

# Olfactory discrimination predicts cognitive decline among community-dwelling older adults

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The presence of olfactory dysfunction in individuals at higher risk of Alzheimer's disease has significant diagnostic and screening implications for preventive and ameliorative drug trials. Olfactory threshold, discrimination and identification can be reliably recorded in the early stages of neurodegenerative diseases. The current study has examined the ability of various olfactory functions in predicting cognitive decline in a community-dwelling sample. A group of 308 participants, aged 46–86 years old, were recruited for this study. After 3 years of follow-up, participants were divided into cognitively declined and non-declined groups based on their performance on a neuropsychological battery. Assessment of olfactory functions using the Sniffin' Sticks battery indicated that, contrary to previous findings, olfactory discrimination, but not olfactory identification, significantly predicted subsequent cognitive decline (odds ratio = 0.869;  $P < 0.05$ ; 95% confidence interval = 0.764–0.988). The current study findings confirm previously reported associations between olfactory and cognitive functions, and indicate that impairment in olfactory discrimination can predict future cognitive decline. These findings further our current understanding of the association between cognition and olfaction, and support olfactory assessment in screening those at higher risk of dementia.

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## Introduction

Olfactory dysfunction has been reliably demonstrated in Alzheimer's disease (AD)<sup>1–3</sup> and mild cognitive impairment.<sup>4,5</sup> Of note, olfactory impairment has also been reported in cognitively healthy individuals positive for apolipoprotein E  $\epsilon 4$  (*APOE- $\epsilon 4$* ) allele, the main genetic risk factor for AD,<sup>6,7</sup> as well as in those with another potential risk factor for AD, namely subjective memory complaints.<sup>8</sup>

Indeed, olfactory dysfunction has been significantly associated with the risk of future AD and AD neuropathology burden in the brain.<sup>9</sup> AD-related neuropathological studies of animals and humans have indicated the following: (i) A negative association between amyloid-beta ( $\beta$ -amyloid) load in the brain and olfaction;<sup>10–12</sup> (ii) A strong association between tau pathology in olfactory system, Braak staging of AD pathology and cognitive decline;<sup>13,14</sup> and (iii) Presence of oxidative damage in the olfactory epithelium in the early stages of AD.<sup>15,16</sup>

Observational and clinical studies have found a significant association between olfactory impairment and subsequent cognitive decline. For example, a large-scale study ( $N = 1920$ ) on the relationship between olfactory identification ability and general cognitive functioning (as measured by Mini Mental State Examination (MMSE)) indicated that olfactory dysfunction at baseline was significantly predictive of future cognitive impairment after 5 years (odds ratio (OR) = 6.62; confidence

interval (CI) = 4.36–10.04).<sup>17</sup> Schubert *et al.*<sup>17</sup> have also reported low sensitivity of 55.1% but high specificity (84.4%) for olfactory assessment in predicting cognitive decline.

However, the olfaction/cognition relationship has not been consistently found, particularly when more complicated olfactory assessment instruments including electrophysiological measures were used in addition to psychophysical methods.<sup>18</sup> Indeed, the different methods utilized to assess olfaction may be responsible for the inconsistent findings.<sup>19</sup> Olfactory abilities are primarily assessed by measuring threshold (lowest detectable concentration of odors), discrimination (ability to differentiate between odors) and identification (ability to identify odors).<sup>20</sup> It has been suggested that olfactory threshold is strongly related to sensory capability, while olfactory discrimination and identification are more closely associated with higher cognitive functions, and thus may be more cognitively loaded.<sup>8,21</sup> A dated, but still informative, review has reported a strong association between cognitive functions and certain aspects of olfactory functioning, concluding that compared with the ability to detect odors, identification of odors is more challenging, perhaps due to a lack of access to verbal or visual representations of odors.<sup>22</sup> Similarly, Schab<sup>23</sup> noted that odor identification may represent a semantic memory function. Some researchers suggest that olfactory identification is primarily predictive of memory decline.<sup>24</sup> It is interesting that while verbal and visual cues

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may affect olfactory information processing, olfactory memories usually last longer than memories formed through other sensory modalities and have more emotional valence.<sup>25,26</sup>

There is strong evidence that neuroanatomical regions involved in episodic memory, including the medial temporal lobe, are also associated with olfactory functioning.<sup>27,28</sup> Interestingly, individuals with hippocampal lesions show significantly poorer olfactory recognition compared with odor threshold.<sup>29</sup>

Olfactory impairment is not confined to people with AD or AD-related cognitive decline, and it has been reported in individuals suffering from other neurodegenerative diseases such as Parkinson's disease, frontotemporal dementia and Lewy body dementia.<sup>30–32</sup> Olfactory deficits have also been reported in psychiatric disorders including schizophrenia and depression.<sup>33,34</sup> As such, olfactory dysfunctions appear not to be specific to AD.<sup>35,36</sup> Further studies are needed to improve the sensitivity and specificity of olfactory screening to identify which olfactory domains are specifically affected at particular stages of preclinical AD.

We hypothesized that olfactory ability at baseline could predict altered cognitive function in a 3-year follow-up assessment. The specific questions examined by the current study were the following: (1) Is there any association between olfaction and cognition at baseline in this cohort of apparently healthy aging individuals? (2) Could baseline olfactory function predict future (3-year) cognitive decline? (3) Which olfactory domain(s) best predict cognitive alteration?

## Materials and methods

**Design.** Participants were derived from a larger, longitudinal study, 'the Western Australia Memory Study' (for more information on this cohort, see refs 8,37–39). Participants were monitored for 3 years, and underwent annual neuropsychological, biochemical and physiological examinations. Herein, the baseline and final assessment (two-point data) results of this study will be examined. The study was approved by the Human Research Ethics Committees of the associated institutions, namely the University of Western Australia, Edith Cowan University and Hollywood Private Hospital. Participants provided informed consent before baseline assessments according to the guidelines of the National Health and Medical Research Council of Australia.

**Participants.** A total of 308 community-dwelling older adults aged 46–86 years old (68% female) were recruited from a larger study cohort. The volunteers' family members were also invited to participate. The *APOE-ε4* genotype was available for 273 participants, of whom 34% were *ε4* allele carriers (*ε2-ε4*, *ε3-ε4*, or *ε4-ε4*). The mean education level for the cohort was 13.5 years ( $\pm 3.77$ ), and inclusion criteria were a minimum of 6 years of education, age 45 and over, and fluency in English. Exclusion criteria for this study included: (i) a baseline score of  $\leq 24$  in MMSE<sup>40</sup> and  $\leq 81$  in the Cambridge Cognitive Examination-Revised (CAMCOG-R);<sup>41</sup> (ii) history of anosmia or any known olfactory problems; and (iii) history or formal diagnosis of medical, neurological or psychiatric diseases and disorders affecting olfactory

capacities (for example, sinusal diseases, upper respiratory tract infection, severe head injury, Parkinson's disease, schizophrenia, and so on).

**Measures.** Olfactory function was assessed using the 'Extended Sniffin' Sticks' battery (Burghart, Wedel, Germany), in which odors are presented using felt-tip pen-like sticks.<sup>42</sup> The Extended Sniffin' Sticks assess three domains of olfactory function, using threshold (T), discrimination (D) and identification (I) as three subscales and enabling calculation of a composite score, namely TDI.<sup>43,44</sup> In this study, the Sniffin' Sticks battery was administered in a triple forced-choice staircase method as outlined previously<sup>45</sup> and also in the test manual (Burghart).

The CAMCOG-R<sup>46</sup> and MMSE<sup>40</sup> were used to assess general cognitive functioning. The CAMCOG-R measures orientation, language, memory, attention, abstract thinking, praxis and calculation abilities, and provides a total score of cognitive functioning. The MMSE is commonly used as a screening measure to assess general cognitive performance in clinical and research settings.<sup>47</sup>

**APOE genotyping.** Blood samples were collected into different blood collection tubes including serum, EDTA (containing prostaglandin E) and heparin (Interpath Services, West VIC, Australia). The DNA was isolated from leukocytes, and APOE genotype was determined using PCR amplification and restriction enzyme digestion as previously described.<sup>48,49</sup>

**Statistical analysis.** All statistical analyses were performed using PASW Statistics 18 for Windows 7. Partial correlation was applied to control for the effects of age. Variables examined in this study including sex, *APOE* genotype, age at baseline, baseline cognitive function and olfactory performance, as measured by Sniffin' Sticks, were entered in a logistic regression model using the enter analysis model. After the completion of 3-year follow-up, participants were divided into two groups: cognitively declined and non-declined. Participants were considered to be 'cognitively declined' if their score on the final cognitive assessment (as measured by CAMCOG-R) was  $\geq 1$  s.d. below their baseline performance.

## Results

**Cohort demographics.** For this study, 308 participants with a mean age of 63.06 ( $\pm 7.25$ ) years undertook neuropsychological testing. Demographic characteristics of the cohort are shown in Table 1. The scores of male/female and *APOE-ε4* carrier and non-carrier groups on the MMSE, Sniffin' Sticks and CAMCOG-R at baseline (Table 1) were all above the cutoff scores, as required in the exclusion criteria (40,41,50, respectively).

Mackay-Sim *et al.*<sup>51</sup> provide guidelines for the classification of differing levels of olfactory impairment using Sniffin' Sticks: (1) severe hyposmia (a score of  $\leq 23$  on Sniffin' Sticks TDI for women and  $\leq 21$  for men); (2) anosmia (a TDI score of  $\leq 16$ ); and (3) mild hyposmia (in women a score of 23–27, and in men

**Table 1** Baseline descriptive results (age, years of education, cognitive measures and olfactory function were assessed and data analyzed in terms of gender and APOE genotype; Total N = 308)

Variables	Male (N = 99)	Female (N = 209)	P	APOE-ε4 <sup>a</sup> non-carrier (N = 202)	APOE-ε4 carrier (N = 99)	P	Total cohort
Age	65.19 (± 7.59)	62.05 (± 6.88)	0.000*	63.43 (± 7.62)	62.70 (± 6.39)	0.413	63.06 (± 7.25)
Education years	14.05 (± 4.14)	13.34 (± 3.56)	0.127	13.58 (± 3.91)	13.41 (± 3.43)	0.713	13.57 (± 3.77)
MMSE	29.05 (± 1.12)	29.20 (± 1.09)	0.281	29.16 (± 1.17)	29.11 (± 0.96)	0.729	29.15 (± 1.10)
CAMCOG-R	98.58 (± 3.58)	98.71 (± 3.34)	0.743	98.75 (± 3.50)	98.49 (± 3.12)	0.536	98.67 (± 3.41)
SS-T	7.03 (± 2.58)	7.58 (± 2.34)	0.063	7.44 (± 2.35)	7.30 (± 2.09)	0.622	7.40 (± 2.37)
SS-D	11.31 (± 2.25)	11.88 (± 2.43)	0.058	11.83 (± 2.37)	11.49 (± 2.41)	0.260	11.69 (± 2.39)
SS-I	12.64 (± 1.80)	12.49 (± 2.04)	0.539	12.54 (± 1.98)	12.56 (± 1.80)	0.919	12.54 (± 1.96)
SS-TDI	30.67 (± 4.53)	31.72 (± 4.63)	0.061	31.54 (± 4.58)	31.08 (± 4.53)	0.414	31.38 (± 4.62)

Abbreviations: CAMCOG-R, The Revised Cambridge Cognitive Examination; MMSE, Mini Mental State Examination; SS-D, Sniffin' Sticks discrimination; SS-I, Sniffin' Sticks identification; SS-T, Sniffin' Sticks threshold; SS-TDI, Sniffin' Sticks composite score.

<sup>a</sup>Apolipoprotein E ε4 allele. \*P ≤ 0.05.

**Table 2** Demographic information and baseline performance of cognitively declined<sup>a</sup> and non-declined participants

Variables	Age	Educ. years <sup>b</sup>	MMSE	CAMCOG-R	SS-T	SS-D	SS-I	SS-TDI
Non-declined (N = 250)	62.59 (± 6.98)	13.65 (± 3.65)	29.20 (± 1.11)	98.63 (± 3.28)	7.53 (± 2.32)	11.90 (± 2.21)	12.62 (± 1.91)	31.79 (± 4.13)
Declined (N = 58)	65.10 (± 8.08)	13.22 (± 4.25)	28.95 (± 1.05)	98.84 (± 3.94)	6.87 (± 2.55)	10.80 (± 2.86)	12.20 (± 2.16)	29.65 (± 6.04)
P	0.017*	0.442	0.124	0.664	0.063	0.009* <sup>c</sup>	0.153	0.013* <sup>c</sup>

Abbreviations: CAMCOG-R, The Revised Cambridge Cognitive Examination; MMSE, Mini Mental State Examination; SS-D, Sniffin' Sticks discrimination; SS-I, Sniffin' Sticks identification; SS-T, Sniffin' Sticks threshold; SS-TDI, Sniffin' Sticks composite score.

<sup>a</sup>Cognitive decline was considered as a score ≥ 1 s.d. below baseline performance on CAMCOG-R in the last assessment. <sup>b</sup>Education years. <sup>c</sup>Equal variance not assumed. \*P ≤ 0.05.

**Table 3** Prediction of cognitive decline<sup>a</sup> using Sniffin' Sticks discrimination in multiple logistic regression analysis (N = 282)<sup>b</sup>

Factors	B	s.e.	Wald	df	P*	OR	95% CI for OR	
							Lower	Upper
Sex	-0.005	0.340	0.000	1	0.988	0.995	0.511	1.937
APOE genotypes	-0.518	0.323	2.579	1	0.108	0.596	0.316	1.121
Age at baseline	0.031	0.023	1.846	1	0.174	1.035	0.986	1.078
Education years	-0.008	0.042	0.039	1	0.843	0.992	0.912	1.078
MMSE	-0.140	0.132	1.119	1	0.290	0.870	0.617	1.127
SS-D	-0.141	0.066	4.582	1	0.032*	0.869	0.764	0.988

Abbreviations: CAMCOG-R, The Revised Cambridge Cognitive Examination; CI, confidence interval; MMSE, Mini Mental State Examination; OR, odds ratio; SS-D, Sniffin' Sticks discrimination.

<sup>a</sup>Cognitive decline was considered as a score ≥ 1 s.d. below baseline performance on the CAMCOG-R in the last assessment. <sup>b</sup>N was 308; however, only 282 were entered in the actual analysis. \*P < 0.05.

a score of 21–29). In our cohort, 6.5, 1.3 and 19.5% met these criteria, respectively.

In this cohort, 194 (62.98) participants were non-smokers, 105 (34.09) were ex-smokers (with at least 2 years of abstinence) and 9 (2.93) participants were smokers. However, as there were no significant differences between the non-smokers and other groups in any of the baseline assessments including age, education, cognitive function (as assessed by MMSE and CAMCOG-R) and olfactory assessments, we did not include smoking as a factor in this study.

**Cognitive performance over time.** There was no significant association between sex and cognitive decline ( $\chi^2_{(1)} = 0.179$ ,  $P = 0.672$ ) or APOE genotypes and cognitive decline ( $\chi^2_{(1)} = 1.773$ ,  $P = 0.183$ ). Participants who were classified as declined ( $n = 58$ ) performed more poorly on olfactory discrimination ( $t = 3.14$ ;  $df = 286$ ;  $P < 0.05$ ) and on cumulative olfactory performance ( $t = 1.33$ ;  $df = 306$ ;  $P < .05$ )

as measured by Sniffin' Sticks TDI (Table 2). The declined group was older at baseline as compared with non-declined group ( $N = 250$ ;  $t = -2.39$ ;  $df = 306$ ;  $P < 0.05$ ), but did not differ on other demographic variables including education and cognitive functioning as measured by MMSE and CAMCOG-R.

Analysis of the association between the variables indicated that age was negatively associated with baseline CAMCOG-R ( $r = -0.171$ ;  $P < 0.01$ ), Sniffin' Sticks T ( $r = -0.193$ ;  $P < 0.01$ ), D ( $r = -0.260$ ;  $P < 0.01$ ), I ( $r = -0.188$ ;  $P < 0.01$ ) and TDI ( $r = -0.296$ ;  $P < 0.01$ ). The CAMCOG-R was significantly associated with baseline Sniffin' Sticks D ( $r = 0.253$ ;  $P < 0.01$ ), I ( $r = 0.271$ ;  $P < 0.01$ ) and TDI ( $r = 0.228$ ;  $P < 0.01$ ), but not with Sniffin' Sticks T ( $r = -0.006$ ;  $P < 0.92$ ). To control the effects of age on the associations between various variables, partial correlation was performed. Partial correlation analysis indicated that even after controlling for the effects of age, baseline CAMCOG-R was still significantly associated with

**Table 4** Predictors of cognitive decline<sup>a</sup> using Sniffin' Sticks total, composite score in multiple logistic regression analysis ( $N=282$ )<sup>b</sup>

Factors	B	s.e.	Wald	df	P*	OR	95% CI for OR	
							Lower	Lower
Sex	0.095	0.333	0.082	1	0.775	1.100	0.572	2.113
APOE genotypes	-0.442	0.316	1.964	1	0.161	0.642	0.346	1.193
Age at baseline	0.034	0.022	2.296	1	0.130	1.035	0.990	1.081
Education years	-0.008	0.042	0.035	1	0.851	0.992	0.914	1.077
MMSE	-0.158	0.130	1.482	1	0.223	0.852	0.663	1.101
SS-TDI	-0.073	0.033	4.842	1	0.028*	0.930	0.872	0.992

Abbreviations: CAMCOG-R, The Revised Cambridge Cognitive Examination; CI, confidence interval; MMSE, Mini Mental State Examination; OR, odds ratio; SS-TDI, Sniffin' Sticks composite score.

<sup>a</sup>Cognitive decline was considered as a score  $\geq 1$  s.d. below baseline performance on the CAMCOG-R in the last assessment. <sup>b</sup> $N$  was 308; however, only 282 were entered in the actual analysis. \* $P < 0.05$ .

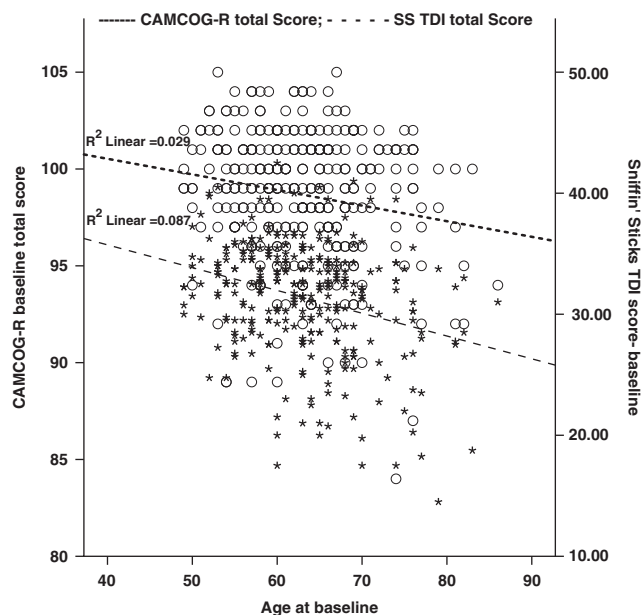
Sniffin' Sticks D ( $r = 0.296$ ,  $P < 0.01$ ), I ( $r = 0.218$ ,  $P < 0.01$ ) and TDI ( $r = 0.277$ ,  $P < 0.01$ ). The association between baseline olfactory functions with cognitive decline after 3 years was further explored using logistic regression analysis (Tables 3 and 4). The 'D' scale was significantly associated with cognitive decline (OR = 0.869;  $P < 0.05$ ; 95% CI = 0.764–0.988); however, neither 'T' (OR = 0.916;  $P < 0.192$ ; 95% CI = 0.803–1.045) nor 'I' (OR = 0.917;  $P < 0.262$ ; 95% CI = 0.787–1.067) was significantly associated with cognitive decline as defined by CAMCOG-R performance in the last assessment (Table 3). Interestingly, baseline cognitive function (as measured by CAMCOG-R) and olfactory abilities showed similar trend of decline (Figure 1). However, other factors including sex, APOE genotype, age at baseline and baseline MMSE score were not significantly associated with cognitive decline in this study.

Logistic regression analysis indicated that higher Sniffin' Sticks TDI (composite) score was associated with lower risk of cognitive decline (OR = 0.872;  $P < 0.05$ ; 95% CI = 0.872–0.992) (Table 4). Other variables, including sex, APOE genotype, age, education and baseline MMSE score, did not indicate a significant predictive value with regards to cognitive decline.

## Discussion

The major novel finding of the current study was that olfactory discrimination (as measured by Sniffin' Sticks D) was a significant predictor of future cognitive decline over a 3-year period. The study also confirmed a series of existing findings, demonstrating that age is associated with both cognitive and olfactory functions. However, there was a significant association between olfactory function and cognitive performance even after controlling for the effects of age, education years, APOE genotype and sex. Three olfactory functions including threshold, discrimination and identification were separately assessed in this study. Interestingly, we found that discrimination was the best predictor of cognitive decline over time. It is important to note that the cognitive changes observed were small and subtle with the study participants performing within the normal range on cognitive measures.

Interestingly, our findings do not support those of other researchers who have reported that impaired olfactory identification is a strong predictor of cognitive impairment.<sup>52–55</sup> Wilson *et al.*<sup>56</sup> further reported that impairment in olfactory identification at baseline was significantly associated with the incidence of mild cognitive impairment. It has been reported



**Figure 1** Dual axis graph showing the association between age, the CAMCOG-R and the Sniffin' Sticks composite score. ○ The Cambridge Cognitive Examination-Revised (CAMCOG-R) total score; \*Sniffin' Sticks TDI (composite score). The dual axes graph with linear trend lines shows the baseline performance on cognitive measure (CAMCOG-R total score) and general olfactory function (as derived from the Sniffin' Sticks composite score). Both the CAMCOG-R (upper line) and SS TDI (below the first line) linear lines show a close trend of decline over time. The mean scores were used for this graph.

that patients who were anosmic at baseline had twice the risk of developing AD compared with controls over a 2-year follow up, and if they had at least one APOE- $\epsilon 4$  allele, the risk increased to 4.9 times.<sup>7</sup> It should be noted that while some researchers report a significant olfactory decline in individuals positive for APOE- $\epsilon 4$  allele,<sup>6</sup> others have failed to find this relationship<sup>8,57</sup> and our current findings are consistent with these latter studies.

The reports on olfactory identification impairments in AD patients and in individuals at higher risk for pathological cognitive decline are not conclusive. That is, impairment in both olfactory identification and threshold have been reported as predictive of cognitive decline and AD.<sup>52,55,58,59</sup> One potential explanation is odor discrimination is primarily impaired in AD individuals while identification problems are

more common among patients with semantic dementia, frontotemporal dementia or corticobasal dementia.<sup>60</sup> Another explanation for our findings is that previous studies have focused primarily, often exclusively, on odor identification and might have not extensively assessed other olfactory domains including threshold and discrimination.<sup>61,62</sup> It has been suggested that olfactory discrimination, similar to identification, requires higher cognitive functions including working memory, judgment and decision making, and its dysfunction may represent generalized cognitive deterioration.<sup>63</sup> Our findings support this interpretation. However, involvement of hippocampal regions in a network underlying odor discrimination<sup>64</sup> increases the probability of a more specific memory-related role in discrimination. Clearly, more studies are needed to clarify the neural regions associated with odor discrimination and cognition. As demonstrated in the present study, controlled, systematic evaluation of the various olfactory domains would contribute to more powerful assessment of the cognitive elements of odor memory and recognition, and thus also possible links to cognitive function.

The association of age with both cognitive<sup>65</sup> and olfactory<sup>25</sup> functions is consistent with the reports indicating that age is a significant covariate. However, the findings reported in this study indicate that the association between cognitive functions and olfactory discrimination and identification is independent of the effects of age. It has been argued that the effects of age on olfaction can be explained by the effects of cognitive decline, not age or age-related hazards affecting olfaction.<sup>66</sup> Age, *per se*, may not account for the so-called age-associated olfactory dysfunction or presbyosmia, as decline in olfactory function with healthy aging seems much lower than previously reported.<sup>67</sup> Given this, our findings support previous reports suggesting that cognitive functions, specifically those with higher verbal component, are significantly associated with olfaction.<sup>66,68</sup>

Another significant finding was the value of measuring multiple domains of olfactory functioning in predicting cognitive decline over 3 years in community-dwelling elderly individuals. Previous reports have mainly focused on the value of measuring specific olfactory domains such as identification in predicting pathological or age-related cognitive decline (for examples, see refs 17,56,69). The study reported here indicated that a comprehensive measure of olfactory function has significant power in predicting cognitive decline in healthy individuals. As various olfactory functions are to some degree reliant on threshold,<sup>70</sup> it is necessary to assess the participants' olfactory acuity before further assessment with more specialized measures such as identification<sup>71</sup> that may then be used for differential diagnosis or screening purposes.

The mechanisms underlying the association between olfaction and cognition have been extensively examined in the last 100 years both by psychophysics and neuroanatomical studies (72,73, for a review of earlier work see Herz and Engen<sup>74</sup>). For example, psychophysics studies have found that olfactory identification was significantly associated with semantic verbal memory, implying that the two may share some cognitive domains.<sup>66,75–77</sup> Neuropathological studies have revealed that brain regions and subsystems involved in

odor information processing, including the olfactory bulb, piriform and orbital prefrontal cortices, have direct projections to perirhinal and entorhinal cortices. These, in turn, have extensive projections to the hippocampus,<sup>78–80</sup> known as the primary brain region involved in initial memory formation,<sup>81–83</sup> and also one of the first regions affected in AD neurodegeneration.<sup>84,85</sup> In addition, the anterior olfactory nucleus and olfactory bulb are the two primary brain regions commonly affected in AD.<sup>86,87</sup> Indeed, change in olfactory identification has been strongly associated with pathological changes in the medial temporal lobe structures.<sup>88</sup> These studies strongly imply a primary role for olfactory dysfunction as an indicator of pathological cognitive decline and dementia.

The current study had some limitations that should be considered when interpreting the findings reported. First, participants were both physically and cognitively within the normal range, at least as far as it can be inferred from the MMSE, CAMCOG-R, years of education and various exclusion criteria applied during the participants recruitment phase. In addition, the participants were divided into declined/non-declined groups based on neuropsychological measures and not a formal diagnostic clinical interview. However, the CAMCOG-R is a comprehensive measure of cognitive function, and while it cannot be considered as a substitute for formal clinical evaluation of the participants, it has demonstrated high sensitivity to cognitive decline.<sup>89,90</sup> Ideally, any future research using this cohort will examine the consistency of the reported results against formal diagnostic criteria. Also, while this study observed a significant association between olfactory D and cognitive decline, it did not examine the underlying mechanisms involved in such a distinctive effect for odor differentiation as compared with other olfactory functions.

In conclusion, the association between the olfactory function and ongoing cognitive decline established in this study provides further evidence in support of the inclusion of a smell assessment alongside other neuropsychological measures in standard health screens for older adults. Many studies have reported olfactory impairments both in preclinical and clinical phases of AD. However, as noted by us and others, the predictive value of olfactory assessment in screening those at a higher risk for AD needs further research<sup>91,92</sup> to improve its sensitivity and specificity.

### Conflict of interest

HRS has performed neuropsychological assessments for Pfizer and previously for Wyeth. His PhD was partially supported by a scholarship from the University of Western Australia. RNM is the founder and owns stock in Alzhyme. SEG is a consultant for, owns stock/options in, and/or has received lecture fees from Amicus, Diagenic, Epix, Smart Pharma and Wyeth/Elan. SEG is also a member of the data safety monitoring board for the Alzheimer Immunotherapy Alliance and holds a grant from Amicus Pharmaceuticals. The findings of this study were partially reported at the Alzheimer's Association International Conference (AA-ICAD), 2011, Paris, France.

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