International Psychogeriatrics (2024), 36:2, 130–141 © The Author(s), 2023. Published by Cambridge University Press on behalf of International Psychogeriatric Association
doi:10.1017/S1041610223000480

The combination of olfactory dysfunction and depression increases the risk of incident dementia in older adults

Shafi Kalam,[1] Katya Numbers,[1] Darren M. Lipnicki,[1] Ben C. P. Lam,[1,2] Henry Brodaty,[1] and Simone Reppermund[1,3]

[1]*Centre for Healthy Brain Ageing (CHeBA), Discipline of Psychiatry & Mental Health, School of Clinical Medicine, Faculty of Medicine & Health, University of New South Wales, Sydney, NSW, Australia*
[2]*School of Psychology and Public Health, La Trobe University, VIC, Australia*
[3]*Department of Developmental Disability Neuropsychiatry (3DN), Discipline of Psychiatry & Mental Health, School of Clinical Medicine, Faculty of Medicine & Health, University of New South Wales, Sydney, NSW, Australia*

ABSTRACT

Objectives: Olfactory dysfunction and depression are common in later life, and both have been presented as risk factors for dementia. Our purpose was to investigate the associations between these two risk factors and determine if they had an additive effect on dementia risk.

Design: Olfactory function was assessed using the Brief Smell Identification Test (BSIT), and depression was classified using a combination of the 15-item Geriatric Depression Scale (GDS) score and current antidepressant use. Cross-sectional associations between depression and olfactory function were examined using correlations. Cox regression analyses were conducted to examine the longitudinal relationship between olfaction and depression and incident dementia across 12-years of follow-up.

Participants: Participants were 780 older adults (aged 70–90 years; 56.5% female) from the Sydney Memory and Ageing Study (MAS) without a diagnosis of dementia at baseline.

Results: Partial correlation revealed a nonsignificant association between baseline depression and olfactory function after accounting for covariates ($r = -.051$, $p = .173$). Cox regression showed that depression at baseline (hazard ratio = 1.706, 95% CI 1.185–2.456, $p = .004$) and lower BSIT scores (HR = .845, 95%CI .789–.905, $p < .001$) were independently associated with a higher risk of incident dementia across 12 years. Entering both predictors together improved the overall predictive power of the model.

Conclusions: Lower olfactory identification scores and depressive symptoms predict incident dementia over 12 years. The use of BSIT scores and depression in conjunction provides a greater ability to predict dementia than either used alone. Assessment of olfactory function and depression screening may provide clinical utility in the early detection of dementia.

Key words: dementia, dementia risk, incident dementia, depression, olfactory dysfunction, affective disorder, cognitive dysfunction, MCI

Introduction

Dementia is a clinical syndrome of cognitive decline which severely interferes with social and individual function. Progression is gradual; individuals with cognitively normal (CN) function may develop mild cognitive impairment (MCI) which advances to dementia over years to decades (Dallora *et al.*, 2020). Dementia affects over 55 million individuals globally, with Alzheimer's disease (AD) being the most common subtype (Nichols, 2022). With an absence of curative pharmacological treatments for dementia, attention has shifted toward early detection and modifiable risk factors, including tobacco use, physical inactivity, metabolic risks, and possibly depression (Almeida *et al.*, 2017).

Late-life depression (LLD) is a potential contributor to dementia; it refers to depression in someone aged above 60 years, regardless of initial onset. Longitudinal studies show that older adults with depression have a 1.71- to 6.75-fold higher risk of developing dementia compared to nondepressed, age-matched controls (Mirza *et al.*, 2016). Effective

Correspondence should be addressed to: Katya Numbers, Centre for Healthy Brain Ageing (CHeBA), School of Clinical Medicine, UNSW Medicine & Health, Discipline of Psychiatry & Mental Health, Level 1, AGSM (Building G27), Gate 11, Botany Street, UNSW Sydney, NSW 2052, Australia. Phone: +61 0459 613 288. Email: k.numbers@unsw.edu.au. Received 08 Dec 2022; revision requested 21 Jan 2023; revised version received 10 Apr 2023; accepted 09 May 2023. First published online 02 June 2023.

treatment for LLD exists, and depression treatment could potentially reduce dementia incidence (Dafsari and Jessen, 2020).

In the other direction, older individuals with existing dementia experience significantly higher incidence of depression (Huang *et al.*, 2011). Moreover, incident dementia correlates strongly with new-onset LLD, but not with a remote history of depression, suggesting that LLD may be a prodrome of dementia, rather than a precipitating factor (Mirza *et al.*, 2016).

Olfaction often deteriorates as part of the normal aging process, affecting around 15–25% of older adults (Choi *et al.*, 2018). The major domains of olfaction include odor identification (OI), threshold, memory, and discrimination (Kotecha *et al.*, 2018). Studies suggest a link between OD and depression (Athanassi *et al.*, 2021; Croy and Hummel, 2017), with evidence of reduced olfactory bulb volume and olfactory function scores in depressed patients (Rottstädt *et al.*, 2018; Taalman *et al.*, 2017; Zucco and Bollini, 2011). There is also evidence that this relationship is reciprocal (Kohli *et al.*, 2016), as some olfactory functions normalize after antidepressant therapy (Rochet *et al.*, 2018). However, only one study has explored the directionality of this relationship longitudinally, finding that older adults with baseline OD were more likely to develop frequent depressive symptoms within 5 or 10 years, but not the reverse (Eliyan *et al.*, 2021).

OD is also a common early symptom of dementia, presenting in 90–100% of individuals with the most common dementia subtypes, namely AD, Parkinson's disease dementia, and frontotemporal dementia (Zou *et al.*, 2016). However, despite the high prevalence of OI impairment in individuals with dementia, assessment of OI is little used in clinical settings (Zou *et al.*, 2016). A review of the literature in 2019 concluded that, among other sensory biomarkers including hearing loss and visual changes, OI impairment most closely predicted conversion to MCI in healthy individuals, proving promising for disease identification in the preclinical stage (Murphy, 2019). Other studies investigating the utility of OI as a potential early marker for dementia pathology found low OI scores could accurately distinguish dementia from CN older participants (Rottstädt *et al.*, 2018) and predict conversion from MCI to dementia (Stanciu *et al.*, 2014).

Research looking at inter-relationships between olfactory function, depression, and dementia is scarce. Chen *et al.* (2021b) found LLD and impaired OI in older adults had an additive effect on symptoms associated with dementia. Individuals with both LLD and impaired OI had more severe structural and functional brain abnormalities compared to those with LLD and intact OI (Chen *et al.*, 2018). However, due to the cross-sectional nature of these studies, they were unable to determine whether the combination of OD and LLD predicted conversion to dementia in CN individuals. Reinforcing this, Murphy (2019) found that OI dysfunction closely paralleled increased reductions in hippocampal and entorhinal cortex volumes, pathologies common to LLD and AD (Byers and Yaffe, 2011; O'Shea *et al.*, 2018).

However, there are studies that found a positive association between impaired OI and dementia without finding a link between OI and LLD (Cha *et al.*, 2022; Marine and Boriana, 2014). It is possible that these incongruent findings are due to heterogeneity in methodology, particularly in the OI measures used (Marine and Boriana, 2014).

Overall, limitations of current studies addressing olfaction, depression, and dementia include small sample sizes and relatively short follow-up periods, resulting in limited statistical power and wide confidence intervals (Pentzek *et al.*, 2007; Zucco and Bollini, 2011). Several studies utilized screening measures of global cognition – such as the Mini-Mental State Exam (MMSE) (Folstein *et al.*, 1975) – to categorize participants into dementia and non-dementia subgroups, rather than expert clinical diagnosis based on comprehensive neuropsychological batteries (Cha *et al.*, 2022; Duff *et al.*, 2002). Some studies employed convenience sampling (Cha *et al.*, 2022; Chen *et al.*, 2018; Chen *et al.*, 2021b), selecting their participants from university hospitals or medical centeres, introducing possible selection bias. Most significantly, the cross-sectional nature of these studies precluded observations regarding dementia incidence in those with OD and/or LLD, limiting investigation of the temporal relationships between these three factors.

While recent cross-sectional research suggests that LLD and impaired OI may have additive contributions to dementia (Chen *et al.*, 2021b), to date, no longitudinal studies investigating this have been published. Furthermore, inconsistent findings in the relationship between OD and LLD make it difficult to ascertain the unique explanatory abilities of OD and depression when predicting incident dementia risk (Stanciu *et al.*, 2014).

To address this gap, this study used data from the Sydney Memory and Ageing Study (MAS). The MAS was a longitudinal study of aging and cognition in a large, well-characterized community-dwelling cohort with a long follow-up time. It also employed validated measures of olfactory function and depressive symptomology; clinical dementia diagnoses were made by expert consensus.

The specific objectives of the current study were as follows:

https://doi.org/10.1017/S1041610223000480 Published online by Cambridge University Press

1. To identify the cross-sectional relationship between olfactory function and depression.
2. To assess the individual and combined effects of baseline olfactory dysfunction and depression on the risk of incident dementia over 12 years of follow-up.

We hypothesized that olfactory function would show an association with depression, and that the ability of these factors to predict dementia would be additive.

Methodology

Participants

Participants were 780 older adults from the MAS, a longitudinal study that followed 1037 community-dwelling older adults (70–90 years) without dementia at baseline, who were recruited between 2005 and 2007 (Wave 1) (Sachdev *et al.*, 2010). Follow-up assessments (Waves 2 onward) were conducted by trained research assistants in 2-year intervals. Wave 1 assessments comprised a medical history interview, questionnaires, a medical examination, and a comprehensive neuropsychological examination designed to assess cognitive domains important for the diagnosis of dementia. Each subsequent wave included neuropsychological testing, a medical history interview, and a medical exam. The final wave of data was collected from the remaining 258 participants at 12-year follow-up in 2018–2020 (Wave 7).

At baseline, participants were required to speak and write English at a level proficient enough to complete a psychometric assessment and consent to participate in the study. Participants were excluded at baseline if they had a previous diagnosis of dementia, psychotic symptoms or a diagnosis of schizophrenia or bipolar disorder, developmental disability, progressive malignancies, or any medical or psychological conditions that might have prevented them from completing assessments (Sachdev *et al.*, 2010). If a participant received a diagnosis of dementia from the study team, after assessment according to The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994), they were also excluded. Further exclusion criteria included an MMSE (Folstein *et al.*, 1975) score of <24 after adjustment for age, education, and non-English-speaking background (NESB) (Anderson *et al.*, 2007).

For the current study, 164 NESB participants were excluded. A further 93 participants were excluded according to specific criteria, including current smokers, participants missing Brief Smell Identification Test (BSIT) data, those with nasopharyngeal cancer or those with reduced sense of smell following surgery. Current smokers were excluded due to their increased risk of OD (Ajmani *et al.*, 2017). NESB participants were excluded as a lack of normative data for this group may have affected the accuracy of their neuropsychological profiles (Anderson *et al.*, 2007; Sachdev *et al.*, 2010).

Measures

Olfaction

Olfactory function, specifically OI, was assessed using the BSIT (Doty *et al.*, 1996). The BSIT is a noninvasive, 12-item test that asks participants to smell an odorant strip and, for each odorant, to identify the corresponding scent from a four-category multiple-choice questionnaire. The participant must choose one of the four options for each odorant and receives a point for every item identified correctly out of the 12 presented. A higher BSIT score relates to better olfactory performance. The BSIT has been found to have good internal reliability and validity (Menon *et al.*, 2013).

Depression

Depressive symptoms were assessed using the 15-item Geriatric Depression Scale (GDS) (Sheikh and Yesavage, 1986), a self-report questionnaire shown to be a valid and reliable measure of depressive symptoms in older adults, including those with MCI (Mitchell *et al.*, 2010). It consists of 15 dichotomous (yes/no) questions and is scored on a 15-point scale, with a greater score indicating greater depressive symptoms.

Global cognition

Global cognitive function was assessed using the MMSE (Folstein *et al.*, 1975), a well-validated test of global cognitive function used to screen for dementia. The MMSE is an 11-question measure that tests five areas of cognitive function, including orientation, attention, recall, and language. It is scored on a 30-point scale with a lower score suggesting a greater degree of cognitive impairment (Anderson *et al.*, 2007).

Framingham cardiovascular risk

Cardiovascular disease (CVD) risk scores were computed according to the Framingham stroke study protocol (D'Agostino *et al.*, 2008). Participants were scored on several known risk factors for cardiovascular incidents, including sex, cholesterol, smoking status, diabetic status, systolic blood pressure, lipoprotein levels, and medication status. These scores were tallied to produce a total CVD risk score.

https://doi.org/10.1017/S1041610223000480 Published online by Cambridge University Press

APOE4

The apolipoprotein E (APOE) genotype is a known risk factor for several diseases. Polymorphic alleles of APOE have been shown to carry different levels of risk of dementia, with the highest risk associated with the e4 allele (APOE4). Each individual carries two copies of the APOE gene (Rasmussen *et al.*, 2018). In this study, those carrying one or two copies of the e4 allele were classified as APOE4 carriers and given a score of 1. Noncarriers received a score of 0.

Clinical diagnosis of dementia

Clinical diagnoses of dementia were made at each wave by a clinical panel comprised of at least three experts, including a neuropsychiatrist, psychogeriatrician, and a neuropsychologist, who discussed all available clinical, neuropsychological, laboratory, and imaging data to reach a diagnosis for participants sent to consensus review. Participants were reviewed if they met the following criteria: MMSE ≤ 24; drop in MMSE ≥ 3 points; impaired activities of daily living not due to physical impairments; elevated scores on an informant-reported scale of instrumental activities of daily living (IADL); or a prior interim diagnosis of dementia.

A diagnosis of dementia was based on DSM-IV criteria (American Psychiatric Association, 1994), which includes the development of one or more cognitive deficit(s) that represent a decline from a previous level of performance that are sufficiently severe as to cause impairment in daily functioning (Bayer IADL scale score ≥ 3.0) (Hindmarch *et al.*, 1998). Participants who had complete neuropsychological test data and did not meet criteria for a dementia diagnosis were classified as "not having dementia" at each wave. Clinical diagnoses were available for Waves 1–7 (12-year follow-up).

Statistical analysis

Baseline demographics

Baseline differences in demographics and test scores for participant groups, such as those with and without dementia, were examined using independent samples t-tests for non-skewed continuous variables, independent samples Mann–Whitney U tests for skewed continuous variables, and chi-square tests for categorical variables.

Correlations among BSIT and depression

Constructing a categorical depression score Due to the highly skewed, nonnormal distribution of GDS scores in the mostly healthy, nondepressed sample at Wave 1, as well as the possible influence of antidepressant use on these scores, a categorical depression variable was constructed according to the following criteria:

- 0 = GDS <5 and not using antidepressants
- 1 = using antidepressants OR GDS ≥ 5 but not both
- 2 = using antidepressants AND GDS ≥ 5

An initial one-way analysis of variance (ANOVA) was performed to examine the association between this tiered depression variable and continuous BSIT scores (see Results). However, due to the small size of the group using antidepressants AND GDS ≥ 5 ($n = 16$), and the nonsignificant differences between the second and third groups, it was condensed to a binary depression variable according to the following:

- 0 = neither depressed nor using antidepressants
- 1 = using antidepressants OR GDS ≥ 5

For the purposes of this study, individuals using antidepressants were classified as depressed regardless of their GDS score. The values "0" and "1" for this variable will correspond to the labels "not depressed" and "depressed."

Correlation analysis The relationship between BSIT and depression was investigated by computing a simple point-biserial correlation and a partial point-biserial correlation controlling for several covariates, including age, sex, education, CVD risk, MMSE score, and *APOE4* carrier status.

Olfaction, depression, and incident dementia

Cox regressions were performed to assess the effects of baseline BSIT scores and baseline depression status on incident dementia across the 12-years of follow-up. Scaled Schoenfeld residuals plots were generated to visually inspect the violation of the proportional hazards assumption. Moreover, interaction effects between survival time and each predictor were examined to further test for the violation of this assumption.

A hierarchical Cox regression model was performed to assess whether the predictive value of BSIT for dementia was above-and-beyond that provided by binary depression. A second model was performed, which adjusted for several relevant covariates including age, sex, education, MMSE, cardiovascular disease risk, and APOE4 carrier status. The first block contained all the covariates, the second block contained the binary depression score, and the third block contained the BSIT scores. Additional analysis exploring whether there was any interaction effect between BSIT scores and

https://doi.org/10.1017/S1041610223000480 Published online by Cambridge University Press

depression status was conducted. Furthermore, we examined a cause-specific hazard model for dementia diagnosis accounting for death. In this model, censoring was specified on the date of death or at the end of follow-up/participant drop-out.

To compare the discrimination ability between depression and BSIT, concordance statistics (c-statistics) (Harrell *et al.*, 1982) were generated to assess how well a model used risk scores to predict time-to-event, acting as a measure of goodness-of-fit (Uno *et al.*, 2011). In particular, we compared a model containing covariates and depression, with another model containing covariates and BSIT. Furthermore, positive redictive value (PPV) and negative predictive value (NPV) were calculated for the binary depression variable, and for olfactory impairment, using the literature standard cutoff of $\leq 8/12$ on the BSIT (El Rassi *et al.*, 2016).

All statistical analyses were performed using IBM SPSS Statistics 26 for Windows (IBM Corporation, 2021). A two-sided p-value $<.05$ was considered statistically significant.

Results

Sample characteristics and baseline comparisons

Table 1 displays group comparisons between English-speaking background participants included and excluded from the study. CVD risk scores were lower and BSIT higher in the included compared to the excluded samples.

By Wave 7, of the 527 participants no longer in the study, 288 (54.6%) passed away, 189 (35.9%) withdrew, and 50 (9.5%) were not assessed for reasons including poor health and geographical relocation. At baseline, participants who remained in the study at the 12-year follow-up were younger, were more educated, and had lower GDS and higher BSIT scores compared to participants who left the study, with a greater proportion of females compared to males. Baseline demographics of participants who remained in the study at Wave 7 versus those that did not are presented in Table 2.

For the current study, we examined group differences between baseline demographics for participants who did ($n = 195$) and did not ($n = 585$) progress to dementia by Wave 7, which are presented in Table 3. At baseline, participants who progressed to dementia were significantly older than those who did not, were more likely to carry *APOE4* alleles, and had lower scores on the BSIT. However, there were no group differences for sex, years of education, MMSE scores, GDS scores, or antidepressant use.

Relationships between B-SIT and depression at baseline

The one-way ANOVA between the three-tier depression variable and BSIT scores revealed no statistically significant difference in BSIT scores between any groups ($F(2, 738) = 1.608$, $p = .201$). However, a downward trend in BSIT scores with each tier of increased depression "severity" was observed ($M = 9.35$, 9.04, 8.75 for the respective depression categories).

A simple correlation between BSIT scores and the binary depression variable at Wave 1 revealed a weakly and negatively associated, but nonsignificant, association ($r = -.060$, $p = .094$). When controlling for age, sex, education, MMSE, CVD risk, and APOE4 carrier status on the relationship between depression and BSIT scores, the association remained nonsignificant ($r = -.051$ $p = .173$).

Prediction of incident dementia

Table 4 displays the results of a hierarchical Cox regression examining the associations between baseline BSIT scores and depression, and risk of dementia over 12 years of follow-up. An unadjusted Cox regression showed that participants classified as depressed at Wave 1 were at a 1.7-fold increased risk of progression to dementia compared to nondepressed participants (HR = 1.742, 95%CI 1.216–2.495, $p = .002$). Adding BSIT scores to the model increased the model fit ($\chi^2 = 37.668$, $p < .001$). Moreover, a lower BSIT score was associated with a higher risk of dementia after adjusting for depression, and a one-unit increase in BSIT score was associated with a 19.6% decrease in the risk of developing dementia (HR = 0.804, 95%CI .754–.857, $p < .001$). Depression remained a significant predictor even after BSIT scores were added to the model (HR = 1.668, 95%CI 1.164–2.389, $p = .005$). No significant interaction effect between depression and BSIT scores was found.

Controlling for covariates did not change the associations. Participants classified as depressed at Wave 1 remained at a 1.7-fold increased risk of progression to dementia compared to nondepressed participants (HR = 1.706, 95%CI 1.185–2.456, $p = .004$). Adding BSIT scores to the model increased the model fit ($\chi^2 = 20.882$, $p < .001$). A lower BSIT score was again associated with a higher risk of dementia, with a one-unit increase in BSIT score associated with a 15.5% reduction in risk of developing dementia (HR = .845, 95%CI .789–.905, $p < .001$). Depression remained a significant predictor even after BSIT scores were added to the model (HR = 1.649, 95%CI 1.145–2.374, $p = .007$). Scaled Schoenfeld residual plots did not indicate any violation of the proportional hazards assumption (see Supplementary

https://doi.org/10.1017/S1041610223000480 Published online by Cambridge University Press

Table 1. Baseline differences between English-speaking background participants included and excluded from the study

VARIABLE	ALL ($N = 873$)	INCLUDED IN STUDY		TEST STATISTIC	*P*-VALUE
		NO ($N = 93$)	YES ($N = 780$)		
Age, years, mean (SD)	78.14 (4.78)	78.18 (4.80)	78.14 (4.78)	$t = .089$	.929
Sex					
Male, *n* (%)	383 (43.9)	44 (47.3)	339 (43.5)	$\chi^2 = .500$	.479
Female, *n* (%)	490 (56.1)	49 (52.7)	441 (56.5)		
Education, years, mean (SD)	11.62 (3.50)	11.05 (3.65)	11.69 (3.48)	$t = -1.677$	.094
MMSE score, median (IQR)	29 (2)	29 (2)	29 (2)	$U = 34{,}912.5$	.542
CVD risk score, mean (SD)	4.1 (3.07)	5.27 (3.45)	3.98 (3.01)	$t = 3.627$	**<.001**
***APOE4* carrier, *n* (%)**	191 (21.9)	23 (24.7)	168 (21.5)	$\chi 2 = .719$	.396
BSIT score, median (IQR)	10 (3)	9 (3)	10 (3)	$U = 30{,}837$	**.013**
GDS score, median (IQR)	2 (2)	2 (2)	2 (2)	$U = 33{,}349$	.459
Antidepressant use, *n* (%)	83 (9.5)	9 (9.7)	74 (9.5)	$\chi^2 = .001$	.977
Depression[a], *n* (%)	149 (17.1)	19 (20.4)	130 (16.7)	$\chi^2 = .801$	.371

MMSE, Mini-Mental State Exam; IQR, interquartile range; CVD, cardiovascular disease; *APOE4,* apolipoprotein e4 allele carrier status; BSIT, Brief Smell Identification Test; GDS, Geriatric Depression Scale.
[a]Depression operationalized as GDS ≥ 5 OR current antidepressant use.

Table 2. Baseline differences between Wave 7 completers and noncompleters

VARIABLE	ALL ($n = 780$)	INCLUDED AT WAVE 7		TEST STATISTIC	*P*-VALUE
		NO ($N = 527$)	YES ($N = 253$)		
Age in years, mean (SD)	78.14 (4.78)	79.24 (4.84)	75.84 (3.73)	$t = 10.798$	**<.001**
Sex					
Males, *n* (%)	339 (43.5)	244 (46.3)	95 (37.5)	$\chi^2 = 5.327$	**.021**
Females, *n* (%)	441 (56.5)	283 (53.7)	158 (62.5)		
Education in years, mean (SD)	11.69 (3.48)	11.44 (3.49)	12.21 (3.40)	$t = -2.919$	**.004**
MMSE score, median (IQR)	29 (2)	29 (2)	29 (2)	$U = 70{,}283.5$	.205
CVD risk score, mean (SD)	3.98 (3.01)	4.11 (2.94)	3.7 (3.14)	$t = 1.765$	.078
APOE4 carrier, *n* (%)	168 (21.5)	111 (21.1)	57 (22.5)	$\chi^2 = .021$	.886
BSIT score, median (IQR)	10 (3)	10 (3)	10 (2)	$U = 80{,}488.5$	**<.001**
GDS score, median (IQR)	2 (2)	2 (2)	1 (1)	$U = 49{,}373.5$	**<.001**
Antidepressant use, *n* (%)	74 (9.5)	53 (10.1)	21 (8.3)	$\chi^2 = .515$	.473
Depression[a], *n* (%)	130 (16.7)	100 (19.0)	30 (11.9)	$\chi^2 = 6.395$	**.011**

SD, standard deviation; MMSE, Mini-Mental State Exam; IQR, interquartile range; CVD, cardiovascular disease; APOE4, apolipoprotein e4 allele; BSIT, Brief Smell Identification Test; GDS, Geriatric Depression Scale.
[a]Depression operationalized as GDS ≥ 5 OR current antidepressant use.

Materials Figure 1), and there was no significant interaction between survival time and each predictor observed.

The cause-specific hazard model accounting for the competing risk of death revealed results similar to those in the main analysis (Supplementary Materials Table 1). Incident dementia was significantly associated with depression (cause-specific HR = 1.612, 95%CI 1.119–2.322, $p = .010$) and lower BSIT scores (csHR = .864, 95%CI .808–.924, $p < .001$) after controlling for covariates.

Concordance statistics were calculated for the two models which used depression or BSIT scores as a predictor of incident dementia. The c-statistic for the model containing covariates and depression was 0.699 (95%CI 0.663–0.734), compared to .723 (95%CI 0.688–0.758) for the model containing the same covariates and BSIT scores. Both c-statistics indicated acceptable model fit and comparable ability in the classification of incident dementia cases. Olfactory impairment had a PPV of 33.0% and NPV of 77.9% for dementia. Depression had a PPV of 28.5% and NPV of 75.6% for dementia.

Discussion

This study first aimed to determine whether olfaction and depression were associated cross-sectionally in a large, community-dwelling sample of older adults

https://doi.org/10.1017/S1041610223000480 Published online by Cambridge University Press

Table 3. Baseline differences between dementia and nondementia groups

VARIABLE	ALL ($n = 780$)	DEMENTIA AT FOLLOW-UP		TEST STATISTIC	*P*-VALUE
		NO ($N = 585$)	YES ($N = 195$)		
Age in years, mean (SD)	78.14 (4.78)	77.87 (4.74)	78.94 (4.80)	$t = -2.721$	**.007**
Sex					
Males, *n* (%)	339 (43.5)	256 (43.8)	83 (42.6)	$\chi^2 = .085$	.770
Females, *n* (%)	441 (56.5)	329 (56.2)	112 (57.4)		
Education in years, mean (SD)	11.69 (3.48)	11.59 (3.38)	12.01 (3.75)	$t = -1.488$	.137
MMSE score, median (IQR)	29 (2)	29 (2)	29 (2)	$U = 53{,}365$	.164
CVD risk score, mean (SD)	3.98 (3.01)	3.98 (2.97)	3.98 (3.12)	$t = -0.006$	.995
APOE4 carrier, *n* (%)	168 (21.5)	106 (18.1)	62 (31.8)	$\chi^2 = 12.928$	**<.001**
BSIT score, median (IQR)	10 (3)	10 (2)	9 (3)	$U = 49{,}874.5$	**.007**
GDS score, median (IQR)	2 (2)	2 (2)	2 (2)	$U = 54{,}767.5$	.479
Antidepressant use, *n* (%)	74 (9.5)	51 (8.7)	23 (11.8)	$\chi^2 = 1.681$	.195
Depression[a], *n* (%)	130 (16.7)	93 (15.9)	37 (19)	$\chi^2 = .940$	.332
Time to diagnosis in years, median (IQR)			7.23 (4.54)		

SD, standard deviation; MMSE, Mini-Mental State Exam; IQR, interquartile range; CVD, cardiovascular disease; APOE4, apolipoprotein e4 allele; BSIT, Brief Smell Identification Test; GDS, Geriatric Depression Scale.
[a]Depression operationalized as GDS ≥ 5 OR current antidepressant use.

Table 4. Hierarchical Cox regression results

A – Unadjusted Cox regression examining relationship between depression and BSIT scores with risk of incident dementia

BLOCK	VARIABLE[A]	*P*-VALUE	HR	95% CL	
				LOWER	UPPER
Step 1	Depression[b]	**.002**	1.742	1.216	2.495
Step 2	BSIT	**<.001**	.804	.754	.857
B – Cox regression controlling for covariates					
Step 1	Age	**<.001**	1.134	1.100	1.168
	Sex	.939	.988	.731	1.335
	Education	.355	1.021	.977	1.067
	MMSE	.014	.872	.783	.972
	CVD risk	.607	1.013	.964	1.064
	APOE4 carrier status	<.001	2.002	1.468	2.727
Step 2	Depression[b]	**.004**	1.706	1.185	2.456
Step 3	BSIT	**<.001**	.845	.789	.905

MMSE, Mini-Mental State Exam; CVD, cardiovascular disease; APOE4, apolipoprotein e4 allele; BSIT, Brief Smell Identification Test; GDS, Geriatric Depression Scale.
[a]df = 1 for all variables.
[b]Depression operationalized as GDS ≥ 5 OR current antidepressant use.
Bolded to denote statistical significance at $p < 0.05$.

without dementia. Next, the study aimed to determine whether olfaction or depression were individually stronger predictors of incident dementia (Almeida *et al.*, 2017; Murphy, 2019; Pacyna *et al.*, 2023), and whether the predictive value improved when both were included in the same model.

Although this study hypothesized that olfactory performance and depression would be correlated cross-sectionally, our results did not support this. While this finding runs contrary to a number of other studies (Athanassi *et al.*, 2021; Chen *et al.*, 2021a; Kohli *et al.*, 2016; Taalman *et al.*, 2017), it is not entirely unusual (Rochet *et al.*, 2018), with multiple studies finding that the depressed individuals maintain similar olfactory function to a healthy cohort (Marine and Boriana, 2014; Pentzek *et al.*, 2007). Scinska *et al.* (2008) were unable to find a correlation between GDS and olfactory identification scores in non-demented older adults, whereas Economou (2003) found no association between BSIT scores and scores on a depression inventory. Moreover, Rossi *et al.* (2015) observed no difference

https://doi.org/10.1017/S1041610223000480 Published online by Cambridge University Press

in OI scores between dementia patients with and without depression. Heterogeneity in definitions for "depression" and "olfactory dysfunction" may explain this discrepancy. Chen *et al.* (2021a) demonstrated that depression scores were higher than controls in anosmic, but not hyposmic patients. Meanwhile, Khil *et al.* (2016) found OI impairment only in patients with major depressive disorder with high symptom severity. Other studies using a clinical diagnosis of depression rather than depression inventory scores produce similar results (Croy and Hummel, 2017), suggesting that a strong association may only emerge when using more severe disease measures. In contrast, participants in the current study were relatively healthy and nondepressed, with a median GDS score of 2/15 and a median BSIT score of 10/12. The absence of a cross-sectional correlation also points away from LLD and OD co-occurring as a prodrome in the early stages of dementia (Singh-Manoux *et al.*, 2017). Future studies following BSIT performance and depression across several time points might observe a more marked correlation closer to dementia diagnosis, or as participants develop more severe olfactory or depressive symptoms.

Furthermore, this study found that olfactory function at baseline was significantly different in the group that progressed to dementia (median BSIT score of 9/12) compared to the group which did not progress to dementia (10/12) (Table 3). Our findings align with the literature demonstrating that those with lower scores on olfactory function tests such as the BSIT have a higher risk of progressing to dementia (Adams *et al.*, 2018; Pacyna *et al.* 2023). This accelerated olfactory deterioration may be due to involvement of the olfactory bulb even in the preclinical stage of dementia pathology (Alves *et al.*, 2014). Detecting subtle olfactory impairment may provide clinicians with early insight into disease risk, although the small median difference of 1 point in our findings may not be clinically practicable. Adams *et al.* (2018) used an olfactory function test to predict dementia in CN, community-dwelling older adults after 5 years and established a PPV of 9%. Adams suggested that this value was due to low disease prevalence and would improve with a longer follow-up period. With 12 years of follow-up, the current study demonstrated that impaired olfaction (using a cutoff of BSIT $\leq$ 8) had a PPV of 33% and an NPV of 77.9%, with a median time of 7 years to dementia conversion (Table 1). Similarly, depression had a PPV of 28.5% and an NPV of 75.6%. In context, better results are achieved using blood/cerebrospinal fluid biomarkers such as p-tau181 (PPV = 50%, NPV = 87%). However, it must be noted that these fluid biomarkers are more invasive and only effective in predicting Alzheimer's dementia (Chatterjee *et al.*, 2022). Thus, as binary variables, olfactory dysfunction and depression may best be used as broad, noninvasive screening tools to assist in predicting dementia many years in advance.

Importantly, this study found that lower BSIT scores and having depression were significant independent predictors of progression to dementia longitudinally, in line with other longitudinal findings (Adams *et al.*, 2018; Chen *et al.*, 2021b; Pacyna *et al.* 2023). This study adds to the literature by demonstrating that their predictive abilities are unique and provide additional predictive value when used in combination, which no other longitudinal study has investigated (Chen *et al.*, 2021b). Stanciu *et al.* (2014) suggested that the association between OD and dementia may be due to shared variance with depressive symptoms. However, our study demonstrates that both variables remained unique significant predictors in the combined model ($p < .001$). Moreover, given the number of participant deaths throughout the duration of the study, the possibility of death as a competing risk was considered. A cause-specific competing risk model was tested, which revealed similar patterns to the primary analysis. Thus, mortality as a competing risk does not significantly alter the above conclusions.

Furthermore, no longitudinal studies have compared the predictive abilities of depression and OD for dementia (Bergmann *et al.*, 2021), and an aim of this study was to determine whether one of these had better diagnostic ability. The concordance statistics for the final two-block models were similar, and the overlap in their confidence intervals suggests that their diagnostic abilities do not differ significantly. Thus, there is no clear evidence for either olfactory dysfunction or depression (as measured in this study) as the superior predictor of dementia. Clinically, these findings are important, suggesting that olfaction and depression screening may best be used in conjunction for discriminating individuals at a greater risk of developing dementia early in the disease course.

The BSIT has limitations such as being single use (Doty *et al.*, 1996; El Rassi *et al.*, 2016) and potentially costly to implement in the growing over-60 population. Targeting olfactory screening toward higher risk older adults using medical history factors may improve the PPV and reduce costs (Adams *et al.*, 2018). Despite these costs, the BSIT is time-efficient, can be sent by mail, and is significantly cheaper than current dementia biomarkers, including cerebrospinal fluid sampling and neuroimaging (Pacyna *et al.* 2023; Wittenberg *et al.*, 2019). Our descriptive results show that a single administration of the BSIT at Wave 1 was sufficient to distinguish conversion to dementia, which occurred on average 7 years later (Table 3). Thus, the value provided by potential early detection of dementia by even

https://doi.org/10.1017/S1041610223000480 Published online by Cambridge University Press

infrequent review of olfactory function would likely outweigh the costs of administration. Sensitivity and specificity analyses in an older adult population, using multiple age-normed BSIT cutoff scores to predict dementia, would lay the groundwork for the use of olfactory function testing for dementia screening clinically.

Our findings also show the value of assessing depressive symptoms in older adults. The 15-item GDS is resource-efficient; capturing GDS scores and recording antidepressant medication is relatively simple to perform regularly, allowing for monitoring of depressive symptoms over time and more targeted early intervention. Beyond its predictive value, future research may again focus on the directionality of the relationship between dementia and depression, and whether treatment of depression could slow or even reverse cognitive decline.

This study has limitations, including a baseline cohort that was generally healthy, well-educated, and largely of White European ancestry (94%), limiting generalizability. Moreover, while the literature broadly supports depression as a predictor or driver of dementia (Byers and Yaffe, 2011), our depression measure consisted of antidepressant use and a single GDS score, rather than a clinical diagnosis of depression. Furthermore, the depression measure was condensed to a binary variable due to the high skew of the GDS scores in the relatively nondepressed baseline cohort. Moreover, all participants using antidepressants were categorized as depressed in order to account for potential depression-in-remission. However, it is possible that some participants were using antidepressants for off-label uses (Wong *et al.*, 2016). Another limitation of measuring BSIT performance and depression at one time point is the inability to examine their change. Repeated assessments of OI and depression would allow analysis of how the rate and severity of deterioration in these factors influences the risk of dementia (Kim *et al.*, 2019). Moreover, a more tiered outcome variable – classifying individuals as CN, MCI, or dementia – could be used to observe the trajectory of cognitive decline rather than just dementia incidence.

Strengths of this study include the large, well-characterized cohort of community-dwelling older adults, with comprehensive records of their physiological health markers and neuropsychological data. The study controlled for highly influential covariates such as APOE4 gene status, which has been strongly linked to dementia incidence (Rasmussen *et al.*, 2018) and cardiovascular risk scores. This improves confidence in our findings as dementia is a multifactorial condition (Dallora *et al.*, 2020). As dementia is a slowly progressing disease, (Dallora *et al.*, 2020) the long 12-year study period allowed us to follow many participants who developed dementia, providing more power to our analyses. Frequent follow-up allowed us to obtain clinical data from participants who were censored before Wave 7, enabling us to conduct survival analyses. Additionally, between the English-speaking background participants included and excluded from the study, there appeared to be no unintended group differences. Those excluded for smoking, nasopharyngeal cancer, and post-surgical anosmia were expected to have higher CVD risk and lower BSIT scores. None of the other variables differed significantly between groups.

Furthermore, the measures used in this study, including the BSIT and GDS-15, were selected for their high validity and ease of administration (Menon *et al.*, 2013; Mitchell *et al.*, 2010). Dichotomizing the depression variable allowed the study to account for antidepressant use, a factor expected to affect GDS scores (Almeida *et al.*, 2017). Point-biserial partial correlations allowed for examining associations between depression and olfactory function without assuming the directionality of the relationship (Demirtas and Hedeker, 2016). Additionally, Cox regression survival analysis was used to investigate the impact of depression and olfactory function on dementia risk as it allowed for a more granular analysis of incidence across all waves and accounted for those who had been censored before Wave 7 (Goerdten *et al.*, 2020). Another strength is the robust method of determining dementia – through a combination of multiple well-validated neuropsychological assessments and consensus diagnosis from an expert panel. Future studies may consider a similarly rigorous approach, particularly using clinical diagnosis, to assess depression.

Conclusion

In conclusion, the present study has shed light on the potential for depression and OI to improve early prediction of dementia. While these associations have been examined previously, the current study addresses the absence of a rigorously designed longitudinal cohort study in which direct evidence of neurodegeneration can be observed in individuals with OI and/or depression (Chen *et al.*, 2018; Chen *et al.*, 2021b; Petersen, *et al.*, 2021). These findings have important clinical implications. In particular, that the use of an olfactory function measure in conjunction with depressive symptomatology can predict progression to dementia over 12 years better than either depression or olfactory impairment alone.

https://doi.org/10.1017/S1041610223000480 Published online by Cambridge University Press

Conflict of interest

The authors declare none.

Acknowledgments

First and foremost, we thank the MAS participants for their enthusiastic support. We also thank the CHeBA Co-Directors, Henry Brodaty and Perminder Sachdev, the MAS research assistants, the CHeBA Data Manager, the Centre Manager, and the CHeBA Communications team. I would like to extend my thanks to my supervisors Dr Simone Reppermund, Dr Katya Numbers, and Dr Darren M. Lipnicki for their support and guidance throughout this project; it goes without saying that I could not have done this without their help. I'm also tremendously grateful to Dr Ben Lam and Saly Mahalingam for their time, generosity, and expertise in all things statistical.

Ethics statement

Written informed consent from participants was obtained. Approval for the current study was obtained from the Human Research Ethics Committee of the University of New South Wales (HC: 05037, 09382, 14327, 190962).

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1041610223000480.

References

Adams, D. R., Kern, D. W., Wroblewski, K. E., McClintock, M. K., Dale, W. and Pinto, J. M. (2018). Olfactory dysfunction predicts subsequent dementia in older U.S. adults. *Journal of the American Geriatrics Society*, 66, 140–144.

Ajmani, G. S., Suh, H. H., Wroblewski, K. E. and Pinto, J. M. (2017). Smoking and olfactory dysfunction: a systematic literature review and meta-analysis. *Laryngoscope*, 127, 1753–1761.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders: DSM-IV*, Washington, DC: American Psychiatric Association.

Almeida, O. P., Hankey, G. J., Yeap, B. B., Golledge, J. and Flicker, L. (2017). Depression as a modifiable factor to decrease the risk of dementia. *Translational Psychiatry*, 7, e1117–e1117.

Alves, J., Petrosyan, A. and Magalhães, R. (2014). Olfactory dysfunction in dementia. *World Journal of Clinical Cases*, 2, 661–667.

Anderson, T. M., Sachdev, P. S., Brodaty, H., Trollor, J. N. and Andrews, G. (2007). Effects of sociodemographic and health variables on mini-mental state exam scores in older Australians. *The American Journal of Geriatric Psychiatry*, 15, 467–476.

Athanassi, A., Dorado Doncel, R., Bath, K. G. and Mandairon, N. (2021). Relationship between depression and olfactory sensory function: a review. *Chemical Senses*, 46, bjab044.

Bergmann, C., Stögmann, E. and Lehrner, J. (2021). Depressive symptoms and olfactory function in patients with subjective cognitive decline, mild cognitive impairment and alzheimer's disease. *Brain Disorders*, 2, 100014.

Byers, A. L. and Yaffe, K. (2011). Depression and risk of developing dementia. *Nature Reviews Neurology*, 7, 323–331.

Cha, H., Kim, S. and Son, Y. (2022). Associations between cognitive function, depression, and olfactory function in elderly people with dementia in Korea. *Frontiers in Aging Neuroscience*, 13, 799897.

Chatterjee, P. *et al.* (2022). Diagnostic and prognostic plasma biomarkers for preclinical Alzheimer's disease. *Alzheimer's & Dementia*, 18, 1141–1154.

Chen, B. *et al.* (2021a). Symptoms of depression in patients with chemosensory disorders. *ORL*, 83, 135–143.

Chen, B. *et al.* (2018). Cognitive impairment and structural abnormalities in late life depression with olfactory identification impairment: an Alzheimer's disease-like pattern. *The International Journal of Neuropsychopharmacology*, 21, 640–648.

Chen, B. *et al.* (2021b). The additive effect of late-life depression and olfactory dysfunction on the risk of dementia was mediated by hypersynchronization of the hippocampus/fusiform gyrus. *Translational Psychiatry*, 11, 172.

Choi, J. S., Hur, K., Chow, M., Shen, J. and Wrobel, B. (2018). Olfactory dysfunction and cognition among older adults in the United States. *International Forum of Allergy & Rhinology*, 8, 648–654.

Croy, I. and Hummel, T. (2017). Olfaction as a marker for depression. *Journal of Neurology*, 264, 631–638.

D'Agostino, R. B., Sr. *et al.* (2008). General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*, 117, 743–753.

Dafsari, F. S. and Jessen, F. (2020). Depression—an underrecognized target for prevention of dementia in Alzheimer's disease. *Translational Psychiatry*, 10, 160.

Dallora, A. L., Minku, L., Mendes, E., Rennemark, M., Anderberg, P. and Sanmartin Berglund, J. (2020). Multifactorial 10-year prior diagnosis prediction model of dementia. *International Journal of Environmental Research and Public Health*, 17, 6674.

Demirtas, H. and Hedeker, D. (2016). Computing the point-biserial correlation under any underlying continuous distribution. *Communications in Statistics-Simulation and Computation*, 45, 2744–2751.

Doty, R. L., Marcus, A. and Lee, W. W. (1996). Development of the 12-item Cross-Cultural Smell Identification Test (CC-SIT). *Laryngoscope*, 106, 353–356.

Duff, K., McCaffrey, R. J. and Solomon, G. S. (2002). The Pocket Smell Test: successfully discriminating probable Alzheimer's dementia from vascular dementia and major

depression. *Journal of Neuropsychiatry and Clinical Neurosciences*, 14, 197–201.

Economou, A. (2003). Olfactory identification in elderly Greek people in relation to memory and attention measures. *Archives of Gerontology and Geriatrics*, 37, 119–130.

El Rassi, E. *et al.* (2016). Sensitivity analysis and diagnostic accuracy of the Brief Smell Identification Test in patients with chronic rhinosinusitis. *International Forum of Allergy & Rhinology*, 6, 287–292.

Eliyan, Y., Wroblewski, K. E., McClintock, M. K. and Pinto, J. M. (2021). Olfactory dysfunction predicts the development of depression in older US adults. *Chemical Senses*, 46, bjaa075.

Folstein, M. F., Folstein, S. E. and McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research*, 12, 189–198.

Goerdten, J., Carrière, I. and Muniz-Terrera, G. (2020). Comparison of Cox proportional hazards regression and generalized Cox regression models applied in dementia risk prediction. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, 6, e12041.

Harrell, F. E., Jr, Califf, R. M., Pryor, D. B., Lee, K. L. and Rosati, R. A. (1982). Evaluating the yield of medical tests. *JAMA*, 247, 2543–2546.

Hindmarch, I., Lehfeld, H., de Jongh, P. and Erzigkeit, H. (1998). The Bayer Activities of Daily Living Scale (B-ADL). *Dementia and Geriatric Cognitive Disorders*, 9, 20–26.

Huang, C. Q., Wang, Z. R., Li, Y. H., Xie, Y. Z. and Liu, Q. X. (2011). Cognitive function and risk for depression in old age: a meta-analysis of published literature. *International Psychogeriatrics*, 23, 516–525.

IBM Corporation (2021). *IBM SPSS Statistics for Windows, Version 28.0*, Armonk, NY: IBM Corporation.

Khil, L., Rahe, C., Wellmann, J., Baune, B. T., Wersching, H. and Berger, K. (2016). Association between major depressive disorder and odor identification impairment. *Journal of Affective Disorders*, 203, 332–338.

Kim, W. J. *et al.* (2019). Cox proportional hazard regression versus a deep learning algorithm in the prediction of dementia: an analysis based on periodic health examination. *JMIR Medical Informatics*, 7, e13139.

Kohli, P., Soler, Z. M., Nguyen, S. A., Muus, J. S. and Schlosser, R. J. (2016). The association between olfaction and depression: a systematic review. *Chemical Senses*, 41, 479–486.

Kotecha, A. M., Corrêa, A. D. C., Fisher, K. M. and Rushworth, J. V. (2018). Olfactory dysfunction as a global biomarker for sniffing out Alzheimer's disease: a meta-analysis. *Biosensors*, 8, 41.

Marine, N. and Boriana, A. (2014). Olfactory markers of depression and Alzheimer's disease. *Neuroscience & Biobehavioral Reviews*, 45, 262–270.

Menon, C., Westervelt, H. J., Jahn, D. R., Dressel, J. A. and O'Bryant, S. E. (2013). Normative performance on the Brief Smell Identification Test (BSIT) in a multi-ethnic bilingual cohort: a Project FRONTIER study. *Clinical Neuropsychologist*, 27, 946–961.

Mirza, S. S. *et al.* (2016). 10-year trajectories of depressive symptoms and risk of dementia: a population-based study. *Lancet Psychiatry*, 3, 628–635.

Mitchell, A. J., Bird, V., Rizzo, M. and Meader, N. (2010). Diagnostic validity and added value of the geriatric depression scale for depression in primary care: a meta-analysis of GDS30 and GDS15. *Journal of Affective Disorders*, 125, 10–17.

Murphy, C. (2019). Olfactory and other sensory impairments in Alzheimer disease. *Nature Reviews Neurology*, 15, 11–24.

Nichols, E. (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *The Lancet*, 7, e105–e125.

O'Shea, D. M. *et al.* (2018). Depressive symptom dimensions and their association with hippocampal and entorhinal cortex volumes in community dwelling older adults. *Frontiers in Aging Neuroscience*, 10, 40–40.

Pacyna, R. R., Han, S. D., Wroblewski, K. E., McClintock, M. K. and Pinto, J. M. (2023). Rapid olfactory decline during aging predicts dementia and GMV loss in AD brain regions. *Alzheimer's & Dementia*, 19, 1479–1490. https://doi.org/10.1002/alz.12717.

Pentzek, M., Grass-Kapanke, B. and Ihl, R. (2007). Odor identification in Alzheimer's disease and depression. *Aging Clinical and Experimental Research*, 19, 255–258.

Petersen, M., Bresolin, M. and Monteiro, A. (2021). 521 - The link between olfactory dysfunction and dementia: the road so far. *International Psychogeriatrics*, 33, 69–70.

Rasmussen, K. L., Tybjærg-Hansen, A., Nordestgaard, B. G. and Frikke-Schmidt, R. (2018). Absolute 10-year risk of dementia by age, sex and APOE genotype: a population-based cohort study. *Canadian Medical Association Journal*, 190, e1033–e1041.

Rochet, M., El-Hage, W., Richa, S., Kazour, F. and Atanasova, B. (2018). Depression, olfaction, and quality of life: a mutual relationship. *Brain Sciences*, 8, 80.

Rossi, M. *et al.* (2015). Olfactory dysfunction evaluation is not affected by comorbid depression in Parkinson's disease. *Movement Disorders*, 30, 1275–1279.

Rottstädt, F. *et al.* (2018). Reduced olfactory bulb volume in depression—a structural moderator analysis. *Human Brain Mapping*, 39, 2573–2582.

Sachdev, P. S. *et al.* (2010). The Sydney Memory and Ageing Study (MAS): methodology and baseline medical and neuropsychiatric characteristics of an elderly epidemiological non-demented cohort of Australians aged 70-90 years. *International Psychogeriatrics*, 22, 1248–1264.

Scinska, A. *et al.* (2008). Depressive symptoms and olfactory function in older adults. *Psychiatry and Clinical Neurosciences*, 62, 450–456.

Sheikh, J. I. and Yesavage, J. A. (1986). Geriatric Depression Scale (GDS): recent evidence and development of a shorter version. *Clinical Gerontologist: The Journal of Aging and Mental Health*, 5, 165–173.

Singh-Manoux, A. *et al.* (2017). Trajectories of depressive symptoms before diagnosis of dementia: a 28-year follow-up study. *JAMA Psychiatry*, 74, 712–718.

Stanciu, I., Larsson, M., Nordin, S., Adolfsson, R., Nilsson, L. G. and Olofsson, J. K. (2014). Olfactory impairment and subjective olfactory complaints independently predict conversion to dementia: a longitudinal, population-based study. *Journal of the International Neuropsychological Society*, 20, 209–217.

https://doi.org/10.1017/S1041610223000480 Published online by Cambridge University Press

Taalman, H., Wallace, C. and Milev, R. (2017). Olfactory functioning and depression: a systematic review. *Frontiers in Psychiatry*, 8, 190–190.

Uno, H., Cai, T., Pencina, M. J., D'Agostino, R. B. and Wei, L. J. (2011). On the C-statistics for evaluating overall adequacy of risk prediction procedures with censored survival data. *Statistics in Medicine*, 30, 1105–1117.

Wittenberg, R., Knapp, M., Karagiannidou, M., Dickson, J. and Schott, J. M. (2019). Economic impacts of introducing diagnostics for mild cognitive impairment Alzheimer's disease patients. *Alzheimer's & Dementia: Translational Research & Clinical Interventions*, 5, 382–387.

Wong, J., Motulsky, A., Eguale, T., Buckeridge, D. L., Abrahamowicz, M. and Tamblyn, R. (2016). Treatment indications for antidepressants prescribed in primary care in Quebec, Canada, 2006-2015. *JAMA*, 315, 2230–2232.

Zou, Y.-M., Lu, D., Liu, L.-P., Zhang, H.-H. and Zhou, Y.-Y. (2016). Olfactory dysfunction in Alzheimer's disease. *Neuropsychiatric Disease and Treatment*, 12, 869–875.

Zucco, G. M. and Bollini, F. (2011). Odour recognition memory and odour identification in patients with mild and severe major depressive disorders. *Psychiatry Research*, 190, 217–220.

https://doi.org/10.1017/S1041610223000480 Published online by Cambridge University Press