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# OLFACTION AND THE 5-YEAR INCIDENCE OF COGNITIVE IMPAIRMENT IN AN EPIDEMIOLOGIC STUDY OF OLDER ADULTS

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## Abstract

**Objectives—**To determine if odor identification ability is associated with the 5-year incidence of cognitive impairment in a large population of older adults with normal cognition at baseline and if olfactory impairment contributes to the prediction of cognitive decline in a population.

**Design—**Population-based longitudinal study.

**Setting—**Beaver Dam, WI.

**Participants—**1920 participants in the Epidemiology of Hearing Loss Study (mean age = 66.9 years).

**Measurements—**Olfaction was measured by the San Diego Odor Identification Test (SDOIT). Incident cognitive impairment was defined as a Mini-Mental State Exam Score (MMSE) < 24 or reported diagnosis of dementia or Alzheimer's disease (AD) at the follow-up among people with MMSE ≥ 24 and no diagnosis of dementia or AD at baseline.

**Results—**There was a significant association between olfactory impairment at baseline and the 5-year incidence of cognitive impairment (Odds Ratio (O.R.) = 6.62, 95% Confidence Interval (C.I.) = 4.36, 10.05). The association remained significant after adjusting for possible confounders (O.R. = 3.72, 95% C.I. = 2.31, 5.99). The Positive Predictive Value of the SDOIT was 15.9%, the Negative Predictive Value was 97.2% and the sensitivity and specificity were 55.1% and 84.4%, respectively, for the 5-year incidence of cognitive impairment.

**Conclusion—**Olfactory impairment at baseline was strongly associated with the 5-year incidence of cognitive impairment as measured by the MMSE. Odor identification testing may be useful in high risk settings, but not in the general population, to identify patients at risk for cognitive decline.

### Keywords

Olfaction; Cognition; Epidemiology; Longitudinal Study

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## INTRODUCTION

The prevalences of olfactory impairment and cognitive impairment increase with age.[1-3] A decrease in olfactory function with age has been attributed to a variety of factors including normal anatomical and physiological changes in aging, surgery, trauma, environmental factors, medications and disease.[4] Olfactory impairment has also been associated with neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease.[5-7]

Some studies have reported that olfaction impairment appears to precede clinical signs of cognitive impairment or AD and have hypothesized that it may be an early indicator of brain changes. People at high risk for AD, those with the Apolipoprotein epsilon 4 genetic risk factor for AD, with existing Mild Cognitive Impairment (MCI) or with a family history of AD, have demonstrated poorer performance on olfactory tests than controls [8-10], and those with olfactory impairment, were more likely to progress to AD.[8] Autopsy studies have found neurofibrillary tangles, pathology thought to be associated with AD, appear first in the entorhinal cortex and olfactory bulb areas of the brain both in people with AD and/or dementia as well younger people with no clinical signs of dementia. [11-13] A recent study found the density of tangles present in the central olfactory system was inversely related to odor identification ability.[14]

Because of the suggestion that olfactory impairment may be an early indicator for cognitive impairment, there has been interest in the possibility of using olfactory testing to assist in diagnosis of AD or predict who will develop AD or cognitive impairment. However there has been limited research on the association of olfaction and cognition in a general population of older adults not at high risk for AD or cognitive impairment. The purpose of this study is to determine if odor identification ability is associated with cognitive function in a large population of older adults with normal cognition at baseline and if olfactory impairment contributes to the prediction of cognitive decline in a general population.

## METHODS

This research was approved by the University of Wisconsin Human Subjects Committee and informed consent was obtained prior to all examinations. Subjects were participants in the Epidemiology of Hearing Loss Study (EHLS), a longitudinal population-based study of sensory loss and aging in older adults in Beaver Dam, WI.[15] A detailed description of the study and its methods has been published elsewhere.[15,16] Briefly, in 1987-88 a private census was conducted of the city and township of Beaver Dam, WI and all residents aged 43-84 years were invited to participate in the Beaver Dam Eye Study (BDES). Of the 5924 people eligible, 4926 (83%) participated (aged 43-84 years).[17] All participants who were alive March 1, 1993 (n=4541) were eligible to participate in the EHLS (n=3753, 82.6% of eligible) which ran concurrent with the 5-year examination of the Beaver Dam Eye Study.[15] The EHLS examination included complete audiometric testing and an extensive interview with questions regarding self-reported hearing ability, hearing health, general health, lifestyle and socioeconomic factors. At the EHLS 5-year examination (1998-2000, n=2800) the San Diego Odor Identification Test (SDOIT) and the Mini-Mental State Exam (MMSE) were administered.[1, 16, 18] To be eligible for these analyses participants had to have completed the SDOIT and not be cognitively impaired (n=2301). Of those eligible, 1920 (83.4%) participants had their cognitive status reassessed five years later (2003-2005) at the 10-year examination (23 (1.0%) were missing cognitive data, 244(10.6%) died before being re-examined, 114 (5.0%) refused to participate). Participants without follow-up were significantly older at the 5-year examination than those with follow-up (mean age 72 years vs. 67 years, respectively, $p<0.0001$) and had slightly lower age-adjusted mean SDOIT and MMSE scores (5.8 vs. 6.5 for SDOIT ($p<0.0001$), and 27.7 vs. 27.9 for MMSE ($p=0.04$), respectively).

### Cognitive function

Cognitive impairment was defined as a score of less than 24 points on the MMSE or a self- or proxy-report of AD or dementia in the absence of a MMSE score. Because of the overall young age of the cohort and time constraints, participants who scored 15 or more points, out of 21 possible, on the orientation, registration, attention and calculation, and recall sections of the MMSE were not administered the language section (9 points possible). Scores from the shortened exam were re-scaled to a 0-30 scale for analyses. The sensitivity was 96% and the specificity was 93% for this combined method using the full MMSE as the gold standard.[19]

### Olfactory examination

Odor identification ability was assessed using the SDOIT, an eight item odor identification test that utilizes common odors typically found in the home, e.g., coffee, chocolate.[20, 21] Details regarding the SDOIT have been published elsewhere.[1, 20, 21] A picture board with illustrations of the eight odorants as well as 12 distracters was presented to help aid in identification and prevent any bias related to naming issues. Participants were allowed to respond verbally or point to the picture of the odorant. Odorants were presented in a random order. Test-retest reliability of this test was $r = 0.86$ when tested with a mean delay of 5 days.[20] The data were analyzed using the raw score, one point for each odor correctly identified (0-8 points possible), and by an impairment classification. Participants identifying fewer than six out of eight odorants were considered impaired.[1]

### Data Analysis

Analyses were conducted with the SAS System (SAS Systems Inc, Gary, NC). The chi-square test for general association and the Mantel-Haenszel chi-square for trend were utilized to identify potential confounders of the relationship between olfactory impairment and the 5-year incidence of cognitive impairment. Fisher's exact test was used when cell sizes were small. Risk factors that had significant associations with both olfaction and cognition were tested in age- and sex-adjusted logistic regression models with cognitive impairment as the outcome. Stepwise regression was performed to determine the final covariates to include in the models. In addition, Analysis of Covariance (ANCOVA) was used assess the relationship between the olfaction score at baseline and the MMSE score at five years.

Risk factors that were tested as potential confounders included age, gender, educational attainment, longest-held occupation, smoking status, MMSE score at baseline, a history of head injury, epilepsy, Parkinson's disease, chemotherapy, diabetes, peripheral vascular disease, cardiovascular disease or stroke, cold or sinus problems in the previous week or nasal congestion on the day of the exam, history of allergies, history of heavy alcohol consumption, and use of antihistamines. The Mental Component Summary Score (MCS) of the Medical Outcomes Study Short Form Health Survey (SF-36) was used as a marker for depression.[22]

To determine the usefulness of the SDOIT as a screening test for the 5-year incidence of cognitive impairment, the predictive values and sensitivity and specificity of the test were calculated using 2×2 tables. In this case, a positive test would be a classification of impairment on the SDOIT and a negative test would be a classification of no olfactory impairment.

## RESULTS

Participants (n=1920) were age 53-95 years (mean age 66.9 years) at the baseline examination (1998-2000) had a mean SDOIT score of 6.6 (range 0-8) and a mean MMSE score of 28.0 (range 24-30). Five years later, the mean SDOIT score for the cohort was 6.5 (range 0-8) and the mean MMSE score was 28.0 (range 10-30). Almost 18% of participants were classified as having olfactory impairment at baseline and more men than women had olfactory impairment

(23.8% vs.13.5%, p<0.001). Olfactory impairment was more prevalent in the older age groups (Table 1.). The 5-year incidence of cognitive impairment was five percent in this subset and the incidence was higher in the older age groups.

A greater percentage of participants with a low SDOIT score, versus those with a higher score, went on to develop cognitive impairment in five years (Table 2). Using the olfactory impairment cut-point (<6 of 8 odorants correctly identified), the 5-year incidence of cognitive impairment was significantly higher for those with olfactory impairment versus those without olfactory impairment (p<0.001).

There was a significant association between olfactory impairment and the 5-year incidence of cognitive impairment (Odds Ratio (O.R.) = 6.62, 95% Confidence Interval (C.I.) = 4.36, 10.05) (Table 3). The association remained significant after adjusting for age at baseline, gender, education and occupation (O.R. = 3.72, 95% C.I. = 2.31, 5.99). Smoking status, diabetes status, a history of head injury, epilepsy, Parkinson's disease, cardiovascular disease or stroke, cold or sinus problems, allergies, and heavy alcohol consumption were tested in the model but were not significant. The MMSE score at baseline was added to the model to control for any bias from the cognitive impairment classification due to migration around the cut-point. The MMSE score at baseline was significant in the model but did not alter the association between olfaction and cognitive impairment (Table 3). Based on a pseudo R-Square statistic and the Hosmer-Lemeshow Goodness of Fit test, model fit was better with both impaired olfaction and baseline MMSE score than with either alone.

Depression, as measured by the MCS Score of the SF-36, was significant as an independent predictor of cognitive impairment (p=0.007) but was not a confounder of the association of olfactory impairment with incident cognitive impairment and was not included in the final model (O.R. for olfactory impairment = 3.24, 95% C.I. = 1.98, 5.29 with MCS in model). An age by gender interaction was tested in the logistic regression model and was not significant. In the ANCOVA model, each one unit decrease in the SDOIT score predicted a 0.23 (p<0.001) decrease in the MMSE score at follow-up in a model adjusted for age at baseline, gender, education, occupation and MMSE score at baseline.

The positive predictive value of the SDOIT was 15.9% and the negative predictive value was 97.2%. After stratifying by age and gender, the highest positive predictive value was for women aged 80-95 years, with the test correctly predicting 34% of the incident cases of cognitive impairment and the negative predictive value for this group was 83.6%. The sensitivity and specificity for the SDOIT and the 5-year incidence of cognitive impairment were 55.1% and 84.4%, respectively.

## DISCUSSION

In this study we found a strong association between olfactory impairment and the 5-year incidence of cognitive impairment. It has been demonstrated in several studies that AD is associated with olfactory deficits [5-7], and that people with mild cognitive impairment or at high risk for AD perform worse on olfactory tests [8-10], but there have been only a few longitudinal studies that have reported on olfactory impairment and the incidence of cognitive decline or impairment. To our knowledge this is the first population-based epidemiologic study of this size to report this finding.

The results of the current study are consistent with the results found in other longitudinal studies. Graves et al, in a community-based study of Japanese-Americans aged 65-95 years, found participants classified as anosmic, had almost twice the risk of cognitive decline over two years as compared to those with normal olfaction.[23] Likewise, Wilson et al found in the Rush Aging and Memory Study that olfactory impairment was associated with a more rapid

decline in certain cognitive domains over three years and, more recently, with the incidence of mild cognitive impairment over five years.[24,25] In a three year study of residents in a continuing care retirement community Royall et al found a greater decline in anosmic subjects compared to subjects with normal olfaction using the University of Pennsylvania Smell Identification Test.[26] Swan and Carmelli found a decline in verbal memory associated with impaired olfaction as measured by the Brief Smell Identification Test.[27] These studies all used different, but related, odor identification tests and had different cognitive measures but found olfactory impairment predicted cognitive decline.[23-27] Likewise, the current study expands the research in this area by finding similar results in a larger population-based study using a different odor identification testand cognitive test. Additionally, the findings of the current study are in a population that is younger (mean age 66.9 years vs. >70 years in other studies) and had a lower rate of incident cognitive impairment than some of the studies (5.1 % vs. 30.1 % in study by Wilson et al, and 9.0% in Graves et al).[23-27]

While this study does not have the ability to determine the mechanism for the association between olfaction impairment and subsequent cognitive decline, previous studies have reported that underlying neuropathological brain changes associated with aging and AD are found in the areas of the brain related to central olfactory processing. [11-14] Neurofibrillary tangles have been seen in younger and elderly non-demented persons in areas of major importance for odor processing, including the anterior olfactory nucleus and mesial temporal areas, particularly in the parahippocampal gyrus, and hippocampus.[13] In mild dementia, these areas continue to be the focal points, and the degree of pathology is significantly increased.[13] Recently, Wilson et al found the density of neurofibrillary tangles within the central olfactory area, the entorhinal cortex and CA1/subiculum region of the hippocampus, were inversely associated with odor identification ability while the density of tangles outside the system was not.[14]

Additionally, an olfactory event-related potential study showed longer latency and smaller amplitude brain responses in both sensory and cognitive components in older versus younger adults.[28] Significantly greater latency differences are seen in patients who have Alzheimer's disease.[29] Murphy et al also found that structural MRI shows a strong relationship between volume of the left hippocampus and odor identification performance in patients with AD.[30] Thus, temporal measures of cortical integrity also are compromised in older adults, and dramatically more so in patients with AD, in areas critical for processing olfactory information. While there is a very strong association between olfactory impairment and subsequent cognitive decline in this study, most participants who had olfactory impairment did not develop cognitive impairment over the five years of this study; a fact reflected by the poor positive predictive value of the SDOIT in this population. The incidence of cognitive impairment is low in this population; over half of our study population was under 70 years of age at the time of the baseline examination and the incidence of cognitive impairment in this age range was only 1.7%. This illustrates a difficulty for using any test as a pre-clinical indicator of the 5-year risk of cognitive decline in populations not at high risk; the positive predictive value of a test will depend on the prevalence (or risk for incidence) of the disease in the population. The overall negative predictive value of the SDOIT however was very high and participants with good odor identification ability had a decreased risk for developing cognitive impairment in the near term. This was also reflected in the specificity of the SDOIT which was high, while the sensitivity was lower. Longer term follow up will be important to determine the predictive value of olfactory impairment for development of cognitive impairment over a longer time span and in old age. The model results suggest that the SDOIT may not be useful in screening a general population but may be useful in a high risk clinical population.

There are a few limitations in this study that should be addressed in future research. The measure of cognition was limited to the MMSE score and self- or proxy-report of AD or dementia and thus may misclassify people with mild cognitive impairment as unaffected.

Participants who were at high risk for AD or dementia may have already been diagnosed at the baseline exam and therefore excluded from these analyses leaving a 'healthy' survivor effect. Additionally, those participants with olfactory impairment at baseline were more likely to die or not return for the exam five years later. If participants who failed to be re-examined progressed to cognitive impairment these associations may have been underestimated.

Although, the only measure of olfactory ability in this study was an odor identification test, studies have found that performance on odor identification tests decline earlier in cognitive impairment than on threshold/detection tests alone.[5] Unlike odor threshold tests which only require the ability to detect an odor and choose it over a blank, odor identification tests require the ability to both detect and identify the odor. Therefore identification tests may require a higher odor of cognitive processing and may be more sensitive to early changes in cognition.

The major strength of this study is the large population-based sample which is representative of the general population not a high risk for cognitive impairment. The mean age of participants in the current study is younger and the incidence of cognitive impairment is lower than in previous studies. Thus, the current findings add significant new information to understanding the association between olfaction and cognition.

## CONCLUSION

Odor identification impairment is associated with incident cognitive impairment over 5-years in this population of older adults free of cognitive impairment at baseline. While physicians may want to consider monitoring cognitive function in patients who present with olfactory impairment, the short-term risk is likely to be low. While the low positive predictive value of the SDOIT limits its use as a screening test for AD or predicting short-term cognitive decline in the general population, the test may be useful in clinical settings. In people with existing cognitive impairment, olfaction testing should be considered in the context of managing issues of nutrition and safety.

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**Table 1**

**Population Characteristics**

| | Total | | Impaired Olfaction at baseline (1998-2000) | | | Incident Impaired Cognition at 5 years (2003-2005) | | |
|---|---|---|---|---|---|---|---|---|
| | n | | n | (%) | p-value | n | (%) | p-value |
| All | 1920 | | 339 | (17.7) | | 98 | (5.1) | |
| Men | 773 | | 184 | (23.8) | <0.001 | 41 | (5.3) | 0.74 |
| Women | 1147 | | 155 | (13.5) | | 57 | (5.0) | |
| Age at baseline (yrs) | | | | | | | | |
| 53-69 | 1228 | | 138 | (11.2) | | 21 | (1.7) | |
| 70-79 | 541 | | 129 | (23.8) | <0.001 | 45 | (8.3) | <0.001 |
| 80-95 | 151 | | 72 | (47.7) | | 32 | (21.2) | |

## Table 2

**The 5-year Incidence of Cognitive Impairment by the SDOIT Score at Baseline**

| SDOIT score | n at risk | n with cognitive impairment | % incidence of cognitive impairment |
|---|---|---|---|
| 0 | 13 | 3 | 23.1 |
| 1 | 20 | 4 | 20.0 |
| 2 | 38 | 10 | 26.3 |
| 3 | 48 | 8 | 16.7 |
| 4 | 82 | 12 | 14.6 |
| 5 | 138 | 17 | 12.3 |
| 6 | 309 | 14 | 4.5 |
| 7 | 540 | 24 | 4.4 |
| 8 | 732 | 6 | 0.8 |
| Total | 1920 | 98 | 5.1 |

SDOIT= San Diego Odor Identification Test

Using the olfactory impairment cut-point (<6 of 8 odorants correctly identified), the 5-year incidence of cognitive impairment was significantly higher for those with olfactory impairment versus those without olfactory impairment ($p<0.001$).

**Table 3**

**Association of Olfaction Impairment and 5-year Incidence of Cognitive Impairment**

| | O.R. | 95 % C.I. |
|---|---|---|
| Olfaction impairment, unadjusted | 6.62 | 4.35, 10.05 |
| Olfaction impairment adjusted for age, gender, education and occupation | 3.72 | 2.31, 5.99 |
| Olfaction impairment adjusted for age, gender, education, occupation and MMSE score at baseline | 3.33 | 2.04, 5.42 |

O.R. = Odds Ratio; C.I. = Confidence Interval