

# Olfactory impairment in mild cognitive impairment with Lewy bodies and Alzheimer's disease

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## ABSTRACT

**Objectives:** Impaired olfaction may be a biomarker for early Lewy body disease, but its value in mild cognitive impairment with Lewy bodies (MCI-LB) is unknown. We compared olfaction in MCI-LB with MCI due to Alzheimer's disease (MCI-AD) and healthy older adults. We hypothesized that olfactory function would be worse in probable MCI-LB than in both MCI-AD and healthy comparison subjects (HC).

**Design:** Cross-sectional study assessing olfaction using Sniffin' Sticks 16 (SS-16) in MCI-LB, MCI-AD, and HC with longitudinal follow-up. Differences were adjusted for age, and receiver operating characteristic (ROC) curves were used for discriminating MCI-LB from MCI-AD and HC.

**Setting:** Participants were recruited from Memory Services in the North East of England.

**Participants:** Thirty-eight probable MCI-LB, 33 MCI-AD, 19 possible MCI-LB, and 32HC.

**Measurements:** Olfaction was assessed using SS-16 and a questionnaire.

**Results:** Participants with probable MCI-LB had worse olfaction than both MCI-AD (age-adjusted mean difference (B) = 2.05, 95% CI: 0.62–3.49,  $p = 0.005$ ) and HC (B = 3.96, 95% CI: 2.51–5.40,  $p < 0.001$ ). The previously identified cutoff score for the SS-16 of  $\leq 10$  had 84% sensitivity for probable MCI-LB (95% CI: 69–94%), but 30% specificity versus MCI-AD. ROC analysis found a lower cutoff of  $\leq 7$  was better (63% sensitivity for MCI-LB, with 73% specificity vs MCI-AD and 97% vs HC). Asking about olfactory impairments was not useful in identifying them.

**Conclusions:** MCI-LB had worse olfaction than MCI-AD and normal aging. A lower cutoff score of  $\leq 7$  is required when using SS-16 in such patients. Olfactory testing may have value in identifying early LB disease in memory services.

**Keywords:** olfaction, smell, Sniffin', Lewy, MCI, mild cognitive impairment, dementia with Lewy bodies, Alzheimer's disease

## Introduction

Olfactory impairment is a common and early feature of many neurodegenerative diseases but is especially prominent in Lewy body (LB) diseases where pathologic involvement of all parts of the olfactory system is recognized (Attems *et al.*, 2014). Its high prevalence and early presence make it a key

prodromal feature of Parkinson's disease (PD), with a review indicating its onset decades before motor symptoms (Savica *et al.*, 2018). However, only a few studies have directly assessed olfaction in dementia with Lewy bodies (DLB), with studies using both clinical (Westervelt *et al.*, 2003; 2016; Williams *et al.*, 2009; Yoon *et al.*, 2015; 2018) and neuropathological diagnoses (Beach *et al.*, 2020; McShane *et al.*, 2001; Olichney *et al.*, 2005) finding greater impairments in DLB than AD.

The early and accurate identification of DLB is recognized as important for optimizing patient management (Taylor *et al.*, 2020). We have reported the diagnostic utility of both dopaminergic imaging with

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<sup>123</sup>I-N-fluoropropyl-2 $\beta$ -carbomethoxy-3 $\beta$ -(4-iodophenyl) (FP-CIT) and cardiac metaiodobenzylguanidine (MIBG) imaging in mild cognitive impairment (MCI). Both had high specificity (88% for each; Roberts *et al.*, 2021a; 2021b) but more modest sensitivity for identifying MCI with Lewy bodies (MCI-LB) compared with MCI-AD. There is therefore a need to find simple, inexpensive tests which can be applied in memory services, with the aim of identifying a large proportion of those with likely LB disease. This would enable these imaging investigations to be focused on people with a much higher probability of having LB disease. One approach is to test for olfactory impairment, especially odor identification.

Although odor identification tests discriminate well between PD and non-PD (Mahlknecht *et al.*, 2016), such studies have typically been undertaken in younger adults and olfactory function declines with age with hyposmia being present in about 25% of older adults (Murphy *et al.*, 2002). Olfactory deficits are also reported in AD, which might seem to further limit the potential value of olfaction tests in identifying DLB, but not only do these occur significantly more often in DLB than AD but also the early involvement of the olfactory organ by LB diseases and the associated prominence of hyposmia in prodromal PD (Savica *et al.*, 2018) suggests that olfactory impairments may discriminate between AD and DLB at the MCI stage. In addition, a large proportion of abnormal olfaction in clinically diagnosed AD is due to comorbid LB disease (Beach *et al.*, 2020). So olfactory testing may be a sensitive test for prodromal DLB. This is supported by a few small studies of olfaction. One found no differences between AD and DLB at the dementia stage, while such differences were present at the earlier MCI stage (Yoo *et al.*, 2018); in a longitudinal study in which olfaction was tested in MCI patients, those who later progressed to DLB had greater impairments compared with those who developed AD dementia with a receiver operator characteristic area under the curve of 84% (Yoon *et al.*, 2015); and a clinical assessment of mild DLB and AD (Mini-Mental State Examination, MMSE = 24) found odor identification again distinguished these two diseases with a high sensitivity for DLB of 81% (Williams *et al.*, 2009).

We therefore carried out the largest comparison, to date, of olfaction in MCI-LB and MCI-AD using the Sniffin' Sticks-16 olfaction test. We hypothesized that not only would olfactory function be worse in probable MCI-LB than in MCI-AD, and in cognitively healthy older adults, but that the previously identified cutoff score of  $\leq 10$  on this test in PD (Mahlknecht *et al.*, 2016) would be too high in this population because of the impairments of

olfaction with increasing age. So we also sought to assess whether a different cutoff for olfactory testing would be more appropriate for identifying MCI-LB than those previously used in PD.

## Methods

### Participants

As detailed previously (Donaghy *et al.*, 2020; Roberts *et al.*, 2021a; 2021b), medically stable patients aged 60 years or older with a clinical diagnosis of MCI were recruited from local memory services in the North-East of England between April 2016 and September 2019. Potential study participants either reported the presence of any core clinical feature of DLB (complex visual hallucinations, rapid eye movement (REM) sleep behavior disorder, cognitive fluctuations, or parkinsonism not preceding cognitive impairment by more than 12 months), or any supportive clinical feature found in DLB, but not specific to this (e.g. mood change or sleep disturbance). Exclusion criteria were dementia at screening, no objective cognitive impairment, or possible vascular or frontotemporal etiology and parkinsonism present for more than a year before the onset of cognitive problems ("one year rule"). In addition, healthy comparison subjects (HC) with no evidence of cognitive impairment or parkinsonism or other brain diseases and a normal structural MRI brain scan were recruited through the Join Dementia Research platform, and from friends or families of the patients. All identified participants provided written informed consent prior to detailed screening and medical review before final inclusion.

Following consent participants underwent a research-level assessment involving a semistructured interview, clinical and neurocognitive assessment and neurological examination by a medical doctor (RD and SL), and imaging with FP-CIT, MIBG, and MRI (Firbank *et al.*, 2021; Roberts *et al.*, 2021a; 2021b) at baseline, and then had longitudinal review at approximately annual follow-ups. Mean (SD) of maximum follow-up were 1.4 (0.98) years, with a maximum of 3.7 years from baseline.

### Clinical assessment, imaging, and differential diagnosis

#### ASSESSMENT

The MDS Unified Parkinson's Disease Rating Scale – Motor Examination (UPDRS-III), Epworth Sleepiness Scale, and Geriatric Depression Scale were administered to patients. The Instrumental Activities of Daily Living scale, North-East Visual Hallucinations Inventory, Neuropsychiatric

Inventory, Mayo Sleep Questionnaire, Clinician Assessment of Fluctuation, and Dementia Cognitive Fluctuation Scale were administered to informants. Clinical Dementia Rating scale and Cumulative Illness Rating Scale for Geriatrics were completed on the basis of the clinical history and other research assessments. A detailed neuropsychological evaluation was also carried out as reported previously (Donaghy *et al.*, 2020) which included the ACE-R, a 100-point cognitive screening test from which MMSE score was derived. Dopaminergic <sup>123</sup>I-N-fluoropropyl-2 $\beta$ -carbo-methoxy-3 $\beta$ -(4-iodophenyl) single-photon emission computed tomography (FP-CIT) and cardiac MIBG imaging were offered to all participants as previously described (Roberts *et al.*, 2021a; 2021b). FP-CIT images were visually rated as normal or abnormal by a five-person panel of experienced image analysts, blind to clinical information. MIBG images were classified as abnormal given a heart:mediastinum uptake ratio of < 1.86 based on data from locally recruited HC (Roberts *et al.*, 2019).

#### DIFFERENTIAL DIAGNOSIS

As detailed previously (Donaghy *et al.*, 2020; Roberts *et al.*, 2021a; 2021b), diagnoses were made by a three-person expert clinical panel (AJT, PCD, and JPT) who independently reviewed research data and health service record and made MCI diagnoses according to NIA-AA criteria (Albert *et al.*, 2011). This consensus panel method has previously been validated against autopsy and is recognized by regulatory authorities as the clinical gold standard (McKeith *et al.*, 2007).

To determine MCI etiology, the presence or absence of core LB symptoms was also rated by the panel, in accordance with the fourth consensus criteria for DLB (McKeith *et al.*, 2017), and those with evidence (including on MRI) of vascular or frontotemporal etiologies, or parkinsonism predating cognitive impairment by more than 1 year, were also excluded. In accordance with the research diagnostic criteria for MCI-LB (McKeith *et al.*, 2020), a diagnosis of probable MCI-LB was made if a patient had two or more core LB symptoms or one core symptom in addition to a positive FP-CIT or MIBG scan. Patients were diagnosed with possible MCI-LB when they had only one core symptom or one or more abnormal scans. MCI-AD was diagnosed following the criteria of Albert *et al.* (2011). Subjective and objective cognitive decline consistent with AD was established, along with generally maintained independence of function in everyday life, and the absence of dementia and other causes were then excluded as above. These diagnoses were updated at

each annual follow-up, and a diagnosis of dementia was made when any participant was judged to no longer be functionally independent. Participants with dementia were not followed up further.

#### SNIFFIN' STICKS ASSESSMENT

Olfactory function was assessed using Sniffin' Sticks-16 (SS-16) which was administered to each participant in accordance with the manufacturer's instructions. The test consists of 16 pens impregnated with specific odors. These were in turn held about 2 cm below the nose of the participant who was then asked to smell and identify the odor from a forced choice of four written alternatives. A pause of about 30 s was allowed between each Sniffin' stick.

#### Analysis

Analyses were conducted in *R* software with the *epiR* and *pROC* packages. Significance was considered as  $p < 0.05$ . Group differences in hyposmia measured by total Sniffin' Sticks scores were assessed with the general linear model, adjusting for age (mean centered). Model diagnostics were checked by plotting residuals against fitted values, and with Q – Q plots.

Receiver operating characteristic (ROC) curves were plotted to assess the discriminatory utility of Sniffin' Sticks total in identifying MCI-LB. Diagnostic cutoffs for discriminating MCI-LB from MCI-AD and HC were identified by Youden's index.

#### Results

The SS-16 was completed by 122 participants (32 HC, 90 MCI) and baseline characteristics are in Table 1 and task performance in Figure 1. A Mann – Whitney *U* test found no significant sex differences in olfactory function ( $p = 0.70$ ). The age-adjusted linear model (see Table 2) demonstrated that there were significant differences in olfactory function overall between groups ( $F(3,117) = 9.83, p < 0.001$ ), with this being worse in probable MCI-LB than MCI-AD, and HC. We also included the possible MCI-LB group for information; this group were more similar to MCI-AD, with significantly better olfactory function than probable MCI-LB.

#### Sniffin' Sticks cutoff $\leq 10$

Using the previously identified cutoff score of  $\leq 10$  (Mahlknecht *et al.*, 2016), the SS-16 had 84% sensitivity for diagnosis of probable MCI-LB (95% CI: 69–94%). Specificity was low in differentiating probable MCI-LB from MCI-AD at 30%

**Table 1.** Baseline characteristics of healthy comparison subjects and MCI subgroups who completed the Sniffin' Sticks Smell Identification Test

	HEALTHY COMPARISON SUBJECTS (N = 32)	PROB. MCI-LB (N = 38)	MCI-AD (N = 33)	Poss. MCI-LB (N = 19)
Age	73.9 (7.17)	74.1 (6.55)	74.3 (7.46)	73.0 (7.29)
Female gender	9 (28%)	5 (13%)	17 (52%)	9 (47%)
Instrumental Activities of Daily Living	–	6 [4, 8]	8 [2, 8]	7 [3, 8]
Addenbrooke's Cognitive Examination - Revised	92.6 (4.39)	83.4 (8.90)	83.0 (8.33)	78.0 (11.6)
Mini Mental State Examination	28.5 [26, 30]	27 [22, 30]	27 [23, 30]	26 [20, 30]
MDS Unified Parkinson's Disease Rating Scale – Part III	5 [0, 16]	21 [1, 50]	8 [0, 62]	14 [1, 40]
Clinical Dementia Rating	0 [0, 0]	0.5 [0, 0.5]	0.5 [0.5, 0.5]	0.5 [0.5, 0.5]
Receiving Cholinesterase Inhibitors or Memantine	0 (0%)	18 (47%)	7 (21%)	4 (21%)
Receiving Levodopa	0 (0%)	4 (11%)	0 (0%)	0 (0%)
Sniffin' Sticks-16 Score	11 [7, 15]	6.5 [0, 16]	9 [0, 15]	9 [0, 14]
SS-16 Score $\leq$ 10	11 (34%)	32 (84%)	23 (70%)	14 (74%)

Count (%), Mean (SD), or Median [Range].

**Table 2.** General linear model for estimated age-adjusted diagnostic group differences in overall performance on the 16-item Sniffin' Sticks Smell Identification Subtest

SNIFFIN' STICKS 16-ITEM IDENTIFICATION SUBTEST				
PREDICTORS	ESTIMATES	CI	P	
Intercept (Probable MCI-LB)	6.63	5.65–7.61	<0.001	
HC versus Probable MCI-LB	3.96	2.51–5.40	<0.001	
MCI-AD versus Probable MCI-LB	2.05	0.62–3.49	0.005	
Possible MCI-LB versus Probable MCI-LB	1.84	0.14–3.53	0.034	
Age (per year)	–0.12	–0.20 to –0.04	0.003	

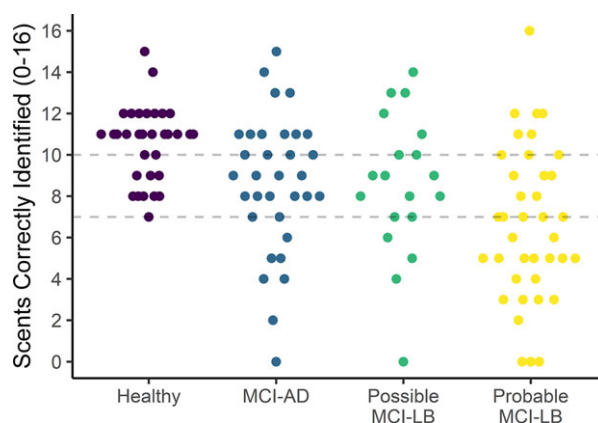
(95% CI: 16–49%), though better in differentiating these from HC (66%, 95% CI: 47–81%).

### ROC analysis

ROC curves were plotted, with best cutoffs identified with Youden's index. A lower cutoff of  $\leq 7$  was found to best distinguish probable MCI-LB from both MCI-AD and HC in this cohort (see Figure 2). This cutoff had 63% sensitivity for probable MCI-LB, but better specificity versus MCI-AD (73%) and HC (97%).

### Correlations with disease severity

Excluding HC, total score on the SS-16 was significantly associated with level of global cognitive

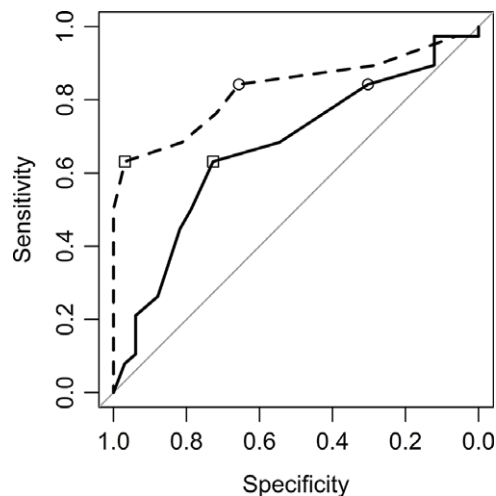
**Figure 1.** SS-16 task performance in each diagnostic group, 10- and 7-point cutoffs marked (dashed lines).

function assessed with the Addenbrooke's Cognitive Examination – Revised (Spearman's  $r = 0.38$ ,  $p < 0.001$ ), but not with levels of motor impairment, as assessed by the Unified Parkinson's Disease Rating Scale Part III (Spearman's  $r = -0.13$ ,  $p = 0.216$ ).

### Comparison with olfactory responses in questionnaire

All participants were asked if they had noticed a loss or reduction in their sense of smell when completing the Questionnaire for Symptoms Suggestive of Lewy Body Disease (QSSLBD). Of the 83 who did not recognize a reduction or loss of their sense of smell, 49 (59%) scored below the SS-16 cutoff. Of the 39 who did report a noticed loss of sense of smell, 31 (79%) scored below the cutoff and eight (21%) were above this threshold.





**Figure 2.** ROC curve for Sniffin' Sticks Smell Identification Test in distinguishing probable MCI-LB from HC (dashed line, AUC = 0.83) and MCI-AD (solid line, AUC = 0.67) with standard 10-point (circle) and 7-point (square) cutoffs marked.

## Discussion

Previous research has demonstrated that olfactory impairment is a highly prevalent and early feature of LB diseases, that in dementia it occurs more frequently in DLB than in AD and suggested such differences may be more prominent in MCI. We conducted a prospective analysis of olfaction in MCI and found as hypothesized that olfactory impairment is more frequent in MCI-LB than both in MCI-AD and in healthy older people and that a lower cutoff may be more appropriate in MCI than in PD ( $\leq 7$  in our study vs  $\leq 10$ ), though this requires replication. We also found that questioning about a loss of sense of smell did not perform well in such patients and testing is required to identify their olfactory impairments.

Previously, we have reported that two imaging biomarkers recommended in diagnostic criteria for both DLB and MCI-LB have high specificity (both 88%) in patients with MCI (Roberts *et al.*, 2021a; 2021b). This is similar to their specificities in dementia but, as expected in earlier disease, we found the sensitivities were lower (66% for FPCIT and 59% for MIBG) in MCI than in dementia (92%; O'Brien *et al.*, 2014). Even at the dementia stage, the diagnosis of DLB is delayed and frequently missed (Surendranathan *et al.*, 2020), with a large study finding only 4.6% of dementia cases diagnosed with DLB in UK memory services (Kane *et al.*, 2018). This compares with a recent autopsy analysis of a large representative UK cohort of dementia in which 26.3% had LB disease sufficiently severe to cause dementia (McAleese *et al.*, 2021). It is likely that even more cases are missed at the MCI stage than in

dementia. Although it is unrealistic to expect every person with a given disease to be identified during life, the magnitude of the gap in DLB suggests that many more people with LB disease in memory services could be identified, a view supported by the wide variation in diagnostic rates in clinical services (Kane *et al.*, 2018). It is also not realistic to expect such services to utilize FPCIT or MIBG in all patients presenting with cognitive impairment and so identifying simple brief tests for early LB disease would enable such diagnostic imaging tests to be targeted on patients with a higher likelihood of having MCI-LB/DLB, thereby facilitating their early identification. This would in turn enable early optimization of treatment for this complex disease with multiple physical and neuropsychiatric symptoms (Taylor *et al.*, 2020). Previously, we have reported that using DLB assessment toolkits was associated with a 35% increase in diagnosis of DLB in memory services (Surendranathan *et al.*, 2021). We suggest that in addition such services could further improve their identification and diagnosis of DLB/MCI-LB by adding Sniffin' Sticks to their assessment protocols. This test is simple, cheap, and popular with patients who enjoy the novelty of identifying the odors.

A major objection to this argument is that because most people in memory services have AD and some of these have abnormal olfaction (test positive), then testing olfaction for diagnostic scanning will still lead to most test positive patients having AD and so most positive tests will still be false with only a minority having LB disease. Using our identified SS-16 cutoff of  $\leq 7$  would mitigate this concern, but this objection assumes that those clinically diagnosed with AD do in fact have (only) AD and do not also have LB disease. We reported that many patients with an AD-like clinical presentation have high-grade LB disease (Thomas *et al.*, 2018) and this is consistent with the high prevalence of LB disease in autopsy studies. In Alzheimer's Disease Neuroimaging Initiative (ADNI) of those clinically diagnosed with AD, 45.5% had LB pathology (Toledo *et al.*, 2013) and in brain bank studies in the US (Schneider *et al.*, 2009), Finland (Oinas *et al.*, 2009), and Japan (Wakisaka *et al.*, 2003) LB pathology was reported in 24.7%, 29% and 41.4% of those with dementia and the above UK study found LB pathology sufficient to cause dementia in 26.3% (McAleese *et al.*, 2021). Thus, many of those in services diagnosed with AD have LB disease and abnormal olfaction in such "AD" is therefore likely due to LB disease with or without comorbid AD.

This point is not merely inferential. Other autopsy studies have consistently shown impairments in olfaction are strongly associated with LB

disease rather than AD. LB density was significantly associated with olfactory impairment in a study comparing olfaction in AD and DLB (McShane *et al.*, 2001); anosmia was about three times more frequent in people who had LB disease together with AD compared with those with pure AD (Olichney *et al.*, 2005); people with no clinical features of any LB disorders but who had LB disease at autopsy had an 11-fold increase in abnormal olfaction when tested during life (Ross *et al.*, 2006), suggesting such testing may be useful in identifying people without clinically manifest LB symptoms. Finally, a recent large study found that people with combined AD and LB pathologies were 17 times more likely to have olfactory impairment on testing with the University of Pennsylvania Smell Identification Test (UPSIT) olfaction test than those who had pure AD pathology (Beach *et al.*, 2020). Such evidence, from different brain banks around the world, strongly suggests that most of those with abnormal olfaction who have been diagnosed with clinical AD do in fact have LB disease either alone or along with AD pathology. This makes it likely that many of those with MCI-AD and abnormal olfaction in our study have LB disease and that apparent false positives in memory services would be highly likely to be true positives with abnormal olfaction correctly identifying the presence of occult LB disease. While such an argument needs direct investigation by future research, the evidence overall suggests olfactory testing is likely to be a useful means of identifying early LB disease.

Our exploratory analyses of SS-16 score with disease severity found that the previously reported association with severity of cognitive impairment (Yoo *et al.*, 2018) appears to be already present through the MCI stage. This suggests that LB disease is present in the olfactory areas as well as neocortical areas during MCI, consistent with the evidence from pathology studies (Attems *et al.*, 2014). The absence of such a correlation with the UPDRS is perhaps to be expected in our patient group since by applying the "one year rule" to recruitment, we restricted this group to people with a recent onset of parkinsonism and so a large proportion of patients had low scores on the MDS UPDRS. However, other patients had higher scores even without parkinsonism due to the effects on aging and diseases such as arthritis, further complicating the use of the UPDRS to identify a relationship with SS-16.

We also chose to explore whether the patient report of hyposmia in the QSSLBD might perform as well as SS-16 and thus be an even simpler way of identifying LB patients. This was not the case because the majority of participants who reported normal olfaction in fact scored abnormally ( $\leq 10$  on

SS-16) and so would be missed if this question were used alone. We conclude that proper olfactory testing is necessary to help identify LB disease in this patient group.

Our study benefits from being a relatively large and well-characterized cohort of probable MCI-LB and MCI-AD with detailed clinical and cognitive assessments and both structural and radionuclide imaging biomarkers and from using an established objective test of olfaction. Although using autopsy diagnosis may be regarded as the gold standard, this is not realistic for MCI studies and our use of consensus clinical panel diagnosis is the standard recognized by regulatory authorities (McKeith *et al.*, 2007) and has been validated against autopsy (McKeith *et al.*, 2007). This is further strengthened by the prospective annual diagnostic reviews in this cohort. However, our study cohort was selected on the basis of the possible presence of symptoms characteristic of LB disease identified in memory services, such as core clinical diagnostic features or supportive features in the diagnostic criteria, such as depression, anxiety, postural hypotension, and falls. While this was necessary to ensure a high proportion of MCI-LB in the study sample, it does mean those diagnosed with MCI-AD may not be entirely representative of all AD in such services. Here though this would suggest that perhaps a higher proportion of those diagnosed with AD have LB disease than even the high frequency that previous autopsy data support, meaning an even larger proportion of those with AD and abnormal olfaction might be true positives for LB disease. Many participants, particularly those with MCI-LB, were receiving cholinesterase inhibitors or memantine. This reflects a willingness of clinicians to use these medications in the MCI phase where they are confident that a neurodegenerative process is present. Finally, although as expected (Kane *et al.*, 2018) there was a significant imbalance in sex between MCI-LB and MCI-AD groups, there was not any evidence for sex differences in olfactory function.

In conclusion, in this prospective analysis of olfaction in MCI, we found impairments were more frequent in MCI-LB than MCI-AD and testing for such abnormal olfaction may be useful for identifying such early LB disease. While direct investigation of this is needed our findings, and the wider research data on LB disease and olfaction, suggest olfactory testing might be a useful way of improving the identification of early LB disease in memory services. Furthermore, the high sensitivity for AD and DLB in MCI suggest it may also be useful in other settings for identifying early LB disease, such as for other recognized prodromal presentations of DLB (delirium onset and psychiatric onset) (McKeith *et al.*, 2020).

## Conflicts of interest

All authors declare no conflicts of interest.

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## Author contributions

AJT: drafting of manuscript, formulation of research question, design of the study, interpretation of data, and review and critique of manuscript; CAH: data collection, analysis and drafting of manuscript; SB: data collection and review and critique of manuscript; RD: data collection and review and critique of manuscript; SL: data collection and review and critique of manuscript; NB: study administration, data collection, and review and critique of manuscript; MF: data collection and review and critique of manuscript; GR: data collection and review and critique of manuscript; LMA: formulation of research question, design of the study, and review and critique of manuscript; JO: design of the study and review and critique of manuscript; JPT: design of the study, data collection, and review and critique of manuscript; PCD: design of the study, formulation of research question, data collection, and review and critique of manuscript.

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