Systematic Review

Olfactory Function in Mild Cognitive Impairment and Alzheimer’s Disease: A Meta-analysis

Hahn Jin Jung, MD; In-Soo Shin, PhD; Ji-Eun Lee, MD, PhD

Objective: Olfactory function is altered in mild cognitive impairment (MCI) and Alzheimer’s disease (AD); therefore, it may serve as a useful tool for the early detection of MCI before its advancement to AD. The aim of this meta-analysis was to investigate olfactory deficits in patients with MCI and AD.

Study Design: Literature search.

Methods: A search was conducted of the electronic databases PubMed, Embase, and Web of Science from their inception until 2017. We included original articles with adequate data on the identification, threshold, and/or discrimination of olfactory function in MCI or AD. The standard mean difference and 95% confidence interval (CI) were calculated. The studies were weighted according to inverse variance estimates. The effect sizes were categorized as small (Cohen’s $d = 0.2$), medium ($d = 0.5$), or large ($d \geq 0.8$) based on these methods. Subgroup analyses were performed based on mean age and sex differences between the groups.

Results: Twelve articles (reporting 21 effects) examining 563 patients with MCI and 788 patients with AD, were included in the meta-analysis. Compared to MCI, AD had moderate to large heterogeneous effects on olfactory function (Cohen’s $d = 0.64$, 95% CI: 0.50, 0.78). Olfactory identification tests demonstrated larger effects ($d = 0.71$, 95% CI: 0.51, 0.91) than did tests of other olfactory domains.

Conclusions: Meta-analysis results revealed that olfactory identification was more profoundly impaired in patients with AD than in those with MCI. These findings suggest that a simple test of odor identification is valuable in differentiating individuals at a risk of AD.

Key Words: Mild cognitive impairment, dementia, Alzheimer’s disease, olfaction, meta-analysis.

Level of Evidence: NA

Laryngoscope, 129:362–369, 2019

INTRODUCTION

Alzheimer’s disease (AD) has a very insidious onset and is a slowly progressing disease. Therefore, it is challenging to detect and identify AD at early stages of the disease. Mild cognitive impairment (MCI) is a transitional state between normal cognition and AD. In particular, amnestic MCI is considered an early stage of AD. Several methods have been proposed for early prediction of MCI before its advancement to AD, including neuropsychological tests, neuroimaging including amyloid positron emission tomography (PET) and volumetric magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) measurements of amyloid-$\beta$ and $\tau$. However, the high cost of PET and MRI, and the invasiveness of CSF analyses make these techniques difficult. Therefore, to date, no marker or tool is considered a single reliable predictor or has proven useful in terms of early recognition of AD.

Several lines of evidence have demonstrated that olfactory function is altered in the pathogenesis of Alzheimer’s disease. Studies involving olfactory epithelium biopsies have shown that amyloid-$\beta$ protein levels and olfactory dysfunction in patients with AD correlate with the AD pathology found in postmortem examinations. In addition, longitudinal studies have examined the relationships of olfactory impairment and the conversion from MCI to AD, and have demonstrated that the changes in olfactory function in patients with AD and MCI are related to adjacent neuroanatomical structures including the hippocampus and entorhinal cortex. These findings suggest that olfaction impairment might be a useful marker of amnestic MCI due to AD.

Tests of olfactory function consist of three domains: identification, threshold, and discrimination. Among them, odor identification has been suggested to be...
associated with cognitive decline, MCI, and/or AD dementia. \textsuperscript{8–12} According to previous studies, the earliest sign of cognitive decline can be detected by olfactory function tests due to the anatomical proximity of the brain structures that control olfaction and cognition. Therefore, many studies in MCI and AD patients examine olfactory function. However, the results of these studies are inconsistent, perhaps due to several methodological concerns. Moreover, no investigations have thoroughly and directly compared olfactory performance in patients with MCI and AD.

In the current study, we hypothesized that psychophysical olfactory function is different between patients with MCI and AD, and that olfactory dysfunction might serve as a screening tool for the early detection of MCI.

**MATERIALS AND METHODS**

**Literature Search Strategy**

This meta-analysis was conducted according to the guidelines of Copper et al. \textsuperscript{13} A systematic review was performed using English databases (PubMed, Embase, and Web of Science) from their inception until July 2017 with the following search items: “mild cognitive impairment” OR “MCI” AND “Alzheimer” OR “Alzheimer’s disease” AND “olfaction” OR “smell” OR “olfactory.” We filtered the results to include only English-written studies on living human subjects. The reference lists of the identified articles and relevant reviews were searched manually for additional studies.

The following selection criteria, based on the PICOS acronym, were used: Participants: patients diagnosed with MCI or AD according to established diagnostic criteria; Intervention: olfactory function test; Comparison: patients with MCI versus those with AD; and Outcomes: odor identification scores, odor threshold scores, odor discrimination scores, and the sum of all three scores.

**Inclusion/Exclusion Criteria**

The inclusion criteria of the studies were as follows: 1) examined patients with clinical AD diagnoses based on either the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria \textsuperscript{14} or the criteria of the third or fourth edition of the Diagnostic and Statistical Manual of Mental Disorders \textsuperscript{15}; 2) examined patients with MCI diagnoses based on established criteria \textsuperscript{16}; 3) described patients with no comorbid dementia that affects olfactory performance; 4) described participants who have the ability to perform at least one psychophysical olfactory test, including identification, threshold, or discrimination; 5) obtained means and standard deviations reported for both groups, or have data available for the calculation of these variables; and 6) were written in English.

We excluded articles using the following criteria: 1) use of animals, 2) described patients with comorbid neurological conditions that affect olfactory function such as multiple system atrophy or Lewy bodies dementia, or 3) were reviews or symposium papers.

The data extraction was performed independently by two reviewers (J.-E.L. and I.-S.S.). Any disagreement was resolved by consensus. If the same data were reported in more than one article, only the article with the more complete data was included. The mean and standard deviation values for the patients with AD and MCI were extracted.

**Included Studies**

After review, 12 studies fulfilled the inclusion criteria. Three studies featured all three components of the olfactory tests (assessments of identification, detection thresholds, and discrimination), one study featured the olfactory identification and threshold tests, and eight studies only reported the olfactory identification scores, which resulted in the inclusion of a total of 21 effects in the analysis. All included studies reported olfactory identification scores. In total, comparisons of 563 patients with MCI and 788 patients with AD were established. The specific details of the included studies are summarized in Tables I and II. Levels of evidence for each study was assessed by the document from https://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1 (Table I). The modified Newcastle-Ottawa scale (NOS) was used to assess the risk of bias of the studies included in this analysis (Table III). The study was awarded a star for each item in the selection and outcome categories. The score ranges from zero to nine stars. Studies that scored six stars or more were considered to be of high quality.

**Methodological Variables**

We sought to broadly define olfactory function to demonstrate the effect size across the three basic olfactory domains, and included studies involving psychophysical tests of 1) odor threshold, 2) odor discrimination, 3) odor identification, and 4) the sum of the three domains. Detection thresholds were usually determined using an ascending staircase procedure, in which the odor concentration becomes progressively stronger. After establishing a concentration at which the subject gives five consecutive correct responses, the order is reversed so that concentrations go from strong to weak. When the subject gives an incorrect answer, the order is reversed to the upward direction, and after two consecutive correct responses, the order is reversed to the downward direction; this continues until seven reversals are completed. The threshold is then estimated as the mean of the last four reversals. The discrimination test requires subjects to make same/different judgments of pairs of stimuli and scores ranging from 0 to maximum odor number used. Odor identification consists of 40 items (odor number could be different in each study) in the form of microencapsulated strips, which release an odor when scratched. Subjects are asked to choose one among four alternative answers (score range: 0 to maximum odor number used).

**Moderator Variables**

A categorical moderator analysis of the olfactory domains was undertaken, including identification, discrimination, and detection. The following demographic moderator variables were coded for subgroup analyses: 1) age and 2) sex (% of male).

**Statistical Analyses**

All statistical analyses were conducted using Comprehensive Meta-analysis software, Version 3 (Biostat, Inc., Englewood, NJ; http://www.meta-analysis.com). The standard mean difference and 95% confidence interval (CI) were calculated, because different olfactory function measures were used in the included studies. The studies were weighted according to their inverse variance estimates. The dependent measure was the effect size of MCI compared with that of AD on tests of olfactory identification, discrimination, and detection threshold, which was expressed as Cohen’s d. \textsuperscript{17} Effect size measures the strength or magnitude of a relationship of interest calculated from standard mean difference of each article. The effect size allows for unit standardizations.
### TABLE I.
Characteristics of the 12 Studies Included in the Current Meta-analysis

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Source</th>
<th>Level of Evidence</th>
<th>Diagnostic Criteria of MCI</th>
<th>Diagnostic Criteria of AD</th>
<th>MCI Sample Size (No.)</th>
<th>AD Sample Size (No.)</th>
<th>MCI Mean Age, yr (SD)</th>
<th>AD Mean Age, yr (SD)</th>
<th>Gender MCI Male (%)</th>
<th>Gender AD Male (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters et al., 2003</td>
<td>German, Memory Clinic of Frankfurt am Main University Hospital</td>
<td>Level 4</td>
<td>Peterson, aMCI</td>
<td>NINCDS-ADRDA</td>
<td>8</td>
<td>14</td>
<td>72.5 (5.0)</td>
<td>72.2 (5.7)</td>
<td>62.5</td>
<td>35.7</td>
</tr>
<tr>
<td>Djordjevic et al., 2008</td>
<td>Canada, McGill University Memory Clinic</td>
<td>Level 4</td>
<td>Peterson, aMCI</td>
<td>NINCDS-ADRDA</td>
<td>51</td>
<td>27</td>
<td>75.4 (range, 59-86)</td>
<td>77.0 (range, 55-88)</td>
<td>49.0</td>
<td>52.0</td>
</tr>
<tr>
<td>Westervelt et al., 2008</td>
<td>U.S.A., medical center-based neuropsychology service</td>
<td>Level 4</td>
<td>Peterson, aMCI</td>
<td>NINCDS-ADRDA</td>
<td>17</td>
<td>44</td>
<td>74.4 (7.2)</td>
<td>76.3 (5.4)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bahar-Fuchs et al., 2010</td>
<td>Austic Health, PiB-PET Project</td>
<td>Level 4</td>
<td>Peterson, aMCI</td>
<td>NINCDS-ADRDA</td>
<td>24</td>
<td>20</td>
<td>74.2 (9.5)</td>
<td>73.4 (8.5)</td>
<td>66</td>
<td>55</td>
</tr>
<tr>
<td>Steinbach et al., 2010</td>
<td>Germany, Ludwig Maximilians University</td>
<td>Level 4</td>
<td>Peterson, MCI</td>
<td>NINCDS-ADRDA</td>
<td>29</td>
<td>30</td>
<td>71.7 (7.7)</td>
<td>73.3 (4.7)</td>
<td>58.6</td>
<td>43.3</td>
</tr>
<tr>
<td>Conti et al., 2013</td>
<td>Italy</td>
<td>Level 4</td>
<td>Peterson, aMCI and non-aMCI</td>
<td>NINCDS-ADRDA</td>
<td>57</td>
<td>27</td>
<td>72.5 (6.8)</td>
<td>76.5 (5.8)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Yoon et al., 2015</td>
<td>Korean, tertiary university hospital</td>
<td>Level 3</td>
<td>Peterson</td>
<td>NINCDS-ADRDA</td>
<td>45</td>
<td>32</td>
<td>69.2 (6.2)</td>
<td>71.2 (5.0)</td>
<td>48.8</td>
<td>43.7</td>
</tr>
<tr>
<td>Vasavada et al., 2015</td>
<td>Penn State University</td>
<td>Level 4</td>
<td>Peterson</td>
<td>NINCDS-ADRDA</td>
<td>21</td>
<td>15</td>
<td>73.2 (9.0)</td>
<td>91.9 (11.9)</td>
<td>47.6</td>
<td>33.3</td>
</tr>
<tr>
<td>Hagemeyer et al., 2016</td>
<td>Mayo Clinic</td>
<td>Level 4</td>
<td>Peterson, aMCI</td>
<td>DSM-IV</td>
<td>19</td>
<td>42</td>
<td>73.6 (11.1)</td>
<td>76.0 (5.6)</td>
<td>47.3</td>
<td>42.9</td>
</tr>
<tr>
<td>Quarmley et al., 2017</td>
<td>University of Pennsylvania's AD center</td>
<td>Level 4</td>
<td>Peterson, MCI</td>
<td>DSM-IV</td>
<td>174</td>
<td>262</td>
<td>72.46 (8.57)</td>
<td>75.14 (8.22)</td>
<td>47.1</td>
<td>37.4</td>
</tr>
<tr>
<td>Ward et al., 2017</td>
<td>University of Iowa</td>
<td>Level 4</td>
<td>Established criteria, MCI</td>
<td>NINCDS-ADRDA</td>
<td>8</td>
<td>13</td>
<td>76.1 (6.29)</td>
<td>76.8 (6.95)</td>
<td>62.5</td>
<td>30.8</td>
</tr>
<tr>
<td>Woodward et al., 2017</td>
<td>Texas Alzheimer Research and Care Consortium</td>
<td>Level 4</td>
<td>Peterson, aMCI</td>
<td>NINCDS-ADRDA</td>
<td>110</td>
<td>262</td>
<td>74.1 (9.03)</td>
<td>75.6 (8.29)</td>
<td>51.8</td>
<td>50.0</td>
</tr>
</tbody>
</table>

AD = Alzheimer's disease; aMCI = amnestic MCI; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th Edition; MCI = mild cognitive impairment; NA = not available; NINCDS-ADRDA = National institute of Neurological and Communicative Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association; SD = standard deviation.
and comparisons among studies involving different units or olfactory tests. The effect sizes were categorized as small (Cohen's $d = 0.2$), medium ($d = 0.5$), or large ($d \geq 0.8$) based on these methods. To address heterogeneity, the random effects model was conducted in all analyses according to the recommendations of DerSimonian and Laird. Moreover, the subgroup analyses were performed based on mean age or sex differences between the groups. Publication bias was assessed using funnel plots, Egger's intercept, and Duval and Tweedie's trim-and-fill procedure. The significance level was set to $P < .05$ (two-sided).

### TABLE II.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Olfactory Test Type</th>
<th>I</th>
<th>T</th>
<th>D</th>
<th>MCI Test Score I</th>
<th>AD Test Score I</th>
<th>MCI Test Score T</th>
<th>AD Test Score T</th>
<th>MCI Test Score D</th>
<th>AD Test Score D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters et al., 2003</td>
<td>I, T, D</td>
<td>16 common odors</td>
<td>n-butanol</td>
<td>Triplet of pens</td>
<td>10.5 (2.3)</td>
<td>10.0 (2.3)</td>
<td>5.4 (1.2)</td>
<td>4.2 (1.6)</td>
<td>9.5 (1.6)</td>
<td>9.6 (2.3)</td>
</tr>
<tr>
<td>Djordjevic et al., 2008</td>
<td>I, T, D</td>
<td>UPSIT (40 items)</td>
<td>PEA</td>
<td>Pens</td>
<td>27.3 (6.9)</td>
<td>19.8 (6.5)</td>
<td>5.3 (2.8)</td>
<td>4.5 (2.7)</td>
<td>10.3 (2.6)</td>
<td>8.8 (2.1)</td>
</tr>
<tr>
<td>Westervelt et al., 2008</td>
<td>I</td>
<td>BSIT</td>
<td>—</td>
<td>—</td>
<td>8.7 (2.5)</td>
<td>6.5 (2.5)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Bahar-Fuchs et al., 2010</td>
<td>I</td>
<td>UPSIT (6 items)</td>
<td>—</td>
<td>—</td>
<td>2.7 (1.1)</td>
<td>2.1 (1.1)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Steinbach et al., 2010</td>
<td>I, T, D</td>
<td>Sniffin' Sticks test</td>
<td>n-butanol</td>
<td>Triplet of pens</td>
<td>9.3 (4.0)</td>
<td>7.7 (3.3)</td>
<td>5.3 (2.8)</td>
<td>4.5 (2.7)</td>
<td>10.3 (2.6)</td>
<td>8.8 (2.1)</td>
</tr>
<tr>
<td>Conti et al., 2013</td>
<td>I, T, odor memory, picture identification</td>
<td>CA-SIT (34 items)</td>
<td>PEA</td>
<td>—</td>
<td>22.4 (6.2)</td>
<td>18.4 (5.1)</td>
<td>11.8 (1.5)</td>
<td>11.5 (1.2)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Yoon et al., 2015</td>
<td>I</td>
<td>CCSIT</td>
<td>—</td>
<td>—</td>
<td>7.3 (1.6)</td>
<td>6.4 (0.8)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vasanava et al., 2015</td>
<td>I</td>
<td>UPSIT (40 items)</td>
<td>—</td>
<td>—</td>
<td>24.2 (8.6)</td>
<td>15.5 (8.4)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hagemeier et al., 2016</td>
<td>I</td>
<td>UPSIT (40 items)</td>
<td>—</td>
<td>—</td>
<td>22.9 (8.6)</td>
<td>21.1 (7.9)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Quarmley et al., 2017</td>
<td>I</td>
<td>Sniffin’s Sticks test</td>
<td>—</td>
<td>—</td>
<td>9.9 (3.2)</td>
<td>7.8 (3.4)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ward et al., 2017</td>
<td>I, odor memory</td>
<td>UPSIT (40 items)</td>
<td>—</td>
<td>—</td>
<td>21.6 (10.1)</td>
<td>16.6 (6.5)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Woodward et al., 2017</td>
<td>I</td>
<td>UPSIT (10 items)</td>
<td>—</td>
<td>—</td>
<td>28.0 (7.9)</td>
<td>18.7 (7.9)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are expressed as mean (standard deviation).

AD = Alzheimer’s disease; BSIT = Brief Smell Identification Test; CA-SIT = Culturally Adapted Smell Identification Test; CCSIT = Cross-Cultural Smell Identification Test; D = discrimination; I = identification; MCI = mild cognitive impairment; NA = not available; PEA, phenylethyl alcohol; T = threshold; UPSIT = University of Pennsylvania Smell Identification Test.
RESULTS

Search Results

The original search of the databases yielded 1,576 electronic records (Fig. 1). A final total of 12 eligible cross-sectional studies comparing patients with MCI (n = 563) and those with AD (n = 788) were included in the analysis. The characteristics of the included studies are shown in Tables I and II.

Overall Meta-analysis Results

The analysis of the effect sizes across the olfactory domains of the patients with MCI versus those with AD revealed medium-to-large effects ($k = 21, d = 0.642, 95\% CI: 0.50 to 0.78$) that were not significantly heterogeneous ($Q = 36.705, P = .013, I^2 = 45.5\%$) ($k$ = number of studies analyzed).

Moderator Analysis

Olfactory domain. The analysis revealed moderate heterogeneity among effect sizes ($P = .01$). All olfactory function decreased more in patients with AD than in patients with MCI. The greater effect size means that the difference is clear. The effect size for odor identification was $d = 0.71$ (95\% CI: 0.51 to 0.91), which differed from the effect sizes for odor discrimination ($d = 0.54, 95\% CI: 0.19 to 0.90$) and odor threshold ($d = 0.31, 95\% CI: −0.01 to 0.63$). The individual study effect sizes on olfactory domain are displayed in Figure 2A–C.

Age. The average ages of the patients with MCI and AD were 73.2 years (range, 59–86 years) and 74.7 years (range, 55–88 years), respectively. The effect of olfactory identification in a subgroup with a mean age difference <2 years between the MCI and AD patients was larger ($d = 0.81, 95\% CI: 0.54 to 1.08$) compared to a
subgroup with a mean age difference over 2 years between the patient groups (\(d = 0.60, 95\% \text{ CI}: 0.44 \text{ to } 0.76\)) (see Supporting Figure 1A in the online version of this article). Subgroup analysis for mean age difference showed no statistical significance (\(\chi^2 = 1.76, df = 1, P = .18\)).

**Sex**

The analysis of sex comprising the sample patient population revealed that most of the studies included in the meta-analysis enrolled more female than male patients in both the MCI and AD patient groups (Table I). In a subgroup analysis, the effect size was greater (\(k = 5, d = 0.77, 95\% \text{ CI}: 0.52 \text{ to } 1.02\)) in subgroups composed of MCI and AD patient groups with differences of <10% in the number of males versus females compared with subgroups composed of MCI and AD patients groups with differences of more than 10% in the number of males versus females (\(k = 6, d = 0.55, 95\% \text{ CI}: 0.25 \text{ to } 0.85\)) (see Supporting Figure 1B in the online version of this article). Subgroup analysis for sex percent difference revealed that there were no statistical differences between groups (\(\chi^2 = 0.98, df = 1, P = .32\)). The analysis of sex composition revealed that there was no interaction between sex and olfactory performance.

**Publication bias.** The analysis of possible response bias revealed a symmetric funnel plot (Fig. 3). We assessed the potential missing studies using Duval and Tweedie’s trim-and-fill method. This procedure indicated that no studies were missing from the analysis, and a point estimate (0.64) was generated that was nearly identical to the original estimate. Finally, we concluded that actual publication bias was unlikely to exist.

**Assessment of the risk of bias**

The selected studies’ risks of bias are presented in Table III. According to the risk of bias analysis, all studies were classified as high quality.

**DISCUSSION**

This study aimed to evaluate the differences in olfactory function between patients with MCI and those with AD. To the best of our knowledge, this is the first meta-analysis to directly compare olfactory dysfunction between these groups. The main finding was that olfactory function was significantly impaired in patients with AD compared to patients with MCI. Notably, the overall effect size on olfactory identification was moderate to high. These results suggested that olfactory identification tests could act as an indicator of the progression from MCI to AD. Unfortunately, there were too few studies of the other olfactory domains to draw any conclusions regarding their suitability as indicators.

Some meta-analyses have validated the finding of olfactory dysfunction in patients with MCI and AD. To date, only three meta-analyses have been conducted on olfactory dysfunction in patients with AD and MCI (one study of patients with AD versus healthy controls, one study of patients with AD versus patients with Parkinson’s disease, and one study of patients with MCI versus healthy controls). The first study reported considerable olfactory impairments in the AD group, due to an effect size with a Cohen’s \(d\) of 3.36, whereas the second study reported a large effect size of 1.73. The first meta-analysis, a medium-to-large effect size (\(d = -0.76\)) was reported for the MCI sample. However, to date, no meta-analyses have directly compared the olfactory function of patients with AD and those with MCI. In our results, a relatively greater deficit in odor identification was observed in patients with AD than in those with MCI, compared with deficits in the other odor domains. As shown in the forest plot in Figure 2, the use of a meta-analytic approach showed that the results across the three studies (with relatively small sample sizes) represented a more powerful estimate of true subject differences, because these studies did not demonstrate any significant differences in identification domain by themselves. Considering that age-related olfactory dysfunction is mainly identified using detection threshold rather than other domains, our findings suggest that the olfactory identification function test can be used as an early diagnostic tool of cognitive impairment, before the appearance of clinical symptoms.

Several studies have proposed that age might affect olfactory dysfunction in patient groups. In our study, a subgroup analysis of age revealed the unexpected observation that a smaller age difference (<2 years) between the two groups resulted in a greater olfactory deficit. These results indicated that the robust and confirmed difference in olfactory deficits found in our study was not merely due to a decrease in olfactory function due to old age, but rather was related to true deficits in olfaction related to AD pathology (see Supporting Figure 1A in the online version of this article). This finding further supports the current concept of the use of olfactory function tests as an early diagnostic tool.

Currently, it is well accepted that older men have a more profound decreases in olfactory function than older women. Thus, the effect of sex differences on olfactory function effect size were evaluated. As shown in Supporting
Figure 1B, the effect size was larger ($d = .77$) in the subgroup of participants who had less than a 10% difference in the age of males versus females, compared with those with a difference of over 10%. The olfactory function scores of a group of patients with AD with a higher percentage of females might outperform a group of males with MCI. These results indicate that the large difference in the percentage of males underlies the lower effect size, because all patient groups with MCI had more males except in one study. This phenomenon suggests that olfactory deficits identified in this study between patients with MCI and patients with AD might reflect AD pathology.

The first limitation of the current meta-analysis was the paucity of studies that conducted tests of threshold and discrimination domains. Furthermore, the identification tests that were used were highly diverse across studies, which is an inevitable result of culture-accustomed olfactory items between countries. Lastly, because all included studies were cross-sectional, it is hard to conclude that the olfactory performance difference between AD and MCI patients can predict the conversion from MCI to AD. For this, further large-scale prospective studies are needed.

**CONCLUSION**

The results of this meta-analysis revealed that olfactory function is vulnerable to the pathological changes that occur in patients with AD and MCI, and that olfactory function appears to be more profoundly impaired in patients with AD than in those with MCI. These results suggest that measurements of olfactory identification might be useful for the early detection of AD.

**BIBLIOGRAPHY**