

# Odor Identification Deficit Predicts Clinical Conversion from Mild Cognitive Impairment to Dementia Due to Alzheimer's Disease

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## Abstract

The aim of this study was to analyze the relationship between olfactory and cognitive functions in subjects affected by mild cognitive impairment (MCI) and to investigate whether olfactory deficits might reflect the likelihood of conversion from MCI to dementia. In this longitudinal study conducted on a sample of MCI outpatients, CA-SIT Smell Identification Test was administered to 88 MCI subjects and 46 healthy control subjects. MCI subjects have been divided into two groups, considering smell identification performances: 40% had normal performances (MCI olfactory-normal), whereas 60% had a moderate olfaction deficit (MCI olfactory-impaired). At 2-year follow-up, the 47% of MCI olfactory-impaired subjects and the 11% of MCI olfactory-normal subjects progressed to dementia. In a logistic regression model, a lower score in MMSE (95%, OR 1.9; IC 1.23–3.01;  $p = .004$ ) and a pathological smell identification at baseline (95%, OR 5.1; IC 1.16–22.6;  $p = .03$ ) were independently associated with the progression to dementia within 2 years. This study confirms that smell identification testing may be useful in high-risk settings to identify patients at risk for developing dementia.

**Keywords:** Mild Cognitive Impairment; Dementia; Alzheimer's disease; Olfactory deficits; Odor identification; Memory

## Introduction

Peripheral or central deficits of the olfactory system have been reported to be associated with a wide range of medical and neurological conditions. In recent years, there has been increasing interest in early and severe olfactory impairment in neurodegenerative disorders. Severe olfactory deficits have been identified in Alzheimer's disease (AD) and idiopathic Parkinson's disease (Doty, 2012; Mesholam, Moeberg, Mahar, & Doty, 1998), in Huntington and Pick diseases (Barrios et al., 2007; Pirogovsky et al., 2007), Korsakoff syndrome (Gregson, Free, & Abbott, 1981; Hulshoff Pol, et al., 2002; Mair, Knoth, Rabchenuk, & Langlais, 1991), parkinsonism-dementia complex of Guam (Kisby et al., 2011), and dementia with Lewy bodies (DLB; McShane et al., 2001).

Kovacs (2004) demonstrated that 86% of normal elderly participants present with Alzheimer-type neuropathology (neurofibrillary tangles, NFTs) in the olfactory bulbs, and one third of them also have amyloid deposition. Previous anatomic studies in AD have extensively demonstrated a specific concentration of lesions (senile plaques, neurofibrillary degeneration) in the peripheral and central olfactory cortex, as well as lesions in layers II and III of the entorhinal cortex (Braak & Braak, 1991). In AD, NFT formation begins in predisposed sites and then spreads to others structures in a predictable sequence according to Braak's stages (transentorhinal, limbic and neocortical). Kovacs also found that NFTs in the olfactory bulb appear in the early Braak's stages, even before spreading to the entorhinal cortex. Moreover, Devanand and colleagues (2010) found a correlation between hippocampal volume and olfactory function, corroborating the hypothesis of a neuroanatomical association between the olfactory system and memory circuits.

Deficits in the ability to identify and recognize odorants are salient in the earliest phases of AD (Koss, Weiffenbach, Haxby, & Friedland, 1988), whereas the ability to detect odors is affected later (Serby, Larson, & Kalkstein, 1991). Olfactory deficits are so prominent in AD that some authors (Bahar-Fuchs, Moss, Rowe, & Savage, 2011; Devanand et al., 2000) have proposed that olfactory dysfunction could be used as an early marker for AD. One of the main questions that remains unresolved, however, is the time course of olfactory deficits in AD. It is unclear whether these deficits occur before, simultaneously, or after the occurrence of other clinical manifestations of the disease.

It is well established that normal aging is often accompanied by a decline in smell functioning as reflected by various tasks, such as detection, perceived intensity, quality discrimination, recognition, memory, and identification (Doty et al., 1984). Paik, Lehman, Seiden, Duncan, and Smith (1992) found that the surface of the olfactory epithelium decreased during aging because of the frequent presence of metaplastic respiratory epithelium; this could explain the age-related decline in olfaction. Community studies have shown, however, that olfactory impairment is associated with an increase in the incidence of cognitive decline in the general population (Schubert et al., 2008), suggesting that a decline in olfactory functioning in older adults may not be solely due to changes in respiratory epithelium.

Mild Cognitive Impairment (MCI) is a diagnostic label that defines a cognitive (amnesic and non-amnesic) syndrome that denotes a transitional stage between normal aging and dementia. Populations affected by MCI have been shown to be at higher risk than the general population for developing dementia (Petersen et al., 2001). In a recent review, Sun, Raji, Maceachern, and Burke (2012) emphasized the positive association between poorer performance on olfactory identification testing and AD, but they point out that few studies have been designed to adequately investigate the ability of olfactory testing to predict AD. They note that, while Devanand and colleagues (2010) demonstrated that patients with olfactory identification deficits were more likely to develop AD than other patients, independent of age, Bahar-Fuchs and colleagues (2011) failed to find a statistically significant relationship.

The purpose of the present study was to further analyze the relationship between olfactory and cognitive functions in MCI patients. Given prior findings in the literature, we hypothesized that patients with MCI who had smell identification deficits would have a neuropsychological profile characterized by prominent memory impairment. Moreover, we hypothesized that olfactory deficits in patients with MCI would have a higher likelihood of conversion from MCI to dementia, in particular dementia due to AD.

## Methods

Participants were recruited from February 2008 to May 2009 at our Alzheimer Evaluation Unit, in northern Italy. Institutional review boards approved this longitudinal study and written informed consent was obtained from both patients and their caregivers.

To be eligible for this study, all 88 participants had to meet the operational criteria for amnesic and non-amnesic MCI (Petersen et al., 2001), including: (a) memory complaint, corroborated by an informant; (b) objective memory impairment, quantitated by scores greater than 1.5 SDs below that of age and education appropriate norms on measures of episodic memory; (c) normal general cognitive functions, as determined by a clinician's judgment based on a structured interview with the patients and caregivers—Clinical Dementia Rating, CDR (Hughes, Berg, Danziger, Coben, & Martin, 1982) and a Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) score  $\geq 24$ ; (d) no or minimal impairment in activities of daily living (Instrumental Activities of Daily Living, IADL, and Basic Activities of Daily Living, BADL; Katz, Downs, Cash, & Grotz, 1970; Lawton & Brody, 1969) as determined by a clinical interview with the patient and an informant; and (e) no cognitive or functional impairment sufficient to meet National Institute of Neurological and Communicative Disorders and Stroke Alzheimer's Disease and Related Disorders Association Criteria for AD (McKhann et al., 1984), as judged by an experienced AD research clinician. Patients could not have a diagnosis of major depression. Participants with a diagnosis of probable or possible AD were excluded. Drug or alcohol abuse or dependence within the previous 5 years was not permitted, as defined by criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (American Psychiatric Association, 2000). Enrollment was not permitted for patients with poorly controlled diabetes or other medical conditions judged to be incompatible with study participation. A computed tomography or magnetic resonance imaging brain scan was required for all MCI participants, in order to exclude any evidence of intracranial infection, infarction, or other focal lesions.

The healthy control group was composed of 46 individuals, matched for age, gender, and education. All 134 participants were non-smokers and not considered to be completely anosmic; all underwent a full clinical and neurological examination with multi-dimensional assessment.

Participants were assessed using the MMSE, CDR, AD Assessment Scale cognitive part—ADAS-Cog-Italian version (Fioravanti et al., 1994)—for the measurement of global cognitive function; the IADL and BADL scales (Katz et al., 1970; Lawton & Brody, 1969) were used to describe the level of functional status; the Geriatric Depression Scale (Sheikh &

Yesavage, 1986) and the Neuropsychiatric Inventory (Cummings et al., 1994) were administered to identify the presence of depressive and psycho-behavioral disturbances.

Participants also underwent a standardized neuropsychological battery that included the Novelli's short story—learning and recall—(Novelli et al., 1986a), Raven's colored matrices (Bingham, Burke, & Murray, 1966), Trail Making Test A and B (Giovagnoli et al., 1996), Rey figure copy and recall (Osterrieth, 1944), semantic and phonemic fluency (Novelli et al., 1986b), and the Clock drawing test (Sunderland et al., 1989). The scores of the neuropsychological tests were adjusted for age and education.

Two years after the baseline, patients with MCI, but not controls, were re-evaluated with the same neuropsychological tests. Conversion to dementia was determined by an experienced clinician. The diagnosis of dementia was based on published criteria for AD (McKhann et al., 1984), vascular dementia (Román et al., 1993), fronto-temporal dementia (The Lund and Manchester Groups, 1994), and DLB (McKeith et al., 1996). Patients who progressed to dementia were classified as Converters, the others were defined as Non-converters. Finally, all participants were screened for their olfactory function (threshold, odor identification, and memory).

### Olfactory Assessment

Olfactory assessment consisted of a psychometric evaluation in four consecutive steps: threshold detection, odor identification, odor memory, and picture identification test.

**Threshold detection.** In order to determine the lowest concentration of a particular olfactory stimulus required to activate peripheral receptors, specific odorants stimulating only the first cranial nerve without irritating trigeminal endings were employed. Phenylethyl alcohol (PEA, Carlo Erba, Milan, Italy) is a rose-like odorant believed to constitute a pure olfactory stimulant. It has been widely championed as an ideal stimulus for the evaluation of olfactory acuity (Doty, 1995). Serial dilutions in twice-distilled water of PEA are placed in transparent glass bottles, with opening diameters of 2.5 cm and volume of 100 ml, containing 80 ml of liquid. Concentrations of the odorant range from  $10^{-7}$  to 1 M (13 solutions: 0.5 log step ascending concentrations). Thirteen bottles contain the odorant (PEA); one bottle contains only the diluent (purified water). Each test consists of presentation to the participant of one bottle containing the odorant and another containing the diluent, with an interval of approximately 10 s between presentations. The participant's task is to determine which of the two solutions evokes a stronger sensation. Threshold is defined as four consecutive correct responses with chance performance on the next weaker concentration.

**Odor identification.** The University of Pennsylvania Smell Identification Test (UPSIT, Sensonics, Haddon Heights, NJ, USA) (Doty, Newhouse, & Azzalina, 1985) is a standardized tool widely used to study the ability to identify an odorant at the supra-threshold level. This “scratch and sniff” test consists of 40 multiple-choice items. The patient is required to mark one of the four alternative odorants presented, even if no smell is perceived. To establish the meaning of a given individual's test score, it is compared with scores from normal persons of equivalent age and gender. However, of the 40 test odors, 6 (root beer, winter-green, turpentine, cheddar cheese, pickle, and gingerbread) were identified incorrectly by more than 20% of the Italian participants (Parola & Liberini, 1999). Therefore, we used a culturally adapted (CA) and validated version of the test (CA-SIT [smell identification test]), developed by Parola and Liberini in 1999, which includes only those 34 odorants that had been identified correctly by more than 80% of normal individuals (data about reliability and validity of the test were published in 1999). None of the odorants eliminated is included in the short form of the UPSIT (10 item) that Tabert, Lin, and Doty (2005) created from the 10 odorants found to be most sensitive to the Alzheimer's process. Because all 10 of these smells are included in the 34-item test (rather than a 40-item one), the test should be more sensitive to cognitive decline than the UPSIT. The normative values traditionally considered for smell identification (CA-SIT) in adult Italian population are as follows (Parola & Liberini, 1999):

- (a) normosmia: 28–34 correct responses at the CA-SIT;
- (b) mild microsmia: 24–27 correct responses at the CA-SIT;
- (c) moderate microsmia: 20–23 correct responses at the CA-SIT;
- (d) severe microsmia: 16–19 correct responses at the CA-SIT;
- (e) total microsmia: 5–15 correct responses at the CA-SIT;
- (f) probable malingering: 0–4 correct responses at the CA-SIT.

In the present study, we established a cutoff below 24 correct responses at the CA-SIT to identify a moderate smell identification deficiency. According to naturalistic studies demonstrating a progressive olfactory decline with aging, mild microsmia can be considered a para-physiologic condition in healthy older people.

**Odor memory.** Participants are told that they will be given a set of 10 different odorants to smell, which they will have to recognize later. Each of 10 target odorants is presented birhinally for approximately 5 s, with an interval of 20 s between presentations. Memory is tested 10 min later. At this time, 5 odorants, chosen from the original set of 10 and matched with 5 new odorants confounders, are presented in the same manner. The participant has to say whether each item was presented before (the participant could answer “yes/no” to the examiner’s question “Did-you already smell this aroma?” without naming the odorant). The olfactory memory score is the sum of correct answers, which varies from 0 to 10 (Parola & Liberini, 1999).

**Picture identification test.** This test, consisting of a 40 visually presented items, requires the participants to identify pictures of odorant stimuli proposed during the olfactory test (such as a picture of an orange), in order to evaluate cognitive function (Parola & Liberini, 1999); participants who score less than 35 of 40 items on the picture identification test (PIT) are considered to have some type of cognitive or linguistic problem, which may confound the interpretation of the olfactory test. Thus, the olfactory evaluation in this subset of patients is considered unreliable. The olfactory performances were adjusted for age.

### Statistical Analysis

Statistical analysis was performed with the *Statistical Package for the Social Sciences*, release 11.5.1 (2002). Descriptive statistics at baseline were performed on socio-demographic, neuropsychological, functional, and psycho-behavioral characteristics. Quantitative variables were expressed as the mean  $\pm$  standard deviation. Analysis of variance models and *t*-tests were used to compare continuous variables and chi-squared tests were used for dichotomous ones. Post hoc comparisons with Bonferroni correction were used to make comparisons between group means at baseline.

A logistic regression model was used to identify whether variables were independently associated with dementia at 2 years in MCI patients. The significance was set at  $p < .05$ .

## Results

### Baseline

At baseline, 40% of MCI patients ( $n = 35$ ) showed a normal smell identification performance (MCI olfactory-normal: CA-SIT  $\geq 24$ ), whereas 60% ( $n = 53$ ) had a pathologic performance (MCI olfactory-impaired: CA-SIT  $< 24$ ). All controls showed normal smell identification performance.

Table 1 shows that the MCI olfactory-impaired group performed statistically worse on the threshold detection task than the MCI olfactory-normal group (mean PEA  $11.3 \pm 1.7$  vs.  $12.3 \pm 0.9$ ;  $p = .002$ ) and than controls (mean PEA  $11.3 \pm 1.7$  vs.  $12.1 \pm 1.1$ ;  $p = .002$ ).

The MCI olfactory-impaired group showed similar results on the odor memory test and the PIT as the MCI olfactory-normal group and controls. Moreover, at baseline, the MCI olfactory-impaired group was significantly older than the MCI olfactory-normal group (mean age in years  $75.9 \pm 6.1$  vs.  $71.1 \pm 6.6$ ;  $p = .001$ ). Global cognition, evaluated with the MMSE, and functional activities, evaluated with IADL, BADL, and CDR scales, were comparable between the two groups (MCI olfactory-normal and MCI olfactory-impaired). At baseline, the neuropsychological characteristics of the two subgroups (MCI olfactory-impaired and MCI olfactory-normal) are described in Table 2. The MCI olfactory-impaired group performed worse than the MCI olfactory-normal group on the episodic verbal memory measure (mean short story  $8.8 \pm 4.9$  vs.  $12.1 \pm 3.7$ ;  $p = .001$ ). No differences were detected on the remaining neuropsychological tests and in regard to the behavioral and psychological symptoms.

### Follow-Up

Two years after the baseline assessment, the patients with MCI were reevaluated. Four patients in the MCI olfactory-impaired group were lost at follow-up: Three participants had died (heart failure, pneumonia, complications of femur fracture), and one patient was removed due to low compliance. Patients who progressed to dementia were classified as Converters, and the others were defined as Non-converters. The diagnosis of dementia was based on the current published criteria (see “Methods”).

Forty-seven percent ( $n = 23$  of 49) of patients in the MCI olfactory-impaired group and 11% ( $n = 4$  of 35) of patients in the MCI olfactory-normal group progressed to dementia. The rate of conversion between the two groups is statistically significant

**Table 1.** Demographic, cognitive, functional, behavioural, and odor characteristics of a sample of 144 participants, 88 MCI patients grouped in MCI olfactory-impaired (smell identification score CA-SIT < 24) and MCI olfactory-normal (smell identification score CA-SIT ≥ 24), and 46 controls, at baseline

	MCI olfactory-impaired ( <i>N</i> = 53)			MCI olfactory-normal ( <i>N</i> = 35)			Controls ( <i>N</i> = 46)		
	Mean	<i>SD</i>	Percent	Mean	<i>SD</i>	Percent	Mean	<i>SD</i>	Percent
CA-SIT scores	16.7*	3.9		27.3	2.2		25.9*	3.1	
Age, years	75.9	6.1		71.1	6.6		73.7	7.3	
Gender (F)			53			60			57
Education, years	7.8	3.7		8.4	3.9		7.3	3.4	
MMSE	27.3	1.7		27.9*	1.4		29.5*	0.6	
IADL lost functions	0.4*	0.7		0.2	0.4		0*	0	
BADL lost functions	0.2*	0.5		0.1	0.4		0*	0	
CDR	0.5	0.0		0.5	0.0		-	-	
GDS	3.8	3.2		2.9	2.4		-	-	
NPI	7.1	6.8		5.5	7.4		-	-	
PEA	11.3*	1.7		12.3	0.9		12.1*	1.1	
Odor memory	6.2	1.4		6.7	1.4		6.9	1.5	
PIT	39.4	1.4		39.7	0.6		39.6	0.5	

*Notes:* The scores of neuropsychological test are adjusted for age and education. The olfactory performances are adjusted for age. MCI = Mild Cognitive Impairment; CA-SIT = culturally adapted smell identification test; NPI = Neuropsychiatric Inventory; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination (0–30); IADL = Instrumental Activities of Daily Living (0–8); BADL = Basic Activities of Daily Living (0–6); CDR = Clinical Dementia Rating Scale (0–5); GDS = Geriatric Depression Inventory (0–15); PEA = phenyl-ethyl alcohol, for threshold detection; PIT = picture identification test.

\**p* < .005.

**Table 2.** Neuropsychological characteristics of a sample of 88 MCI patients subgrouped in MCI olfactory-impaired (smell identification score < 24; *N* = 53) and MCI olfactory-normal (smell identification score ≥ 24; *N* = 35)

	MCI olfactory-impaired ( <i>N</i> = 53)		MCI olfactory-normal ( <i>N</i> = 35)		<i>p</i> -value
	Mean	<i>SD</i>	Mean	<i>SD</i>	
Clock drawing	8.0	2.1	7.9	2.0	NS
Short story	8.8	4.9	12.1	3.7	.001
Phonological verbal fluency	33.2	9.7	34.2	10.3	NS
Semantic verbal fluency	13.3	3.7	14.0	3.8	NS
Raven's colored matrices	27.4	5.8	27.6	4.1	NS
Trail Making Test A	61.7	71.7	48.7	29.7	NS
Trail Making Test B	240.2	188.1	185.1	185.9	NS
Rey's figure copy	30.8	5.8	31.3	5.5	NS
Rey's figure recall	11.8	9.1	12.8	7.0	NS

*Note:* The scores of neuropsychological tests are adjusted for age and education.

(*p* = .000). Most converters met clinical diagnostic criteria for AD (99%), while one patient (MCI olfactory normal) was diagnosed as having vascular dementia.

At baseline, Converter (*n* = 27) and Non-converter (*n* = 57) MCI patients were significantly different in age (mean  $76.5 \pm 5.8$  vs.  $72.5 \pm 6.8$  years; *p* = .01), smell identification (CA-SIT < 24: 85% vs. 46%; *p* = .000), MMSE (mean  $26.4 \pm 1.4$  vs.  $28.1 \pm 1.5$ ; *p* = .000), short story (mean  $6.6 \pm 4.0$  vs.  $11.9 \pm 4.1$ ; *p* = .000), Raven's colored matrices (mean  $25.6 \pm 5.0$  vs.  $28.7 \pm 4.8$ ; *p* = .01), Trail Making Test B (TMT-B; mean  $268.5 \pm 172.5$  vs.  $181.2 \pm 183.6$ ; *p* = .04), and Rey's figure recall (mean  $8.3 \pm 6.5$  vs.  $14.0 \pm 8.5$ ; *p* = .003). Converters and Non-converters, at baseline, were also significantly different for functional status (IADL, functions lost  $0.7 \pm 0.7$  vs.  $0.2 \pm 0.4$ ; BADL, functions lost  $0.4 \pm 0.6$  vs.  $0.1 \pm 0.3$ ) (Table 3).

Finally, we used an ROC curve in order to identify the optimal CA-SIT cutoff score, which can predict the conversion to dementia, distinguishing converters from Non-converters at the follow-up point. We found that baseline olfaction total scores of < 24 led to 85% sensitivity and 55% specificity for the diagnosis of dementia (AUC = 70%), including a progressive decrease in sensitivity and an increase in specificity with lower olfaction scores.

In order to detect which of these variables was independently related to conversion to dementia in MCI patients, at 2-year follow-up, a logistic regression model was used, including as variables: age, pathological CA-SIT, MMSE, IADL, BADL,

**Table 3.** Demographic, neuropsychological, functional, and olfactory characteristics of a sample of 84 MCI patients subgrouped Non-converters and Converters to dementia at 2-year follow-up

	Non-converters ( <i>N</i> = 57)			Converters ( <i>N</i> = 27)			<i>p</i> -value
	Mean	<i>SD</i>	Percent	Mean	<i>SD</i>	Percent	
Age, years	72.5	6.8		76.5	5.8		.001
MMSE	28.1	1.5		26.4	1.4		.000
Clock drawing	8.3	1.8		7.6	1.9		NS
Short story	11.9	4.1		6.6	4.0		.000
Phonological verbal fluency	33.8	9.9		33.3	10.7		NS
Semantic verbal fluency	13.6	3.3		13.6	4.7		NS
Raven's colored matrices	28.7	4.9		25.6	5.0		.01
Trail Making Test A	55.0	65.9		61.4	47.4		NS
Trail Making Test B	181.2	183.7		268.5	172.5		0.04
Rey's figure copy	31.9	5.1		29.7	5.6		NS
Rey's figure recall	14.0	8.4		8.3	6.5		0.003
BADL, functions lost	0.1	0.3		0.4	0.6		0.003
IADL, functions lost	0.2	0.4		0.7	0.7		0.000
Smell identification (pathological)			46			85	0.000
CA-SIT	22.4	6.2		18.4	5.1		0.005
PEA	11.8	1.5		11.5	1.2		NS
Odor memory	6.7	1.6		6.3	1.3		NS

The scores of neuropsychological tests are adjusted for age and education. The olfactory performances are adjusted for age. MMSE = Mini-Mental State Examination (0–30); BADL = Basic Activities of Daily Living (0–6); IADL = Instrumental Activities of Daily Living (0–8); CA-SIT = culturally adapted smell identification test; PEA = phenylethyl alcohol, for threshold detection.

**Table 4.** Risk of progression to dementia after 2-year follow-up in a sample of 84 MCI patients

	OR	95% CI	<i>p</i> -value
Age, years	1.02	0.90–1.15	.80
Smell identification (pathological)	5.13	1.16–22.60	.03
MMSE	1.93	1.23–3.01	.00
IADL, lost functions	1.53	0.49–4.76	.46
BADL, lost functions	4.67	0.87–25.07	.07
Short story	0.28	0.06–1.29	.10
Raven's colored matrices	0.05	0.00–1.73	.10
Trail Making Test B	0.84	0.20–3.52	.81
Rey's figure recall	1.18	0.27–5.09	.82

Notes: MMSE = Mini-Mental State Examination (0–30); BADL = Basic Activities of Daily Living (0–6); IADL = Instrumental Activities of Daily Living (0–8).

short story, Raven's colored matrices, TMT-B, and Rey's figure recall scores. Table 4 shows that a lower score in MMSE (95%, OR 1.9; IC 1.23–3.01; *p* = .004) and a pathological smell identification at baseline (95%, OR 5.1; IC 1.16–22.6; *p* = .03) were independently associated with the progression to dementia within 2 years.

Discussion

In the present study, we assessed olfactory function and cognitive performance in a consecutive series of 88 patients with MCI and 46 normal controls. Moderate olfactory dysfunction, particularly smell identification and detection thresholds, was demonstrated in a large percentage (60%) of patients with MCI (olfactory-impaired), confirming previous studies (Makowska, Kloszewska, Grabowska, Szatkowska, & Rymarczyk, 2011; Westervelt, Bruce, Coon, & Tremont, 2008).

Our data showed that the MCI olfactory-impaired group was similar to the MCI olfactory-normal group at baseline in terms of global cognition (MMSE), but a significant difference was found in episodic verbal memory. This result is in line with previous findings (Devanand et al., 2010) that highlight a significant correlation between smell identification score and hippocampal volume, a structure that is thought to play an important role in the consolidation of long-term memory. The concomitant presence of smell identification deficit and poor verbal memory performance supports the hypothesis that ability to identify and recognize

odorants could depend on the involvement of medial temporal lobe structures, which are affected in the early stages of AD and considered responsible for both smell identification and memory processes.

In line with previous studies (Rozzini et al., 2008), a high percentage of MCI patients with memory impairment converted to dementia at the 2-year follow-up. In particular, the high percentage (47%) of MCI olfactory-impaired patients who converted to dementia of Alzheimer's type 2 years after the baseline corroborates the hypothesis that smell identification deficits occur in the earliest phase of this illness. Furthermore, these findings demonstrate that olfactory identification deficits are not merely associated with AD, but are useful predictors of conversion to dementia of Alzheimer's type. In fact, using a logistic regression model, we demonstrated that the presence of low smell identification scores (CA-SIT < 24) in MCI was a strong predictor of dementia, independent from other factors, such as age, functional status (IADL and BADL), MMSE, verbal and visual memory, attention, and other cognitive domains (short story, Raven's colored matrices, TMT-B, Rey's figure recall).

Devanand and colleagues (2000) had measured olfaction using an arbitrary cutoff for the UPSIT ( $\leq 34$ ) that led to sensitivity and specificity values similar to those presented in the present study for the CA-SIT < 24. They observed that low olfaction (UPSIT  $\leq 34$ ) predicted AD only when associated with lack of awareness, but this finding is not yet confirmed by more recent studies (Bahar-Fuchs et al., 2011; Wehling, Nordin, Espeseth, Reinvang, & Lundervold, 2011).

Our data confirmed the utility of smell identification deficits in predicting conversion to dementia due to AD among patients affected by MCI; thus, early olfactory deficits are poor prognostic indicator of the disease course. This finding supports the hypothesis that olfactory assessment, as a part of neurocognitive evaluation, may assist in differentiating between individuals with initial cognitive impairment that are more or less likely to develop dementia in a long-term follow-up. Despite the fact that the olfactory assessment offers a good level of sensitivity and specificity for the detection of the risk of developing subsequent dementia, these measures should not be interpreted without being integrated into a broad clinical and neuropsychological assessment.

The current study had some limitations that should be considered when interpreting the findings reported. First, the choice of the cutoff (CA-SIT < 24) for smell identification deficits was arbitrary at the baseline, because of the lack of normative data for Italian healthy population. Based on the literature (Doty et al., 1995), mild microsmia (CA-SIT 24–27) can be considered physiological in normal aging, so justifying the cutoff. Nevertheless, at 2-years follow-up, we demonstrated with an ROC curve that this cut score led to 85% sensitivity and 55% specificity for the diagnosis of dementia (AUC = 70%), similar to the values found for the UPSIT scores used by Devanand and colleagues (2000) in their study. The optimal tradeoff between sensitivity and specificity appeared to be in the 20–24 scoring range.

Second, the cutoff used for classifying this subpopulation of MCI did not distinguish among the sexes, even though it is well known that women outperform men at all ages (Lehrner et al., 1993). A different cutoff for women and men would likely enhance the predictive power of the test.

Third, it is well documented that many conditions (exposure to chemical and physical agents, tobacco smoking, drug intake, rhino-sinusal and respiratory disorders, several neurological and medical diseases) can interfere with olfactory function. These factors reduce the reliability of the SIT (CA-SIT) and its extensive use in clinical practice. We excluded confounding conditions to the extent possible.

Finally, at 2-year follow-up, the complete olfactory assessment has not been administered to the study sample, and the control group was not cognitively assessed, due to clinical practice restrictions.

The relative small size of the sample is in line with other similar studies. Given these limitations and the paucity of other data on the use of the CA-SIT in predicting AD in patients with MCI, our findings require independent replication before specific cutoff scores on the CA-SIT can be recommended for use in clinical practice, even though our results are consistent with previous findings using the UPSIT. Nevertheless, our data provide further evidence of the association between cognition and olfaction, supporting olfactory assessment in screening individuals at higher risk of developing dementia. The CA-SIT could add value to traditional neuropsychological tests, being a strong and independent predictor of progression to dementia within 2 years.

In conclusion, our study offers a significant new contribution to the current research in this area, addressing some of the limitations of prior studies. We demonstrated that olfactory identification testing, as a part of a neurocognitive evaluation, is a useful prognostic instrument for Alzheimer's dementia, independently of age and other confounding factors. Further extended longitudinal studies are needed to validate standardized criteria.

## Conflict of Interest

None declared.

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