






# Sleep-disordered breathing was associated with lower health-related quality of life and cognitive function in a cross-sectional study of older adults

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## Abstract

**Background and objective:** The clinical significance of sleep-disordered breathing (SDB) in older age is uncertain. This study determined the prevalence and associations of SDB with mood, daytime sleepiness, quality of life (QOL) and cognition in a relatively healthy older Australian cohort.

**Methods:** A cross-sectional analysis was conducted from the Study of Neurocognitive Outcomes, Radiological and retinal Effects of Aspirin in Sleep Apnoea. Participants completed an unattended limited channel sleep study to measure the oxygen desaturation index (ODI) to define mild (ODI 5–15) and moderate/severe (ODI  $\geq$  15) SDB, the Centre for Epidemiological Studies Scale, the Epworth Sleepiness Scale, the 12-item Short-Form for QOL and neuropsychological tests.

**Results:** Of the 1399 participants (mean age 74.0 years), 36% (273 of 753) of men and 25% (164 of 646) of women had moderate/severe SDB. SDB was associated with lower physical health-related QOL (mild SDB: beta coefficient [ $\beta$ ]  $-2.5$ , 95% CI  $-3.6$  to  $-1.3$ ,  $p < 0.001$ ; moderate/severe SDB:  $\beta -1.8$ , 95% CI  $-3.0$  to  $-0.6$ ,  $p = 0.005$ ) and

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with lower global composite cognition (mild SDB:  $\beta$   $-0.1$ , 95% CI  $-0.2$  to  $0.0$ ,  $p = 0.022$ ; moderate/severe SDB:  $\beta$   $-0.1$ , 95% CI  $-0.2$  to  $0.0$ ,  $p = 0.032$ ) compared to no SDB. SDB was not associated with daytime sleepiness nor depression.

**Conclusion:** SDB was associated with lower physical health-related quality of life and cognitive function. Given the high prevalence of SDB in older age, assessing QOL and cognition may better delineate subgroups requiring further management, and provide useful treatment target measures for this age group.

#### KEYWORDS

ageing, cognition, dementia, quality of life, sleep-disordered breathing

## INTRODUCTION

Sleep-disordered breathing (SDB) refers to temporary reductions (hypopnoeas) and cessations (apnoeas) in respiration that occur during sleep, leading to intermittent de-oxygenation, intra-thoracic pressure swings, sympathetic activation and imperceptible arousals from sleep.<sup>1</sup> In middle-age, these mechanisms underpin the commonly observed associations of SDB with cardiovascular<sup>2</sup> and cerebrovascular diseases,<sup>3</sup> daytime sleepiness,<sup>4</sup> depression<sup>5</sup> and reduced quality of life (QOL).<sup>6</sup>

SDB prevalence increases with age<sup>7</sup> and is frequently detected in at least 50% of individuals aged 70 years and above.<sup>8–10</sup> The clinical significance remains uncertain, possibly without the same impacts on daytime sleepiness,<sup>11</sup> QOL<sup>6</sup> or mortality risk<sup>12</sup> as observed in the middle-aged. Dementia, however, is a significant health issue for older people, and there are several mechanisms by which SDB may potentiate the neurodegenerative processes that lead to dementia due to Alzheimer's disease (AD) and/or vascular pathologies.<sup>13–17</sup> SDB has been linked to an increased risk of both impaired cognitive function, which usually precedes dementia, and of dementia itself, albeit inconsistently.<sup>18–22</sup>

Resolving the clinical implications of SDB in older age is thus imperative. The Study of Neurocognitive Outcomes, Radiological and retinal Effects of Aspirin in Sleep Apnoea (SNORE-ASA) is investigating the association of SDB with cognitive decline, and with neuroimaging and retinal biomarkers of vascular pathology. The SNORE-ASA will also determine to what extent aspirin, with anti-platelet and anti-inflammatory properties, attenuates cognitive and imaging biomarker changes over 3 years in a cohort without major cognitive impairments.<sup>23</sup> This study outlines the gender-specific prevalence of SDB in this large older community-based cohort and investigates the associations of SDB with QOL, mood, daytime sleepiness and cognition.

## METHODS

### Study design

A cross-sectional analysis of baseline data from the ASPirin in Reducing Events in the Elderly (ASPREE) and SNORE-ASA studies was conducted. The ASPREE study was a

### SUMMARY AT A GLANCE

The clinical implications for sleep-disordered breathing (SDB) in older age remain uncertain. This study of healthy community-dwelling older Australians reports significant associations between SDB and a lower physical health-related quality of life, in contrast to other studies of SDB in older age, and between SDB and lower cognitive function.

multicentre, randomized, placebo-controlled, double-blind clinical trial conducted in Australia and the United States determining the effects of daily aspirin 100 mg on dementia-free and disability-free survival.<sup>24,25</sup> The SNORE-ASA sub-study was offered in Australia only.

### Study participants

The ASPREE participants, all aged 70+ years, were recruited, from March 2010 to November 2014, through general practitioners. Exclusion criteria were a history of occlusive cardiovascular disease (CVD), atrial fibrillation (AF), heart failure, uncontrolled hypertension, current anti-thrombotic therapy, anaemia, dementia, a score of  $<78/100$  on the Modified Mini-Mental State Examination (3MS) or physical disability.<sup>24</sup>

The SNORE-ASA participation was offered during ASPREE clinical trial randomization visits in Victoria, South Australia and the Australian Capital Territory from March 2012 to November 2014. Additional exclusion criteria were a known diagnosis of obstructive sleep apnoea (OSA) and/or current treatment with continuous positive airway pressure (CPAP) therapy.<sup>23</sup>

### Sleep measures

A limited channel, unattended home sleep study was obtained using the ApneaLink Plus device (Resmed Inc, Sydney, Australia), containing a nasal cannula to detect hypopnoeas and apnoeas, a pulse oximeter and thoracic belt

with pneumatic strain gauge to detect respiratory effort.<sup>26</sup> The output was reviewed by one of the three sleep medicine physicians (MTN, GH and FJO). A minimum trace duration of 4 hours, free of significant artefact, was required.

SDB was defined using the oxygen desaturation index 3% (ODI)—a count of how many times per hour the baseline oxygen saturation level drops by a minimum of 3%. SDB severity categories were based on standard cut-offs: mild (ODI 5 to <15), moderate (ODI 15 to <30) and severe (ODI  $\geq$  30).<sup>10</sup> For multivariable analyses, moderate and severe SDB (based on an ODI  $\geq$  15) were combined.<sup>9,27</sup>

The second sleep exposure of interest was the OSA syndrome, defined as an ODI  $\geq$  5 and daytime sleepiness, as defined by an Epworth Sleepiness Scale<sup>28</sup> score of  $\geq$ 10 (range 0–24). The lowest and average oxygen saturation measures were also presented as descriptors of the study cohort.

## Study outcomes

The 10-question/30-point Center for Epidemiological Studies-Depression Scale,<sup>29</sup> with a cut-off of  $\geq$ 8, indicated depression.<sup>30</sup> The Medical Outcomes Study Short Form 12 assessed QOL with two summary scores: the physical health component score (PCS) and mental health component score (MCS) (scores 0–100, median 50, SD 10, with higher scores indicating better QOL).<sup>31</sup>

Cognition was assessed by the 3MS (global cognition, maximal score 100)<sup>32</sup>; the Hopkins Verbal Learning Test-Revised delayed recall (HVLT-R) (episodic memory, maximal score 12)<sup>33</sup>; the single letter Controlled Oral Word Association Test (COWAT-F) (executive function, higher score indicating better performance)<sup>34</sup>; and the Symbol Digit Modalities Test (SDMT) (for psychomotor speed, maximal score 110).<sup>35</sup> A composite of these tests using standardized z-scores was derived.

## Statistical analysis

Participant characteristics were described separately for men and women given known differences in gender-specific SDB prevalence.<sup>10</sup> For all continuous variables, probability plots indicated no significant departure from normality, so were presented as means and SD. Categorical variables were presented as counts and percentages. The SNORE-ASA participant characteristics were compared with the ASPREE participants recruited through the same sites but who, for any reason, were not included in the final SNORE-ASA cohort, using chi-square tests and Student's *t*-test.

The associations of SDB or the OSA syndrome, with the outcome of depression, and the association of the former with daytime sleepiness were explored using multivariable binary logistic regression models, reporting results as odds ratios (OR). Associations of SDB and the OSA syndrome with the outcomes of the PCS and MCS, individual cognitive

tests and the composite cognitive score were explored using multivariate linear regression models, reporting all these results as beta coefficients ( $\beta$ ). All models were adjusted for age, gender, education, alcohol use, smoking status and body mass index (BMI). Diabetes and hypertension are included in Table 1 for a description of the cohort; however, as both may be causally related to SDB, they were not included in models to avoid over-adjustment. Interaction effects between measures of SDB and gender were tested and found non-significant in all except two models (MCS and HVLT-R); results were stratified by gender only for these two outcomes. Model outputs were each explored for multicollinearity and in all models the variance inflation factors were less than 2, indicating that there was no multicollinearity among model estimates. All analyses were performed with Stata (StataCorp. 2019. Stata Statistical Software: Release 16. StataCorp LLC, College Station, TX). Statistical significance was considered at  $p < 0.05$ .

## RESULTS

A total of 7830 participants were recruited to ASPREE from Australian sites that were also offering SNORE-ASA participation. Of these, 347 were ineligible due to a known diagnosis of OSA and many were uninterested in the sub-study (Figure 1). One thousand eight hundred and thirty-four completed additional cognitive tests for SNORE-ASA; however, only 1592 chose to complete the home sleep study, of whom 1399 had at least 4 h of ApneaLink recording free of significant artefact. This group formed the SNORE-ASA cohort (Figure 1).

Compared to ASPREE participants recruited at the same study sites, but who were not part of the final cohort ( $n = 6431$ ), SNORE-ASA participants were younger on average (mean age 74.0 vs. 75.3 years), and a higher proportion were men (53.8% vs. 44.4%) and had greater than 11 years of formal education (58.0% vs. 52.0%) (Table S1 in the Supporting Information).

The SNORE-ASA cohort characteristics are presented in Table 1. SDB was present in 80.7% of the cohort, similar for both men and women; 9% overall had daytime sleepiness. The proportion of participants with moderate/severe SDB was higher for men (36%) (mean ODI 13.6 [11.1]) than for women (25%) (mean ODI 11.2 [8.7]). The OSA syndrome was present in 7.7% and 5.9% of men and women, respectively.

SDB was not associated with daytime sleepiness nor depression (Table 2). The interaction term with gender and moderate/severe SDB was statistically significant for the QOL MCS score ( $p = 0.049$ ). In the gender-stratified analyses, there was no association with mild ( $\beta = 0.2$ , 95% CI  $-1.0$  to  $1.4$ ,  $p = 0.754$ ) or moderate/severe SDB ( $\beta = -0.8$ , 95% CI  $-2.2$  to  $0.5$ ,  $p = 0.204$ ) in men, nor for women with mild ( $\beta = 0.8$ , 95% CI  $-0.8$  to  $2.4$ ,  $p = 0.294$ ) or moderate/severe SDB ( $\beta = 1.6$ , 95% CI  $-0.3$  to  $3.4$ ,  $p = 0.096$ ). The QOL PCS scores were on average lower among individuals

**TABLE 1** Characteristics and SDB measures for 1399 SNORE-ASA participants by gender

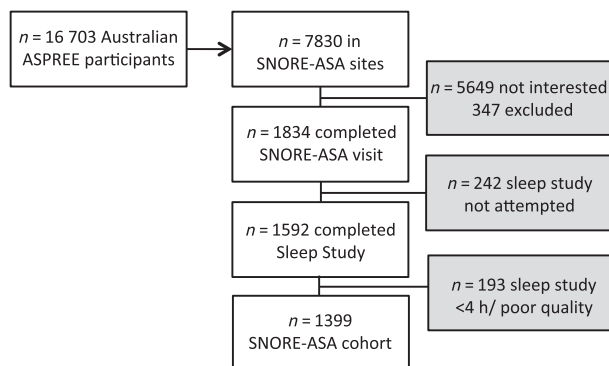
	All <i>n</i> = 1399	Men <i>n</i> = 753	Women <i>n</i> = 646
Age, mean (SD)	74.0 (3.7)	74.0 (3.7)	74.0 (3.7)
Education, <i>n</i> (%)			
<12 years	587 (42.0)	295 (39.2)	292 (45.2)
≥12 years	812 (58.0)	458 (60.8)	354 (54.8)
BMI, mean (SD)	28.2 (4.3)	28.1 (3.6)	28.5 (5.0)
Alcohol, <i>n</i> (%)			
Current heavier use	189 (13.5)	155 (20.6)	34 (5.3)
Current moderate use	971 (69.4)	497 (66.0)	474 (73.4)
Former/never	239 (17.1)	101 (13.4)	138 (21.4)
Smoking current/former, <i>n</i> (%)	653 (46.7)	416 (55.3)	237 (36.7)
Hypertension, <i>n</i> (%)	103 (73.8)	568 (75.4)	465 (72.0)
Diabetes, <i>n</i> (%)	136 (9.7)	88 (11.7)	48 (7.4)
Depression, <i>n</i> (%)	127 (9.1)	44 (5.8)	83 (12.9)
Quality of life, mean (SD)			
SF-12 PCS	49.3 (8.3)	50.3 (7.3)	48.1 (9.2)
SF-12 MCS	55.9 (6.9)	56.5 (6.3)	55.2 (7.4)
Cognitive tests, mean (SD)			
3MS	93.8 (4.2)	93.2 (4.3)	94.5 (4.0)
HVLTR	7.9 (2.8)	7.5 (2.8)	8.3 (2.7)
SDMT	38.9 (9.4)	37.8 (9.5)	40.3 (9.1)
COWAT	12.3 (4.6)	11.8 (4.4)	12.9 (4.7)
Sleep measures			
ODI, mean (SD)	12.5 (10.1)	13.6 (11.1)	11.2 (8.7)
SDB (ODI ≥ 5), <i>n</i> (%)	1129 (80.7)	607 (80.6)	522 (80.8)
Severity of SDB (ODI), <i>n</i> (%)			
Normal <5	270 (19.3)	146 (19.4)	124 (19.2)
Mild (5 to <15)	692 (49.5)	334 (44.4)	358 (55.4)
Moderate (15 to <30)	340 (24.3)	202 (26.8)	138 (21.4)
Severe (≥30)	97 (6.9)	71 (9.4)	26 (4.0)
Average saturation, mean (SD)	93.1 (1.9)	93.2 (1.7)	93.1 (2.0)
Lowest desaturation, mean (SD)	82.9 (6.8)	83.4 (6.1)	82.2 (7.5)
ESS, mean (SD)	4.9 (3.3)	5.2 (3.3)	4.5 (3.3)
ESS ≥ 10, <i>n</i> (%)	120 (9.0)	78 (10.8)	42 (6.9)
OSA syndrome, <i>n</i> (%)	96 (6.8)	58 (7.7)	38 (5.9)

Abbreviations: 3MS, Modified Mini-Mental State Examination; alcohol, current heavy use: ≥125 g/week, current moderate use: <125 g/week, former/never: 0 g/week; BMI, Body mass index, weight in kilograms divided by height in metres squared; COWAT, Controlled Oral Word Association Test; Diabetes Mellitus, self-report, or fasting glucose of >7 mmol/L or on treatment for diabetes mellitus; ESS, Epworth Sleepiness Scale; HVLTR, Hopkins Verbal Learning Test-Revised Delayed Recall; Hypertension, average blood pressure reading of >140 mm Hg systolic blood pressure and/or >90 mm Hg diastolic blood pressure and/or on antihypertensive therapy; MCS, mental health component score; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; PCS, physical health component score; SDB, sleep-disordered breathing; SDMT, Symbol Digit Modalities Test; SF-12, Medical Outcomes Study Short Form 12; SNORE-ASA, the Study of Neurocognitive Outcomes, Radiological and retinal Effects of Aspirin in Sleep Apnoea.

with mild SDB ( $\beta = -2.5$ , 95% CI  $-3.6$  to  $-1.3$ ,  $p < 0.001$ ) and with moderate/severe SDB ( $\beta = -1.8$ , 95% CI  $-3.0$  to  $-0.6$ ,  $p = 0.005$ ), compared to individuals without SDB, and were also lower in those with the OSA syndrome ( $\beta = -2.9$ , 95% CI  $-4.5$  to  $-1.3$ ,  $p < 0.001$ ).

The associations of SDB and OSA syndrome with cognition are displayed in Table 3. Compared to individuals with no SDB, the adjusted mean COWAT score was lower for individuals with mild SDB ( $\beta = -0.7$ , 95% CI  $-1.4$  to  $-0.1$ ,

$p = 0.023$ ), while the adjusted mean SDMT score was lower for individuals with moderate/severe SDB ( $\beta = -1.8$ , 95% CI  $-3.2$  to  $-0.4$ ,  $p = 0.013$ ). The interaction term for gender and SDB was significant in the HVLTR model ( $p = 0.037$  for moderate/severe SDB). In analyses stratified by gender, the mean HVLTR was not different for men with mild SDB ( $\beta = -0.4$ , 95% CI  $-0.9$  to  $0.2$ ,  $p = 0.185$ ), but was significantly lower for men with moderate/severe SDB ( $\beta = -0.6$ , 95% CI  $-1.1$  to  $0.0$ ,  $p = 0.043$ ). In women,



**FIGURE 1** Recruitment flow chart of participants in the final study cohort. ASPREE, ASPirin in Reducing Events in the Elderly; h, hour; *n*, number; SNORE-ASA, Study of Neurocognitive Outcomes, Radiological and retinal Effects of Aspirin in Sleep Apnoea

**TABLE 2** The association of SDB and OSA syndrome with daytime sleepiness, mood and QOL in 1399 older adults: ORs and regression beta coefficients from multivariable logistic and linear regression models, respectively

Sleep exposures	Daytime sleepiness (ESS $\geq 10$ ) OR (95% CI)	Depression (CES-D $\geq 8$ ) OR (95% CI)	QOL PCS $\beta$ (95% CI)	QOL MCS $\beta$ (95% CI)
<b>SDB</b>				
Normal (ODI <5)	Ref	Ref	Ref	Ref
Mild (5 to <15)	1.0 (0.6 to 1.7) <i>p</i> = 0.915	0.8 (0.5 to 1.4) <i>p</i> = 0.536	-2.5 (-3.6 to -1.3) <i>p</i> < 0.001	0.4 (-0.5 to 1.4) <i>p</i> = 0.370
Moderate/severe ( $\geq 15$ )	1.0 (0.5 to 1.7) <i>p</i> = 0.900	1.1 (0.7 to 2.0) <i>p</i> = 0.631	-1.8 (-3.0 to -0.6) <i>p</i> = 0.005	0.1 (-0.9 to 1.2) <i>p</i> = 0.803 <sup>a</sup>
<b>OSA syndrome</b>				
Normal	N/A <sup>b</sup>	Ref	Ref	Ref
Present	N/A <sup>b</sup>	1.7 (0.9 to 3.2) <i>p</i> = 0.130	-2.9 (-4.5 to -1.3) <i>p</i> = <0.001	-1.4 (-2.8 to 0.0) <i>p</i> = 0.050

Note: All models were adjusted for age, gender, education, smoking, alcohol use and BMI.

Abbreviations:  $\beta$ , beta coefficient; CES-D, Center for Epidemiological Studies Depression Scale; ESS, Epworth Sleepiness Scale; MCS, Short Form 12 mental health component score; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; PCS, Short Form 12 physical health component score; QOL, quality of life; Ref, reference; SDB, sleep-disordered breathing.

<sup>a</sup>Significant interaction term for SDB and gender, see text for results of analyses stratified by gender.

<sup>b</sup>Outcomes of daytime sleepiness are not relevant for the exposure of the OSA syndrome as the presence of daytime sleepiness is one component of this syndrome.

**TABLE 3** The associations of SDB and OSA syndrome with cognitive function tests in 1399 men and women aged 70 plus years: Regression beta coefficients from multivariable linear regression models

Sleep exposures	Global cognition 3MS $\beta$ (95% CI)	Delayed recall HVLT-R $\beta$ (95% CI)	Psychomotor speed SDMT $\beta$ (95% CI)	Executive function COWAT $\beta$ (95% CI)	Composite z-score $\beta$ (95% CI)
<b>SDB</b>					
Normal (ODI <5)	Ref	Ref	Ref	Ref	Ref
Mild (ODI 5 to <15)	-0.5 (-1.1 to 0.1) <i>p</i> = 0.093	-0.1 (-0.5 to 0.3) <i>p</i> = 0.573	-1.0 (-2.3 to 0.2) <i>p</i> = 0.108	-0.7 (-1.4 to -0.1) <i>p</i> = 0.023	-0.1 (-0.2 to 0.0) <i>p</i> = 0.022
Moderate/severe (ODI $\geq 15$ )	-0.4 (-1.0 to 0.3) <i>p</i> = 0.286	-0.2 (-0.6 to 0.2) <i>p</i> = 0.384 <sup>a</sup>	-1.8 (-3.2 to -0.4) <i>p</i> = 0.013	-0.5 (-1.2 to 0.2) <i>p</i> = 0.184	-0.1 (-0.2 to 0.0) <i>p</i> = 0.032
<b>OSA syndrome</b>					
Normal	Ref	Ref	Ref	Ref	Ref
Present	0.0 (-0.9 to 0.8) <i>p</i> = 0.930	0.1 (-0.5 to 0.6) <i>p</i> = 0.825	-0.8 (-2.6 to 1.0) <i>p</i> = 0.390	0.8 (-0.1 to 1.8) <i>p</i> = 0.081	0.0 (-0.1 to 0.2) <i>p</i> = 0.740

Note: All models were adjusted for age, gender, education, smoking, alcohol use and BMI.

Abbreviations:  $\beta$ , beta coefficient; 3MS, Modified Mini-Mental State Examination; COWAT, Controlled Oral Word Association Test; HVLT-R, Hopkins Verbal Learning Test-Revised Delayed Recall; ODI, oxygen desaturation index; OSA, obstructive sleep apnoea; Ref, reference; SDB, sleep-disordered breathing; SDMT, Symbol Digit Modalities Test.

<sup>a</sup>Interaction was statistically significant, and the model was stratified by sex (see text for results).

these associations were not significant (mild SDB:  $\beta = 0.2$ , 95% CI  $-0.4$  to  $0.7$ ,  $p = 0.490$ ; moderate/severe SDB:  $\beta = 0.4$ , 95% CI  $-0.3$  to  $1.0$ ,  $p = 0.263$ ). SDB was associated with a lower mean composite cognitive measure for individuals with both mild SDB ( $\beta = -0.1$ , 95% CI  $-0.2$  to  $0.0$ ,  $p = 0.022$ ) and moderate/severe SDB ( $\beta = -0.1$ , 95% CI  $-0.2$  to  $0.0$ ,  $p = 0.032$ ).

## DISCUSSION

In this large cohort of older Australians, SDB prevalence was 81%, and was associated with lower physical health-related QOL and overall cognition, but not with daytime sleepiness, depression nor mental health QOL. Despite known differences in the gender-specific prevalence of SDB,<sup>10</sup> these associations did not differ significantly between men and women.

The prevalence of SDB of at least moderate severity (in 36% and 25% of men and women, respectively) was lower than that observed in other older community-based cohorts. The HypnoLaus study of 902 adults aged  $\geq 60$  years reported that 66% of men and 35% of women had an ODI of  $\geq 15$ .<sup>10</sup> A community-based study of 827 men and women aged 68 years reported that 53% had an apnoea-hypopnoea index (AHI) of  $>15$ .<sup>8</sup> The SNORE-ASA participants, however, had lower rates of smoking and diabetes compared to the age-matched Australian population,<sup>36</sup> and the comorbidities of SDB of AF, CVD and dementia were ASPREE exclusion criteria.<sup>24</sup> Few studies have reported the prevalence of objectively measured SDB in Australian older adults,<sup>6</sup> with adults aged  $\geq 70$  years not included in the largest such study.<sup>37</sup> Given that the 'normal' cut-off of an ODI of  $\geq 5$  was exceeded by over 80% of this relatively healthy cohort, the results suggest that SDB may even be expected as part of normal ageing.

The lack of an association between SDB and daytime sleepiness is in line with several other studies in older age,<sup>11,38</sup> suggesting that daytime sleepiness may not be useful as either a measure for SDB screening or as a target for treatment in this age group. Furthermore, no association was found between SDB and depression nor with the QOL MCS. Few studies have examined the association of depression with SDB in older people as opposed to middle-aged.<sup>5</sup>

The association between both SDB and the OSA syndrome, with a lower QOL PCS, is novel. The MAILES study of community-based men reported associations between SDB and lower QOL for those younger, but not older, than 70 years.<sup>6</sup> A further study demonstrated associations between SDB and QOL in those aged  $<65$  years, but not those  $>65$  years.<sup>39</sup> Both had smaller sample sizes, and moreover, assessed SDB based on the AHI. The ODI is a more robust measure of impact of SDB on oxygenation, and for this age group may be the more relevant measure. Indeed, a randomized controlled trial of CPAP in older adults with SDB, as defined by the ODI, demonstrated improvements in QOL in those treated with CPAP.<sup>40</sup> Given this, assessing QOL in older adults with SDB may be particularly useful in delineating subgroups for treatment.

There is also current interest in whether SDB is a dementia risk factor.<sup>41</sup> Sleep, which is disrupted in SDB,

facilitates operation of the glymphatic system, which is integral for neurotoxin clearance,<sup>13</sup> including the clearance of beta-amyloid which drives AD pathology.<sup>14,15</sup> The intermittent hypoxia of SDB, and resultant sympathetic activation, blood pressure variability and endothelial dysfunction may further potentiate neurodegenerative change, including via an effect on cerebral vasculature.<sup>16,17</sup> Several studies have now linked SDB to dementia risk<sup>18,19</sup> and to biomarkers of AD and vascular dementia.<sup>41</sup> This association, however, is not conclusive.<sup>20,21,42</sup> Some studies have relied upon a clinical diagnosis of SDB<sup>43</sup> which is more likely to be symptomatic with daytime sleepiness, a symptom itself associated with dementia risk.<sup>44</sup> Several large community-based studies employing detailed neuropsychological batteries have not reported associations between SDB and significantly impaired cognition, including in longitudinal analyses and when SDB was measured in later mid-life<sup>45,46</sup>—a time when exposure to SDB arguably would be the most critical in dementia pathogenesis.

If SDB increases dementia risk, an association between SDB and lower scores on cognitive tests should be detectable even in this SNORE-ASA cohort that was free of major cognitive impairment, especially as subtle cognitive impairments usually precede dementia.<sup>47</sup> Indeed, small, but significant, associations were found for SDB (of any severity) with lower scores on a test of psychomotor speed, with a composite cognitive score, between moderate/severe SDB and lower scores on delayed recall for men only, and for mild, but not moderate/severe SDB, with lower scores on executive function. Impairments in psychomotor speed and executive function can reflect vascular pathology,<sup>48</sup> whereas impaired delayed recall may predict incident dementia due to AD.<sup>49</sup>

Some caution in interpretation is required. The strongest signals were for psychomotor speed and executive function, which may have driven the overall association with reduced composite cognition. The association of mild, but not moderate/severe SDB, with reduced executive function is counterintuitive. A smaller number of participants in the moderate/severe group may have impacted the statistical significance of this result; however, and of note, there was still a trend towards lower scores for the moderate/severe group, as there was for SDB of any severity and all other cognitive tests not reaching statistical significance. While the magnitude of the lower scores associated with SDB for each test was small, collectively they may signify an increased risk of future cognitive decline and dementia. Longitudinal data are needed to definitely determine the direction of this association.

Study limitations are that several SDB co-morbidities were exclusion criteria, the limited channel sleep study may lack sensitivity for milder SDB and was self-administered, potentially deterring participation from individuals with poorer cognition. Thus, it has likely underestimated the true prevalence of SDB and the magnitude of the association of SDB with cognition and QOL. However, the study utilized robust and comprehensive outcome assessments, and is the largest study of SDB in an older Australian cohort to date.

In conclusion, this study has confirmed the ubiquitous nature of SDB in older age, demonstrated an association with reduced cognitive function and has shown that SDB as measured by the ODI is associated with reduced physical health QOL. For this age group, in which SDB is so common, QOL and cognitive assessments may best guide treatment decisions and targets for SDB, especially as treatment of SDB has been shown to improve QOL in older age. Whether treatment of SDB is a reversible factor towards the development of dementia remains to be seen.

## AUTHOR CONTRIBUTION

**Stephanie A. Ward:** Conceptualization (lead); data curation (equal); formal analysis (lead); funding acquisition (equal); investigation (lead); methodology (lead); project administration (equal); writing – original draft (lead). **Elsdon Storey:** Conceptualization (equal); formal analysis (equal); funding acquisition (lead); methodology (equal); project administration (equal); writing – review and editing (equal). **Danijela Gasevic:** Formal analysis (equal); writing – review and editing (lead). **Matthew T. Naughton:** Conceptualization (equal); data curation (equal); funding acquisition (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **Garun S. Hamilton:** Conceptualization (equal); data curation (equal); funding acquisition (equal); methodology (equal); writing – review and editing (equal). **Ruth E. Trevaks:** Project administration (lead); writing – review and editing (equal). **Rory Wolfe:** Conceptualization (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **Fergal J. O'Donoghue:** Conceptualization (equal); funding acquisition (equal); methodology (equal); writing – review and editing (equal). **Nigel Stocks:** Project administration (equal); writing – review and editing (equal). **Walter P. Abhayaratna:** Data curation (equal); project administration (equal); writing – review and editing (equal). **Sharyn Fitzgerald:** Project administration (equal); writing – review and editing (equal). **Suzanne G. Orchard:** Project administration (equal); writing – review and editing (equal). **Joanne Ryan:** Formal analysis (equal); writing – review and editing (equal). **John J. McNeil:** Funding acquisition (equal); writing – review and editing (equal). **Christopher Reid:** Methodology (equal); project administration (supporting); writing – review and editing (equal). **Robyn L. Woods:** Conceptualization (equal); data curation (equal); formal analysis (equal); funding acquisition (equal); methodology (equal); project administration (equal); writing – review and editing (lead).

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## CONFLICTS OF INTEREST

Resmed leased some of the ApneaLink Plus devices used in the study and provided the nasal cannula for the devices free of cost. Garun S. Hamilton and Matthew T. Naughton have both received equipment free of charge for use in research from Resmed, and Garun S. Hamilton from Phillips Respironics and Air Liquide Healthcare for the same purpose. Fergal J. O'Donoghue has received a grant from Resmed for research purposes and also received equipment free of charge to conduct research from Resmed and Phillips Respironics.

## DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

## HUMAN ETHICS APPROVAL DECLARATION

Ethics approvals for ASPREE and SNORE-ASA were received from the Monash Human Research Ethics Committee (MUHREC CF07/3730-2006000745) and the Alfred Hospital Ethics Committee (452/11), respectively. All participants provided informed consent.

*Clinical trial registration:* ASPREE Trial—ISRCTN83772183 at [www.isrctn.com](http://www.isrctn.com) and NCT01038583 at [www.clinicaltrials.gov](http://www.clinicaltrials.gov). SNORE-ASA ASPREE sub-study—ACTRN12612000891820 at Australian New Zealand Clinical Trials Registry at [www.anzctr.org.au](http://www.anzctr.org.au)


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## SUPPORTING INFORMATION

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