

# Olfactory dysfunction in Alzheimer's disease

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**Abstract:** Alzheimer's disease (AD) is a common neurodegenerative disorder with the earliest clinical symptom of olfactory dysfunction, which is a potential clinical marker for AD severity and progression. However, many questions remain unanswered. This article reviews relevant research on olfactory dysfunction in AD and evaluates the predictive value of olfactory dysfunction for the epidemiological, pathophysiological, and clinical features of AD, as well as for the conversion of cognitive impairment to AD. We summarize problems of existing studies and provide a useful reference for further studies in AD olfactory dysfunction and for clinical applications of olfactory testing.

**Keywords:** olfactory dysfunction, Alzheimer's disease, olfactory testing, progress

## Introduction

Alzheimer's disease (AD) is a common neurodegenerative disorder, which accounts for 60%–80% of all cases of dementia. As the population ages, the prevalence of AD will rise sharply in the next few decades.<sup>1</sup> The gradual onset and slow progression of AD pose a challenge for early differentiation from other causes of cognitive decline, including healthy aging and mild cognitive impairment (MCI). In recent years, studies of AD biomarkers have made early diagnosis of AD possible. Reliable and sensitive clinical biomarkers for early diagnosis of AD are particularly critical for AD identification. Currently, some clinical biomarkers, such as Pittsburgh compound B, amyloid beta 42, phosphorylated tau, and cerebrospinal fluid inflammatory factors,<sup>2,3</sup> have not yet been widely used in large-scale clinical applications due to cost or lack of uniform clinical guidelines. Hence, an inexpensive, simple, and practical diagnostic strategy for AD is urgently needed.

Olfactory dysfunction in AD has been reported as early as 1974.<sup>4</sup> After 40 years of research, olfactory dysfunction in AD was better understood. Some studies confirmed that olfactory dysfunction was possibly one of the earliest clinical symptoms of AD.<sup>5,6</sup> In addition, typical AD pathology first involves the entorhinal cortex. The disease then gradually spreads to the whole brain and eventually affects the entire cerebral cortex.<sup>7</sup> Combining olfactory function tests with conventional diagnostic methods could help improve the sensitivity and specificity of AD diagnosis, thereby facilitating early recognition and diagnosis of AD.<sup>8</sup> This review article summarizes and evaluates the research progress of olfactory dysfunction in AD to explore further its possible research directions in the future.

## Epidemiology of olfactory dysfunction in the elderly patients and dementia

Recently, olfactory dysfunction has attracted the renewed interest of scientists, because olfactory dysfunction has the potential to be an early marker of neurodegenerative

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conditions, such as AD, Parkinson's disease (PD), schizophrenia, and multiple sclerosis.<sup>9</sup> But our understanding of olfactory dysfunction is still very limited. In addition, our knowledge of the prevalence of olfactory dysfunction in the population of normally aging individuals and in related diseases is very poor. Doty et al assessed the sense of smell in 1,955 individuals aged from 5 years to 99 years using smell identification test and found that half of the population with ages ranging 65–80 years had significant olfactory dysfunction. The prevalence of olfactory dysfunction at 80 years or older was >75%.<sup>10</sup> Murphy et al conducted a cross-sectional population-based survey with 2,491 adults aged from 53 years to 97 years and found that the average prevalence of olfactory dysfunction of this population was 24.5%. The prevalence of olfactory dysfunction increased with aging. Patients with ages ranging 80–97 years had a prevalence of olfactory dysfunction of 62.5%.<sup>11</sup> Smoking, stroke, epilepsy, nasal congestion, and upper respiratory tract infection were associated with an increased prevalence of olfactory dysfunction. In healthy adults, aging was the most relevant factor for a decline in the sense of smell and it was more significant than smoking.<sup>12</sup> These data have been confirmed in cross-sectional and cohort studies.<sup>13</sup> In general, age-related olfactory dysfunction was more severe in male than in female patients, although there were individual differences. This sex difference may be related to differences in the number of human olfactory bulb cells in individuals. A recent study confirmed sex differences in the total number of olfactory bulb cells in humans, indicating that females had 40%–50% more olfactory bulb cells than males, which might affect olfactory function in different sexes.<sup>14</sup> Age-related olfactory dysfunction may be caused by age-related ossification and closure of the foramina of the cribriform plate, as well as accumulation of different types of olfactory receptor cell damage due to age-related brain degeneration throughout one's lifetime.<sup>12,13</sup>

Olfactory dysfunction is an early symptom of dementia and has a relatively high prevalence in various types of dementia, reaching up to 100% in AD, 90% in Parkinson's disease dementia, 96% in frontotemporal dementia (FTLD), and 15% in vascular dementia.<sup>15–17</sup> Olfactory dysfunction is often unnoticed. Unlike auditory and visual changes, clinicians rarely detect olfactory dysfunction. Therefore, clinicians and caregivers should be particularly alert to potential olfactory dysfunction in the elderly patients for early detection, diagnosis, and treatment of dementia. Although different test methods for olfactory dysfunction and different demographic and sociological data result in heterogeneity in the epidemiology of olfactory dysfunction, the high prevalence

of olfactory dysfunction among patients with dementia is an indisputable fact. Data from existing studies are primarily from developed countries, with small survey sampling sizes and study designs mainly based on cross-sectional surveys but lacking incidence and cohort studies. Epidemiological surveys of olfactory dysfunction in races and populations of developing countries have been rarely reported, primarily due to insufficiencies in health care coverage, awareness, and degree of attention to olfactory dysfunction in these countries.

## Pathological mechanisms of olfactory dysfunction in AD

The exact pathophysiological mechanism of olfactory dysfunction in AD is not fully understood. Current research suggests that olfactory dysfunction in AD is associated with pathological changes of tau protein in the olfactory bulb and olfactory projection area.<sup>18,19</sup> Wilson et al performed olfactory function tests in 166 participants at baseline and performed brain autopsy in 77 AD patients who subsequently died, AD pathology and Lewy bodies were quantified in multiple brain regions, including portions of the central olfactory system and found that the density of neurofibrillary tangles was the main pathological factor that affected olfactory function, especially in the entorhinal cortex, hippocampus CA1 region, and subiculum. No significant association was found between neurofibrillary tangles, senile plaque deposition, and olfactory function in other brain regions.<sup>20</sup> Bahar-Fuchs et al<sup>21</sup> conducted olfactory function tests and Pittsburgh compound B-positron emission tomography (PET) on 19 healthy volunteers, 24 amnesic MCI patients, and 20 AD patients and found that AD-related olfactory dysfunction was not directly related to amyloid beta burden. These studies also confirmed that AD-related olfactory dysfunction was induced by pathological changes in tau protein.

Pathological examination provides the most direct and powerful evidence of pathological changes within the entorhinal cortex for early stage AD. Braak and Braak classified AD pathological changes into I–VI stages based on distribution of neurofibrillary tangles and neuritic plaques. Neurofibrillary tangles and neuritic plaques in stages I–II were mainly distributed in and throughout the transentorhinal cortex.<sup>7</sup> Olfactory system-related brain tissues in AD patients exhibited significant histopathological changes. Christen-Zaech et al analyzed autopsy information of 110 cases and found that the number of cases with olfactory impairment (degenerative changes such as senile plaques, neurofibrillary tangles, and curly fibers) was very high, >84% of the cases with cortical

AD-type lesions. Degenerative olfactory changes were present in all 19 definite AD cases and only in two of the 19 controls. Therefore, Christen-Zaech et al<sup>22</sup> suggested that the olfactory bulb and olfactory tract were sites with some of the earliest pathological changes in AD patients.

The olfactory nervous system has a variety of neurotransmitters, and the exact mechanisms through which neurotransmitters are involved in olfactory transduction remain unclear. Under normal circumstances, the olfactory system is rich in acetylcholine, glutamate,  $\gamma$ -aminobutyric acid, and other neurotransmitters. A deficit in these neurotransmitters, especially acetylcholine, is considered one of the major causes of memory impairment and other cognitive dysfunctions. A previous study confirmed reduction of acetylcholine in AD patients, which might induce olfactory dysfunction.<sup>23</sup> Olfactory dysfunction in patients with idiopathic Parkinson's disease could not be reversed or improved by treatment with dopaminergic agents.<sup>24</sup> Treatment efficacy of cholinesterase inhibitors in AD-related olfactory dysfunction has not been determined. Velayudhan et al conducted an unblinded and uncontrolled study and demonstrated that the cholinesterase inhibitor, donepezil, could greatly improve olfactory function of AD patients. This result suggested that functional changes in olfactory recognition could be used to predict therapeutic effects in AD patients.<sup>25</sup> Hence, olfactory recognition may be used as an effective indicator in clinical tests to evaluate the treatment efficacy of AD therapy. Nevertheless, the study of Velayudhan et al<sup>25</sup> was an unblinded and uncontrolled trial, and their findings only had preliminary significance. Further studies will be necessary to confirm their findings.

## Characteristics of olfactory dysfunction in AD

Olfactory dysfunction in AD mainly presents as an impairment in olfactory recognition, which occurs during the early stage of the disease and worsens with the progression of AD.<sup>5</sup> Serby et al used the University of Pennsylvania Smell Identification Test (UPSIT) to conduct olfactory function tests in 55 AD patients. The study indicated that the early stages of AD showed impairment in olfactory recognition, and an increased olfactory threshold was only present during the late stage of the disease. The functional score of olfactory recognition was associated with the score of the Mini-Mental State Examination, but olfactory threshold was not associated with Mini-Mental State Examination scores.<sup>5</sup> Previous findings have suggested that changes in olfactory threshold did not occur in the early stage of AD.<sup>26,27</sup> However, another study indicated that changes in olfactory threshold occurred

in patients with early stage AD and even MCI.<sup>28</sup> Inconsistent findings in the different studies might be due to different methods and/or stimulants used in olfactory threshold detection. Reliability of some olfactory threshold detection methods was low, which could be due to small sample size. Hence, further confirmation using a unified and effective test in a large-scale clinical trial with strictly selected samples will be necessary to study the relationship between changes in olfactory threshold and AD.

Rahayel et al<sup>29</sup> conducted a meta-analysis on olfactory dysfunction in AD and PD (total inclusion of 81 studies) and showed that impairments of olfactory recognition and recognition tasks in AD and PD patients were more severe than the impairment of olfactory detection threshold. These results were more severe in AD patients than in PD patients, suggesting that olfactory recognition and olfactory identification are more likely to be impaired in AD. In addition, deficits in olfactory detection threshold of PD patients were more severe than those in AD patients, indicating that olfactory impairment in PD was primarily poor olfactory perception, whereas olfactory impairment in AD mostly involved advanced olfactory cognitive tasks. In summary, we believe that olfactory recognition and recognition tasks are among the most interesting research topics, which should be included in subclinical detection of AD.

Olfactory dysfunction occurs not only in AD but also in a variety of neurodegenerative diseases. The prevalence and severity of olfactory dysfunction in different neurodegenerative diseases vary drastically. Olfactory recognition tests in AD, semantic dementia, FTLN, and corticobasal degeneration showed that olfactory recognition was severely impaired in semantic dementia and AD patients, but only mildly impaired in FTLN and corticobasal degeneration patients.<sup>30</sup> Severe olfactory dysfunction was found in patients with AD, PD, and the Guam type of Parkinson's disease dementia (with an UPSIT score <20), while olfactory dysfunction in patients with Huntington's disease, progressive supranuclear palsy, and amyotrophic lateral sclerosis was not severe.<sup>12</sup> These data indicated that differential diagnosis of these neurodegenerative diseases using olfactory function tests helped in clinical practice.

## Imaging studies of olfactory dysfunction in AD

Many neuroimaging studies have measured AD neuropathological changes in the regional processing center of the medial temporal lobe and other brain regions associated with AD. Loss of left hippocampal volume was highly associated

with the performance of oral and odor recognition tasks in AD patients.<sup>31</sup> Hippocampal volume of patients with olfactory recognition impairment associated with amnesic MCI/AD was smaller than in normal healthy controls.<sup>32</sup> Using functional magnetic resonance imaging (fMRI), Wang et al<sup>33</sup> showed that the blood oxygenation level-dependent signal in the primary olfactory cortex was weaker in patients with early stage AD than in healthy controls. Furthermore, the intensity of the Blood Oxygen Level Dependent (BOLD) signal and the area of the brain in which this signal was, increased as the concentrations of the tested odorants increased in these AD patients, while no such change was found in the healthy controls. These findings confirmed that olfactory fMRI was sensitive to AD-related degeneration in olfactory function and recognition in the early stage of the disease.<sup>33</sup> Murphy et al conducted another fMRI study and showed that in the elderly patients, especially those with AD, the connection between the orbitofrontal cortex and the medial temporal lobe was interrupted, resulting in decreased activation in the entire cortex, particularly in the medial temporal lobe. Functional network analysis has shown that interruptions in the connections between the orbitofrontal cortex and the medial temporal lobe might reflect age-related changes in the large-scale olfactory processing network.<sup>34</sup> Förster et al conducted resting-state fluorodeoxyglucose-PET to analyze different olfactory regions and assess olfactory performance in patients with early stage AD. The results showed that olfactory recognition was associated with peak values of normal fluorodeoxyglucose in the right superior parietal lobule, gyrus occipitotemporalis medialis, inferior frontal gyrus, and precuneus of patients with early stage AD, whereas odor discrimination scores correlated with a single cluster in the left postcentral cortex and odor threshold scores correlated with clusters in the right thalamus and cerebellum, supporting the theory of a parallel organized olfactory system.<sup>35</sup>

The study of imaging of olfactory dysfunction in AD still remains at the preclinical stage; the existing research focuses on using fMRI/PET to investigate the relation between the olfactory dysfunction and the olfactory cortex or neuronetwork. Due to the complexity of the olfactory system, there is no specific clinical diagnostic value, and the clinical application of imaging in olfactory function still has a long way to go.

## Prediction value of olfactory function tests in AD progression

A previous study showed that 18%–30% of MCI cases were at a risk of converting to AD 3 years after diagnosis.<sup>36</sup>

To improve the accuracy of AD diagnosis and to identify high-risk populations, improved prediction of conversion from MCI to AD is needed. Olfactory function tests have been used as markers to predict the risk of MCI converting to AD. Wilson et al conducted a cohort study in 471 healthy elderly individuals or MCI patients and found a close relationship between the level of pathological changes in the cerebral cortex and the degree of risk in developing prodromal AD. This relationship still existed given the presence of other common behaviors and genetic markers of AD.<sup>37</sup> Other recent research monitored the predictive value of olfactory recognition and function tests in AD cases that had converted from MCI. Results of a 2-year follow-up interview showed that 47% of MCI patients with olfactory impairment and 11% of MCI patients with a normal sense of smell eventually developed AD.<sup>38</sup> This study demonstrated that olfactory recognition and function testing was a very important tool for screening a population at high risk for AD. A cohort study of 148 MCI outpatients in a 3-year follow-up showed that a combination of five out of eight potential predictors (olfactory function impairment, UPSIT, verbal memory, hippocampus volume, and entorhinal cortex volume) had a strong predictive value (90% specificity and 85.2% sensitivity) for AD converted from MCI.<sup>39</sup> Lojkowska et al conducted a 24-month follow-up study in 49 MCI patients and 33 controls. Changes in olfactory functions, cognitive functions, and volume of medial temporal lobe structures (hippocampus, parahippocampal gyrus, and amygdala) were evaluated. In the MCI group, a prediction of strong cognitive functions deterioration based on poor performance in olfactory identification tests shows sensitivity of 57% and specificity of 88%. The test based on cognitive functions only shows a sensitivity of 44% and specificity of 89%. Combined tests having the criteria of poor olfactory identification performance and poor results of neuropsychological tests showed a sensitivity of 100% and specificity of 84%. The study reveals that the accuracy of predicting AD conversion from MCI could be enhanced by using both olfactory and neuropsychological tests. A follow-up study of hippocampus volume reduction, olfactory identification performance, and cognitive functions deterioration will further increase prediction accuracy.<sup>40</sup>

Devanand et al conducted a prospective observational study in a multiethnic community cohort in North Manhattan, NY. A total of 1,037 participants without dementia were evaluated with the 40-item UPSIT. In 757 participants, follow-up occurred at 2 years and 4 years. In logistic regression analyses, lower baseline UPSIT scores were associated with cognitive decline (relative risk 1.067 per point interval;



95% confidence interval [CI]: 1.040, 1.095;  $P < 0.0001$ ) and remained significant (relative risk 1.065 per point interval; 95% CI: 1.034, 1.095;  $P < 0.0001$ ) after including covariates. UPSIT, but not selective reminding test-total immediate recall, predicted cognitive decline in participants without baseline cognitive impairment. In discrete time survival analyses, lower baseline UPSIT scores were associated with transition to AD (hazard ratio 1.099 per point interval; 95% CI: 1.067, 1.131;  $P < 0.0001$ ) and remained highly significant (hazard ratio 1.072 per point interval; 95% CI: 1.036, 1.109;  $P < 0.0001$ ) after including demographic, cognitive, and functional covariates.<sup>41</sup> The study by Devanand et al<sup>41</sup> confirmed that impairment in olfactory recognition in a population with normal cognitive function more accurately predicted decline of cognitive function than assessment of verbal episodic memory and supported the cross-cultural application of inexpensive olfactory recognition tests as biomarkers for predicting decline in cognitive function and early stage AD. In addition, in the future, olfactory recognition testing is expected to assist in patient selection and stratification in treatment trials for patients with cognitive impairment or prevention trials for healthy people with good cognition.

There have been several reports on AD-specific impairment of olfactory recognition. Stamps et al conducted a retrospective case-control study to assess the effectiveness of a brief olfactory test for the diagnosis of AD. This study made the test subjects to close their eyes and assessed their ability to detect the odor of peanut butter through one nostril at a time and measuring the distance between the subject's nostril and the peanut butter container. The results showed that the distance to the left nostril for detecting the odor was significantly shorter in AD patients than in MCI patients and normal controls. Therefore, Stamps et al<sup>42</sup> proposed that left and right nostril odor detection was a sensitive and specific test for AD. However, a recent study by Doty et al replicated and expanded the study by Stamps et al but did not repeat the results or the significant asymmetry of odor detection in AD patients.<sup>42,43</sup>

The severity of olfactory dysfunction is correlated with certain clinical manifestations in AD patients. A previous study included 57 mild-to-moderate, late-onset AD patients and 24 age-matched healthy elderly individuals and showed that increasingly severe olfactory dysfunction heralded more clinical symptoms or severe illness of AD.<sup>44</sup> Another study that used olfactory recognition testing to evaluate the relationship between olfactory recognition and neuropsychiatric symptoms in 172 AD patients, 112 MCI patients, and 132 neurologically and psychiatrically healthy controls

showed that olfactory recognition was associated with the level of apathy but not with depression or other neuropsychiatric symptoms.<sup>45</sup>

Since olfactory dysfunction is frequently overlooked by doctors and patients,<sup>46</sup> it is not often the earliest clinical manifestation described in AD patients. Patients with a low olfactory function score are considered more likely to develop AD, especially those with a low olfactory function score who are not aware of their problems in sense of smell. Furthermore, only 6% of AD patients complained of decline in olfactory function during the early stage of the disease, but 90% of AD patients demonstrated a significant impairment of olfactory function in an olfactory test.<sup>6</sup> Patients with a low olfactory function score are considered more likely to develop AD, especially those who are not aware of their problems in sense of smell. Stanciu et al<sup>47</sup> conducted a population-based cohort study and showed that subjective olfactory dysfunction was an independent predictor for dementia. Therefore, Stanciu et al suggested that assessment of subjective olfactory dysfunction might play a complementary role in evaluating the risk of dementia.<sup>47</sup> However, Bahar-Fuchs et al conducted a 12-month retrospective observational study and found no connection between decline of olfactory function and AD development from amnesic MCI.<sup>48</sup> Further study to confirm the relationship between subjective olfactory dysfunction and risk of AD is necessary. In addition, no significant correlation was found between subjective and objective olfactory dysfunction.<sup>6,49</sup> Hence, the prediction accuracy of olfactory function scores using subjective olfactory dysfunction is extremely poor.

## Conclusion

Olfactory function may be used as a clinical marker for severity and progression of AD. However, many questions must still be answered. For example, it is unclear how to identify and differentiate age-related olfactory changes and olfactory dysfunction caused by diseases. It is also unclear during which disease stage AD pathological changes are limited to the olfactory structures. Moreover, the validity and clinical relevance in predicting AD using a combination of assessments including olfactory dysfunction and other biomarkers of AD remain unclear. Further research is necessary to clarify these uncertainties.

Olfactory function tests are inexpensive and simple to perform at the bedside. They are potential, sensitive clinical markers among the many AD markers. Since different olfactory tests have great variability, a brief, easy, sensitive, accurate, and convenient olfactory test is needed in

daily clinical practice. Although, there is sufficient evidence showing that olfactory tests can identify and differentiate AD cases from normal controls, further research to identify AD and other types of dementia using olfactory tests is needed. Most AD-related olfactory studies had small sample sizes.<sup>8</sup> Many findings from existing reports must be confirmed by rigorously designed cohort studies.<sup>19</sup> Future studies should also investigate which combinations of biomarkers and olfactory assessments are most effective in predicting the conversion risk of dementia.

Studies in olfactory function can determine its role and effectiveness in clinical practice. Based on currently available knowledge, we should recognize the importance of olfactory assessment in daily clinical practice. In addition, olfactory function tests should be incorporated in the assessment of populations at high risk for dementia to test methodologically and systematically for subclinical AD.<sup>50</sup>

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