)	14.3 (3.1)	14.1 (2.7)	14.1 (2.7)	14.7 (2.7)	.02
APOE ε4, No. (%)	362 (25.4)	74 (24.9)	115 (28.3)	71 (24.2)	102 (23.8)	.45
Diabetes mellitus, No. (%)	274 (19.2)	49 (16.4)	84 (20.5)	69 (23.5)	72 (16.8)	.07
Hypertension, No. (%)	1120 (78.3)	241 (80.9)	328 (80.2)	229 (77.9)	322 (75.1)	.19
Stroke, No. (%)	57 (4.0)	13 (4.4)	18 (4.4)	13 (4.4)	13 (3.0)	.69
Smoking, ever, No. (%)	678 (47.4)	153 (51.3)	193 (47.2)	139 (47.3)	193 (45.0)	.78
Alcohol problem, No. (%)	53 (3.7)	13 (4.5)	14 (3.4)	13 (4.4)	13 (3.1)	.69
Follow-up, y	3.5 (1.1)	3.4 (1.2)	3.6 (1.1)	3.5 (1.1)	3.6 (1.1)	.06
Incident MCI, No. (%) <sup>b</sup>	250 (17.5)	72 (24.2)	84 (20.5)	42 (14.3)	52 (12.1)	<.001
Cognitive domain z score						
Memory	0.0 (1.0)	-0.2 (1.0)	0.0 (1.0)	0.0 (1.0)	0.2 (1.0)	<.001
Executive function	0.0 (1.0)	-0.3 (1.1)	-0.1 (1.0)	0.1 (0.9)	0.2 (1.0)	<.001
Language	0.0 (1.0)	-0.3 (1.1)	-0.1 (1.0)	0.1 (0.9)	0.3 (1.0)	<.001
Visuospatial	0.0 (1.0)	-0.1 (1.0)	-0.1 (1.1)	0.0 (1.0)	0.1 (1.0)	.18
Global	0.0 (1.0)	-0.3 (1.0)	-0.1 (1.0)	0.1 (0.9)	0.2 (1.0)	<.001
Cognitive test scores						
AVLT	7.7 (3.4)	6.9 (3.4)	7.6 (3.3)	7.9 (3.6)	8.1 (3.4)	<.001
Logical memory II	18.7 (7.3)	18.1 (7.1)	18.2 (7.0)	18.9 (7.2)	19.6 (7.7)	.04
Visual reproduction II	22.4 (8.0)	21.0 (8.2)	22.2 (8.1)	22.5 (7.7)	23.6 (7.9)	.001
DSS	43.7 (10.0)	41.1 (9.8)	42.8 (10.4)	44.7 (9.3)	45.7 (9.8)	<.001
TMTB	195.4 (48.2)	185.7 (54.4)	193.5 (46.3)	197.7 (49.1)	202.4 (43.7)	<.001
BNT	55.1 (4.2)	54.4 (5.0)	55.0 (4.2)	55.3 (3.7)	55.6 (3.8)	.02
Category fluency	43.3 (9.3)	39.7 (8.6)	42.2 (8.9)	43.8 (9.0)	46.4 (9.5)	<.001
Picture Completion	13.4 (3.1)	13.4 (2.8)	13.1 (3.3)	13.5 (3.1)	13.6 (3.0)	.22
Block Design	23.6 (8.1)	22.9 (8.3)	23.4 (8.2)	23.7 (7.7)	24.2 (8.1)	.38
STMS	34.7 (2.3)	34.4 (2.4)	34.5 (2.3)	34.7 (2.1)	35.0 (2.3)	.001

Abbreviations: APOE, apolipoprotein E; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; B-SIT, Brief Smell Identification Test; DSS, Digit Symbol Substitution; MCI, mild cognitive impairment; Q, quartile; STMS, Short Test of Mental Status; TMTB, Trail Making Test B.

<sup>a</sup> P value for trend based on  $\chi^2$  test for categorical variables and Kruskal-Wallis

test for continuous variables.

<sup>b</sup> The MCI subtype was unknown for 38 participants who participated only by telephone at the time of MCI diagnosis and did not undergo neuropsychological testing.

model plus the STMS; and the augmented model including variables in the basic model, STMS, informant-based measures (Functional Activities Questionnaire and Clinical Dementia Rating), Unified Parkinson's Disease Rating Scale, gait speed, and neuropsychiatric symptoms (from Neuropsychiatric Inventory Questionnaire, Beck Depression Inventory, and Beck Anxiety Inventory).<sup>37</sup> We ran separate Cox models to predict MCI, including the risk scores with and without the B-SIT score, and computed the differences in model fit assessed as the C statistic (concordance).

#### Mixed-Effects Models

Among cognitively normal participants, we used linear mixed-effects models to investigate the association of B-SIT score with decline in cognitive z scores and the STMS during follow-up. All the analyses were performed using SAS version 9.3 (SAS Institute).

## Results

### Characteristics of Cognitively Normal Participants

Of the 1630 participants who were cognitively normal at the time of the smell test, 33 died before follow-up and 167 were lost to follow-up. Among the 1430 cognitively normal participants included, the mean (SD) age was 79.5 (5.3) years, 49.4% were men, the mean duration of education was 14.3 years, and 25.4% were APOE ε4 carriers (Table 1). Over a mean 3.5 years of follow-up, there were 250 incident MCI cases. The frequency of incident MCI decreased with increasing B-SIT scores.

### Characteristics of Participants With Prevalent MCI

Of the 317 participants with prevalent MCI, 75 had no follow-up and 21 died. Of the 221 included (aMCI, 185; naMCI, 36), the frequency of MCI decreased with increasing B-SIT score

Table 2. Characteristics of Prevalent MCI Cases by B-SIT Scores at Baseline

Characteristics	Mean (SD)					P Value for Trend <sup>a</sup>
	All (N = 221)	Q1 (n = 59)	Q2 (n = 45)	Q3 (n = 54)	Q4 (n = 63)	
Smell score, range	1-12	1-5	5.25-7.5	8-9.5	10-12	
Male, No. (%)	122 (55.2)	34 (57.6)	31 (68.9)	26 (48.1)	31 (49.2)	.14
Age, y	82.1 (6.0)	84.0 (5.0)	82.8 (6.2)	81.5 (5.7)	80.4 (6.4)	.005
Education, y	13.4 (2.9)	13.2 (3.2)	14.1 (3.2)	13.3 (2.7)	13.1 (2.6)	.29
APOE ε4, No. (%) <sup>a</sup>	73 (33.2)	18 (31.0)	19 (42.2)	17 (31.5)	19 (30.2)	.55
Diabetes, No. (%)	63 (28.5)	14 (23.7)	16 (35.6)	17 (31.5)	16 (25.4)	.51
Hypertension, No. (%)	189 (85.5)	54 (91.5)	35 (77.8)	48 (88.9)	52 (82.5)	.18
Stroke, No. (%)	29 (13.1)	7 (11.9)	8 (17.8)	6 (11.1)	8 (12.7)	.77
Smoking, ever, No. (%)	101 (45.7)	28 (47.5)	18 (40.0)	24 (44.4)	31 (49.2)	.80
Alcohol problem, No. (%)	11 (5.0)	3 (5.1)	1 (2.3)	3 (5.6)	4 (6.5)	.80
Follow-up, y	3.1 (1.1)	2.9 (1.2)	2.9 (1.0)	3.2 (1.1)	3.2 (1.2)	.34
Incident dementia, No. (%) <sup>b</sup>	64 (29.0)	26 (44.1)	10 (22.2)	19 (35.2)	9 (14.3)	.002
Incident AD, No. (%)	54 (24.4)	23 (39.0)	9 (20.0)	14 (25.9)	8 (12.7)	NA
Cognitive domain z scores						
Memory	-1.9 (0.9)	-2.1 (0.8)	-2.0 (0.8)	-1.9 (1.0)	-1.6 (0.8)	.004
Executive function	-1.4 (1.4)	-1.7 (1.3)	-1.5 (1.4)	-1.5 (1.5)	-1.1 (1.3)	.18
Language	-1.6 (1.4)	-1.9 (1.4)	-1.6 (1.5)	-1.7 (1.3)	-1.2 (1.3)	.03
Visuospatial	-1.0 (1.1)	-1.2 (1.2)	-0.8 (1.1)	-1.1 (1.3)	-1.0 (1.0)	.41
Global	-1.9 (1.1)	-2.3 (1.1)	-1.9 (1.0)	-2.1 (1.0)	-1.6 (0.8)	.02
Cognitive test scores						
AVLT	2.8 (3.0)	2.1 (2.4)	2.2 (2.8)	2.8 (3.0)	4.1 (3.2)	.002
Logical memory II	8.8 (6.3)	8.4 (6.5)	7.8 (4.8)	9.4 (6.7)	9.4 (6.7)	.68
Visual reproduction II	9.6 (7.9)	8.1 (7.6)	9.3 (8.8)	8.4 (7.4)	12.0 (7.4)	.006
DSS	33.9 (10.2)	30.3 (8.2)	33.5 (9.4)	34.8 (11.8)	36.6 (10.1)	.02
TMTB	125.2 (76.3)	118.5 (79.1)	123.2 (77.0)	115.9 (77.9)	139.3 (72.1)	.39
BNT	49.1 (7.3)	47.5 (7.4)	48.8 (8.1)	49.4 (6.8)	50.4 (6.7)	.13
Category fluency	33.0 (9.0)	31.6 (8.9)	33.0 (9.2)	31.4 (8.3)	35.6 (9.1)	.03
Picture Completion	10.4 (3.7)	10.1 (3.9)	10.9 (3.6)	10.1 (4.0)	10.5 (3.5)	.69
Block Design	17.5 (8.2)	16.3 (8.6)	19.3 (8.3)	17.3 (8.7)	17.7 (7.2)	.32
STMS	30.1 (2.7)	30.1 (2.3)	29.8 (2.9)	30.1 (2.7)	30.5 (2.7)	.64

Abbreviations: AD, Alzheimer disease dementia; APOE, apolipoprotein E; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; B-SIT, Brief Smell Identification Test; DSS, Digit Symbol Substitution; MCI, mild cognitive impairment; NA, not applicable; Q, quartile; STMS, Short Test of Mental Status; TMTB, Trail Making Test B.

<sup>a</sup> P value for trend;  $\chi^2$  test for categorical variables and Kruskal-Wallis test for continuous variables.

<sup>b</sup> Dementia type was unknown for 2 participants; only 8 participants had non-Alzheimer-type dementia.

(Table 2). Over a mean 3.1 years of follow-up, there were 64 incident dementia cases. The frequency of any or AD dementia decreased, and cognitive performance increased with increasing B-SIT scores.

### Impaired Olfaction and Incident MCI

The risk of MCI increased with decreasing B-SIT scores (Table 3). There was a significant dose-response association across worsening olfaction categories. The associations remained significant after adjustment for or exclusion of persons with a history of stroke (data are not presented). There was no significant interaction of smell with sex or with APOE ε4 allele. However, the hazard ratio (HR [95% CI]) for MCI in men with B-SIT scores less than 9 (vs ≥9) was higher (HR, 2.35 [1.59-3.49];  $P < .001$ ) than that for women with scores less than 9 (HR, 1.54 [1.10-2.18];  $P = .01$ ;  $P$  for interaction = .11). Similarly, the HR in APOE ε4 car-

riers with B-SIT scores less than 9 was higher (2.09 [1.35-3.24]) than for ε4 noncarriers with scores less than 9 (HR, 1.72 [1.26-2.36]; both  $P < .001$ ;  $P$  for interaction = .47).

### Impaired Olfaction and MCI Subtypes

Impaired olfaction was associated with any MCI and with aMCI (Table 3). With additional adjustment for baseline global z score and APOE ε4 allele, the risk of aMCI for the worst B-SIT categories remained significantly elevated for quartile (Q) 1 vs Q4 (HR, 1.67 [95% CI, 1.03-2.73];  $P = .04$ ;  $P$  for trend = .02) and for B-SIT score less than 9 vs 9 or greater (HR, 1.91 [95% CI, 1.37-2.66];  $P < .001$ ), and marginally significant for anosmia vs normosmia (HR, 1.69 [95% CI, 0.93-3.05];  $P = .08$ ;  $P$  for trend = .07). Hazard ratios for the intermediate categories were nonsignificantly elevated (data not presented). The B-SIT score was not associated with naMCI.

Table 3. Association of B-SIT Scores With Risk of Any MCI, MCI Subtypes, Any Dementia, and AD Dementia

Smell Test Score	Incident MCI <sup>a</sup>			Incident aMCI			Incident naMCI		
	Participants/ Events, No.	HR (95% CI)	P Value	Participants/ Events, No.	HR (95% CI)	P Value	Participants/ Events, No.	HR (95% CI)	P Value
Continuous <sup>b</sup>	1430/250	1.10 (1.05-1.16)	<.001	1392/162	1.13 (1.06-1.20)	<.001	1392/50	0.97 (0.85-1.11)	.68
Quartiles (smell score range)									
4 (11-12)	429/52	1 [Reference]		425/30	1 [Reference]		425/18	1 [Reference]	
3 (9.25-10.5)	294/42	1.07 (0.71-1.61)	.76	283/24	1.12 (0.65-1.92)	.68	283/7	0.55 (0.23-1.32)	.18
2 (8-9)	409/84	1.47 (1.03-2.09)	.03	402/62	1.95 (1.25-3.03)	.003	402/15	0.73 (0.36-1.48)	.38
1 (1-7.5)	298/72	1.82 (1.26-2.64)	.001	282/46	2.18 (1.36-3.51)	.001	282/10	0.73 (0.32-1.64)	.45
P value for trend	<.001			<.001			.46		
Categorical									
Normosmia	431/52	1 [Reference]		427/30	1 [Reference]		427/18	1 [Reference]	
Microsmia	863/164	1.39 (1.01-1.91)	.04	836/111	1.70 (1.13-2.57)	.01	836/26	0.65 (0.35-1.20)	.17
Anosmia	136/34	1.82 (1.16-2.86)	.009	129/21	2.15 (1.21-3.81)	.009	129/6	0.92 (0.34-2.47)	.87
P value for trend	.007			.004			.46		
Dichotomized									
≥9	953/130	1 [Reference]		935/79	1 [Reference]		935/33	1 [Reference]	
<9	477/120	1.85 (1.43-2.39)	<.001	457/83	2.21 (1.61-3.03)	<.001	457/17	1.01 (0.55-1.86)	.96
Continuous <sup>b</sup>	221/64	1.15 (1.05-1.26) <sup>c,d</sup>	.002	185/49	1.19 (1.07-1.32) <sup>e</sup>	<.001			
Quartiles (smell score range)									
4 (10-12)	63/9	1 [Reference]		47/5	1 [Reference]				
3 (8-9.5)	54/19	2.61 (1.17-5.86) <sup>c,d</sup>	.02	49/13	3.02 (1.06-8.57) <sup>e</sup>	.04			
2 (5.25-7.5)	45/10	1.89 (0.75-4.75) <sup>c,d</sup>	.18	35/9	3.63 (1.19-11.1) <sup>e</sup>	.02			
1 (0-5)	59/26	3.48 (1.59-7.61) <sup>c,d</sup>	.002	54/22	5.20 (1.90-14.2) <sup>e</sup>	.001			
P value for trend	.004			.001					
Dichotomized									
≥9	94/20	1 [Reference]		77/14	1 [Reference]				
<9	127/44	1.82 (1.05-3.16) <sup>c,d</sup>	.03	108/35	2.17 (1.14-4.15)	.02			

Abbreviations: AD, Alzheimer disease dementia; aMCI, amnesic MCI; B-SIT, Brief Smell Identification Test; HR, hazard ratio; MCI, mild cognitive impairment; naMCI, nonamnesic MCI.

<sup>a</sup> Estimates are adjusted for sex and education, with age as the time scale. The MCI subtype was unknown for 38 participants who participated only by telephone evaluation at the time of MCI diagnosis and did not undergo neuropsychological testing.

<sup>b</sup> The B-SIT score here represents the number of incorrect responses. Alternatively, with B-SIT scored as the number of correct responses, the corresponding estimate (HR [95% CI] for risk of incident MCI is 0.91 [0.86-0.96],  $P < .001$ ). This estimate is comparable with estimates for baseline cognitive test scores in predicting incident MCI: Auditory Verbal

Learning Test (HR [95% CI]): 0.81 (0.78-0.85),  $P < .001$ ; Logical Memory II: 0.91 (0.89-0.93),  $P < .001$ ; Visual Reproduction II: 0.93 (0.91-0.94),  $P < .001$ ; Picture Completion: 0.92 (0.88-0.95),  $P < .001$ ; Block Design: 0.93 (0.92-0.95),  $P < .001$ ; Digit Symbol Substitution: 0.93 (0.92-0.95),  $P < .001$ ; Trail Making Test B: 0.99 (0.99-0.99),  $P < .001$ ; Boston Naming Test: 0.90 (0.88-0.92),  $P < .001$ ; and category fluency: 0.93 (0.91-0.95),  $P < .001$ .

<sup>c</sup> Estimates are not reported for osmia groups because there were no dementia events among the normosmia group for comparison.

<sup>d</sup> Any MCI to dementia.

<sup>e</sup> Amnesic MCI to AD dementia.

### Impaired Olfaction and Changes in Cognitive z Scores

In linear mixed-effects models, each unit decrease in B-SIT score was correlated with worse performance in domain z scores at baseline (Table 4). Longitudinally, each unit decrease in baseline B-SIT score was significantly associated with decline in performance in memory ( $\beta = -0.013$ ,  $P < .001$ ), executive function ( $\beta = -0.016$ ,  $P < .001$ ), language ( $\beta = -0.013$ ,  $P < .001$ ), and global z scores ( $\beta = -0.015$ ,  $P < .001$ ). Similar cross-sectional and longitudinal association patterns were present for the individual test scores, except for Picture Completion.

### Impact of B-SIT Score on Risk Prediction Models for MCI

The B-SIT score (continuous) was significantly associated with MCI in a model with the basic risk scores (HR, 1.10 [95% CI, 1.04-1.16];  $P < .001$ ), and the C statistic improved from 0.590 to

0.620. In the basic plus STMS model, the B-SIT score remained significant (HR, 1.10 [95% CI, 1.04-1.16];  $P < .001$ ), and the model C statistic improved modestly from 0.704 to 0.717. Similarly, in the augmented model, the B-SIT score remained significant (HR, 1.09 [95% CI, 1.03-1.16];  $P = .002$ ), and the model C statistic improved from 0.716 to 0.726.

### Impaired Olfaction and Progression From MCI to Dementia

Among 221 prevalent MCI cases (122 single-domain aMCI; 63 multidomain aMCI; and 36 naMCI), the risk of dementia increased with decreasing B-SIT score, with a significant dose response across B-SIT categories (Table 3). The worst B-SIT categories strongly predicted progression from aMCI to AD dementia. In multivariable models, the estimates for the worst olfaction categories remained significant even after addi-

**Table 4. Cross-sectional and Longitudinal Associations of Smell Test Scores With Cognitive Domain z Scores in Cognitively Normal Individuals (Mixed-Effect Models)<sup>a</sup>**

Cognitive Scores	Baseline $\beta$ (SE)	P Value	Time $\beta$ (SE)	P Value	Smell by Time $\beta$ (SE)	P Value
Domain z score						
Memory	-0.036 (0.01)	.001	-0.043 (0.01)	<.001	-0.013 (0.002)	<.001
Executive function	-0.022 (0.01)	.04	-0.117 (0.01)	<.001	-0.016 (0.003)	<.001
Language	-0.065 (0.01)	<.001	-0.074 (0.01)	<.001	-0.013 (0.002)	<.001
Visuospatial	-0.009 (0.01)	.42	-0.037 (0.01)	.004	-0.003 (0.002)	.23
Global	-0.043 (0.01)	<.001	-0.091 (0.01)	<.001	-0.015 (0.002)	<.001
Test z score						
AVLT	-0.024 (0.01)	.03	-0.041 (0.01)	<.001	-0.009 (0.003)	<.001
Log memory II	-0.024 (0.01)	.03	-0.019 (0.01)	.005	-0.009 (0.003)	.002
Visual reproduction II	-0.030 (0.01)	.006	-0.034 (0.01)	<.001	-0.009 (0.003)	.003
DSS	-0.027 (0.01)	.01	-0.087 (0.01)	<.001	-0.008 (0.002)	<.001
TMTB	-0.011 (0.01)	.31	-0.114 (0.01)	<.001	-0.017 (0.003)	<.001
BNT	-0.043 (0.01)	<.001	-0.036 (0.01)	<.001	-0.013 (0.002)	<.001
Category fluency	-0.063 (0.01)	<.001	-0.084 (0.01)	<.001	-0.008 (0.002)	.001
Picture Completion	-0.007 (0.01)	.52	0.008 (0.01)	.22	-0.000 (0.003)	.90
Block Design	-0.005 (0.01)	.63	-0.071 (0.01)	<.001	-0.006 (0.002)	.007
STMS	-0.023 (0.03)	.36	-0.113 (0.02)	<.001	-0.033 (0.009)	<.001

Abbreviations: AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; B-SIT, Brief Smell Identification Test; DSS, Digit Symbol Substitution; MCI, mild cognitive impairment; STMS, Short Test of Mental Status; TMTB, Trail Making Test B.

<sup>a</sup>Models are adjusted for age, sex, education, and test naive (ie, whether the

participant was test naive at baseline or not). Baseline represents the cross-sectional association between smell test score and cognitive performance; time refers to the annual change in the cognitive z score (the outcome), and smell by time refers to the annual rate of change in the cognitive z score for each unit decrease in the smell score.

tional adjustment for baseline global z score (Q1 vs Q4: HR, 3.32 [95% CI, 1.16-9.44];  $P = .03$ ); less than 9 vs 9 or greater (HR, 2.07 [95% CI, 1.01-4.25];  $P = .048$ ), and after further adjustment for stroke (data not presented).

## Discussion

In this elderly cohort, impaired olfaction was associated with incident MCI and aMCI and with greater decline in cognitive performance during follow-up. After accounting for several established risk factors for MCI, the smell score remained significantly associated with MCI and improved the model fit for predicting MCI. Impaired olfaction was associated with progression from MCI to dementia and from aMCI to AD dementia.

Clinical implications of our findings are that odor identification tests may have use for early detection of persons at risk of cognitive outcomes. The B-SIT is easily administered in the outpatient setting, does not require administration or interpretation by trained personnel, has normative data, is relatively inexpensive, and is noninvasive. Thus, the B-SIT could be beneficial for screening to identify cognitively normal persons and persons with MCI who could benefit from early interventions to prevent or modulate risk for progression. The findings also suggest that a combination of the B-SIT with other predictors of AD dementia may have use for identifying persons who should undergo expensive or invasive diagnostic testing to detect AD dementia pathology or recruitment to primary or secondary prevention trials. However, the latter requires further evaluation.

The results from mixed models for continuous cognitive outcomes are consistent with the results for the dichotomous outcome of MCI risk. They suggest that impaired olfaction is associated with worse cognitive performance among cognitively normal individuals, and predicts decline in cognitive performance in nearly all cognitive domains. The greater declines in memory, executive function, and language suggest that brain regions that mediate performance in these domains may be involved early in the disease process.

Potential mechanisms for the present findings may involve neurodegenerative changes in the olfactory bulb and tracts and central brain regions that involve memory and olfaction.<sup>38</sup> The olfactory bulb is thought to be involved because smell loss occurs only in neurodegenerative conditions where there is olfactory pathology such as AD and Parkinson disease.<sup>39</sup> Markers of AD pathology (neurofibrillary tangles) have been observed in the olfactory bulb and tracts prior to onset of AD dementia-related symptoms, suggesting that olfactory deficits may be early markers of AD risk.<sup>38,40,41</sup> The presence of AD pathology in the entorhinal cortex, hippocampus, and other temporal regions leads to an inability to store and retrieve memories of smell and thereby to correctly identify odors.<sup>42,43</sup> Cholinergic deficits resulting from several mechanisms, including damage to the nucleus basalis (a key cholinergic nucleus that projects to brain regions involved in olfaction), are involved in olfactory loss in AD dementia and Parkinson disease. These deficits help distinguish between neurodegenerative diseases with (Parkinson disease and AD) and without (progressive supranuclear palsy and corticobasal syndrome) impairment in olfaction.<sup>39</sup> Reduced levels of choline acetyl transferase and dopamine in the olfactory

tubercle and other brain regions,<sup>44</sup> as well as decreased norepinephrine related to damage or neurodegeneration in the locus coeruleus (a key source of norepinephrine to the olfactory bulb), have been hypothesized to play a role in impaired olfaction in AD.

Our findings replicate those from other longitudinal studies on olfaction and incident MCI or cognitive decline. In a multiethnic urban community, impaired olfaction was a stronger predictor of incident MCI than episodic memory.<sup>10</sup> In the Rush Memory and Aging Study,<sup>2</sup> worse olfaction was associated with incident MCI and declines in cognitive outcomes. In other studies, impaired olfaction was associated with declines in verbal and visual memory<sup>5</sup> and in global cognition.<sup>4</sup>

Cross-sectional and case-control studies have also reported associations of impaired olfaction and MCI or cognitive measures. In a case-control study of MCI and AD cases recruited from a neuropsychology clinic, cases had significantly worse scores than control individuals.<sup>14</sup> In a cross-sectional study of MCI cases, severe hyposmia was associated with worse performance on memory tests and executive function.<sup>15</sup> Among middle-aged participants, impaired olfaction was associated with worse performance on tests of executive function.<sup>45</sup> In the Rush Memory and Aging Study, worse olfaction was associated with worse cognitive performance at baseline,<sup>2</sup> and in a Chinese sample, impaired olfaction was associated with MCI.<sup>16</sup>

The association of impaired olfaction with MCI progression to dementia is consistent with longitudinal findings from other studies.<sup>9-11</sup> Among patients from a memory clinic and volunteer control individuals, a combination of markers (smell test scores, functional measures, cognitive test scores, and imaging measures) more strongly predicted progression from MCI to dementia than age and Mini-Mental State Examination score.<sup>12</sup> In one prospective study, worse smell scores from a 10-item test predicted conversion from MCI to AD dementia,<sup>3</sup> and in another, the B-SIT performed highly in distinguishing between AD dementia cases and control individuals.<sup>13</sup> Cross-sectionally, impaired olfaction was associated with AD in a Japanese cohort.<sup>46</sup>

To our knowledge, relatively few investigators have specifically examined the associations of MCI subtypes with AD dementia. The strong association for transition from aMCI to AD dementia is consistent with an underlying AD pathophysiology. Consistent with our findings, one study reported a stronger association of impaired olfaction with progression from aMCI to AD dementia than from naMCI to AD dementia, and a combination of the smell test score and memory impairment score improved prediction of AD dementia compared with memory scores alone.<sup>10</sup> We did not detect an association of impaired olfaction with risk of naMCI owing to lack of power (50 incident naMCI cases). We also did not have power to examine associations of prevalent naMCI with risk of non-AD dementias (only 10 incident non-AD dementia cases). By contrast, other investigators have reported associations of impaired olfaction with vascular dementia,<sup>8</sup> as well as with Parkinson disease and the presence of Lewy bodies, with implications for Lewy body dementia.<sup>7</sup> In contrast to the present findings, one study did not observe an association of impaired olfaction with

declines in global cognition (Mini-Mental State Examination score) or with executive function.<sup>5</sup> However, in a previous study, impaired olfaction was associated with AD biomarkers including elevated cortical amyloid and thinner entorhinal cortex.<sup>47</sup>

The present findings were robust to changes in cutpoints for olfaction, and the associations persisted even after adjustment for or exclusion of persons with a history of stroke. Despite the absence of a significant interaction with sex and APOE  $\epsilon 4$  allele, the estimates and direction of risk were consistent with studies reporting stronger associations of impaired olfaction with cognitive impairment in APOE  $\epsilon 4$  allele carriers than noncarriers.<sup>4,16,48,49</sup> Consistent with the present study, another study did not find a significant interaction of B-SIT score with APOE genotype.<sup>5</sup>

There were some potential limitations to our study. We did not directly assess odor detection; however, this is unlikely to bias our findings because odor detection tests correlate highly with odor identification tests, and patients with AD and a number of other neurodegenerative diseases demonstrate deficits in both detection and identification.<sup>44,50</sup> We excluded 23 participants with Parkinson disease and 12 with alcoholism (CAGE stage 4),<sup>51</sup> but were unable to identify and exclude people with a history of head trauma, allergies, nasal condition, or nasal diseases that could impact olfaction if present.<sup>52</sup> The predominant northern European ancestry of participants raised questions about generalizability. Nevertheless, studies in multiethnic and nonwhite cohorts have reported similar associations.<sup>10,16,46</sup> The use of the B-SIT compared with the longer 40-item University of Pennsylvania Smell Identification Test has been questioned.<sup>14</sup> However, the B-SIT has been shown to reliably predict cognitive decline and MCI, distinguish between AD cases and control individuals in other studies,<sup>2-6,13</sup> and have a test-retest reliability coefficient of 0.71 consistent with the expected estimate for a 12-item test.<sup>36,53</sup>

There were several strengths of our study. The study was population based, reducing the potential for selection bias. The study included a large cohort of cognitively normal participants and MCI cases, with equal representation of both sexes. Reliable and valid information on covariates was abstracted from community medical records rather than by self-report. Participants were comprehensively characterized for MCI and dementia at each evaluation using previously published criteria and without consideration of previous diagnoses, thereby reducing the potential for bias in ascertainment of diagnoses. The prospective design allowed us to assess the role of impaired olfaction as a marker for early detection of persons at risk for MCI and dementia.

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## Conclusions

Our findings suggest that impaired olfaction is associated with incident aMCI and with progression from aMCI to AD dementia, and may be useful as a marker for early detection of persons at risk for aMCI or AD dementia.

## ARTICLE INFORMATION

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**Correction:** There was an error in the first sentence of the fourth paragraph of the Methods section. The sentence should read as follows: "Olfaction was assessed using the Brief Smell Identification Test (B-SIT) version A,36 which consists of 6 food-related and 6 non-food-related smells (cherry, clove, strawberry, menthol, pineapple, lemon, leather, lilac, smoke, soap, natural gas, and rose)." This article was corrected online on February 15, 2016.

**Author Contributions:** Dr Roberts 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.

**Study concept and design:** Roberts, Petersen.

**Acquisition, analysis, or interpretation of data:** All authors.

**Drafting of the manuscript:** Roberts.

**Critical revision of the manuscript for important intellectual content:** All authors.

**Statistical analysis:** Christianson, Kremers.

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