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RESEARCH ARTICLE

Associations of baseline obstructive sleep apnea and sleep macroarchitecture with cognitive function after 8 years in middle-aged and older men from a community-based cohort study

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Summary

Previous prospective studies examining associations of obstructive sleep apnea and sleep macroarchitecture with future cognitive function recruited older participants, many demonstrating baseline cognitive impairment. This study examined obstructive sleep apnea and sleep macroarchitecture predictors of visual attention, processing speed, and executive function after 8 years among younger community-dwelling men. Florey Adelaide Male Ageing Study participants ($n = 477$) underwent home-based polysomnography, with 157 completing Trail-Making Tests A and B and the Mini-Mental State Examination. Associations of obstructive sleep apnea (apnea–hypopnea index, oxygen desaturation index, and hypoxic burden index) and sleep macroarchitecture (sleep stage percentages and total sleep time) parameters with future cognitive function were examined using regression models adjusted for baseline demographic, biomedical, and behavioural factors, and cognitive task performance. The mean (standard deviation) age of the men at baseline was 58.9 (8.9) years, with severe obstructive sleep apnea (apnea–hypopnea index ≥30 events/h) in 9.6%. The median (interquartile range) follow-up was 8.3 (7.9–8.6) years. A minority of men (14.6%) were cognitively impaired at baseline (Mini-Mental State Examination score <28/30). A higher percentage of light sleep was associated with better Trail-Making Test A performance ($B = -0.04$, 95% confidence interval [CI] −0.06, −0.01; $p = 0.003$), whereas higher mean oxygen saturation was associated with worse performance ($B = 0.11$, 95% CI 0.02, 0.19; $p = 0.012$). While obstructive sleep apnea and sleep macroarchitecture might predict cognitive decline, future studies should

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consider arousal events and non-routine hypoxaemia measures, which may show associations with cognitive decline.

KEYWORDS
cognitive function, NREM sleep, OSA, REM sleep

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent sleep-related breathing disorder (Benjafield et al., 2019) characterised by repetitive pharyngeal collapse leading to intermittent hypoxaemia and sleep fragmentation through frequent brief arousals and awakenings (Eckert et al., 2009). OSA disrupts electroencephalographic (EEG) markers of sleep macroarchitecture, resulting in reduced rapid eye movement (REM) and deep non-REM (NREM) Stage 3 (N3) sleep and increased light NREM Stage 1 (N1) sleep compared to age- and sex-matched controls (Heinzer et al., 2001; McCall et al., 1995).

Seven prospective cohort studies (clinical and community-based) examined associations of baseline OSA or sleep macroarchitecture with cognitive decline (Lutsey et al., 2016; Martin et al., 2015; Osorio et al., 2015; Pase et al., 2017; Ramos et al., 2020; Song et al., 2015; Yaffe et al., 2011). Six studies reported associations of OSA or sleep macroarchitecture parameters with cognitive decline, including a greater number of obstructive breathing episodes (apnea–hypopnea index [AHI]), an increased frequency of intermittent hypoxaemia (oxygen desaturation index [ODI]) (Martin et al., 2015; Osorio et al., 2015; Yaffe et al., 2011), a total sleep time (TST) of >9 h (used to quantify long sleep) (Ramos et al., 2020), a lower percentage of REM sleep (Pase et al., 2017), and increased time in N1 sleep (Song et al., 2015) with cognitive decline. Conversely, one study did not report any associations of OSA or sleep macroarchitecture with cognitive decline (Lutsey et al., 2016).

Previous prospective cohort studies recruited older participants (aged ≥60 years at baseline), many demonstrating baseline cognitive impairment (Lutsey et al., 2016; Martin et al., 2015; Osorio et al., 2015; Pase et al., 2017; Ramos et al., 2020; Song et al., 2015; Yaffe et al., 2011). Moreover, several studies investigated cognitive function after a relatively short follow-up (4–6 years) (Martin et al., 2015; Osorio et al., 2015; Ramos et al., 2020). The findings suggest that OSA and sleep macroarchitecture parameters might have prognostic utility for identifying individuals at risk of future impairment, including mild cognitive impairment and Alzheimer's disease/dementia (Mini-Mental State Examination [MMSE]), impaired visual attention and processing speed (Trail-Making Test [TMT]), and impaired episodic memory and learning (Brief Spanish-English Verbal Learning Test).

Emerging evidence suggests that the total OSA-specific oxygen desaturation or area under the curve recorded for individual apnea and hypopnea events predicts cardiovascular disease-related outcomes and all-cause mortality (Azarbarzin et al., 2019; Azarbarzin et al., 2020; Butler et al., 2019; Trzepizur et al., 2022). The hypoxic burden index (HBI), a measure of the degree and duration of oxygen desaturation (Chen et al., 2018), may have prognostic utility for predicting cognitive dysfunction and decline. However, no community-based cohort studies have investigated associations of HBI with future cognitive dysfunction and decline.

No studies in younger community-based samples are available to establish the prognostic utility of polysomnography (PSG) indices of OSA severity, hypoxaemia, and sleep disruption as markers of future cognitive decline risk. This study aimed to investigate independent associations of baseline OSA and sleep macroarchitecture parameters with cognitive function and decline (visual attention, processing speed, and executive function) after 8 years among a sample of community-dwelling men who were on average aged <60 years at baseline. It was hypothesised that markers of more severe OSA, hypoxaemia, and sleep disruption would predict cognitive decline over 8 years independent of potential baseline demographic, biomedical, and behavioural confounders, and cognitive task performance.

2 | METHODS

2.1 | Study participants

The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study includes 2569 urban, community-dwelling men harmonised from two prospective community-based cohort studies: the Florey Adelaide Male Ageing Study (FAMAS) and North-West Adelaide Health Study (NWAHS). The present prospective study included FAMAS participants aged 35–80 years at baseline (2002–2006) residing in north-west Adelaide (Martin, Haren, Middleton, & Wittert, 2007; Martin, Haren, Taylor, et al., 2007).

During a computer-assisted telephone interview follow-up in 2010 ($n = 858$), FAMAS participants reporting no previous OSA diagnosis ($n = 767$) were invited to undergo PSG (2010–2011) as part of a sub-study of the MAILES Study (Adams et al., 2016; Grant et al., 2014). Approximately 75% of eligible participants ($n = 575$) agreed to participate, with time and budget constraints resulting in a final sample of 477 (Figure 1). The FAMAS was conducted in accordance with the Declaration of Helsinki and approved by the Royal Adelaide Hospital Human Research Ethics Committee (approval number: 020305). All participants provided written informed consent.

2.2 | Baseline sleep study assessment

As described previously (Parker et al., 2022; Parker, Appleton, et al., 2021; Parker, Melaku, et al., 2021), participants underwent

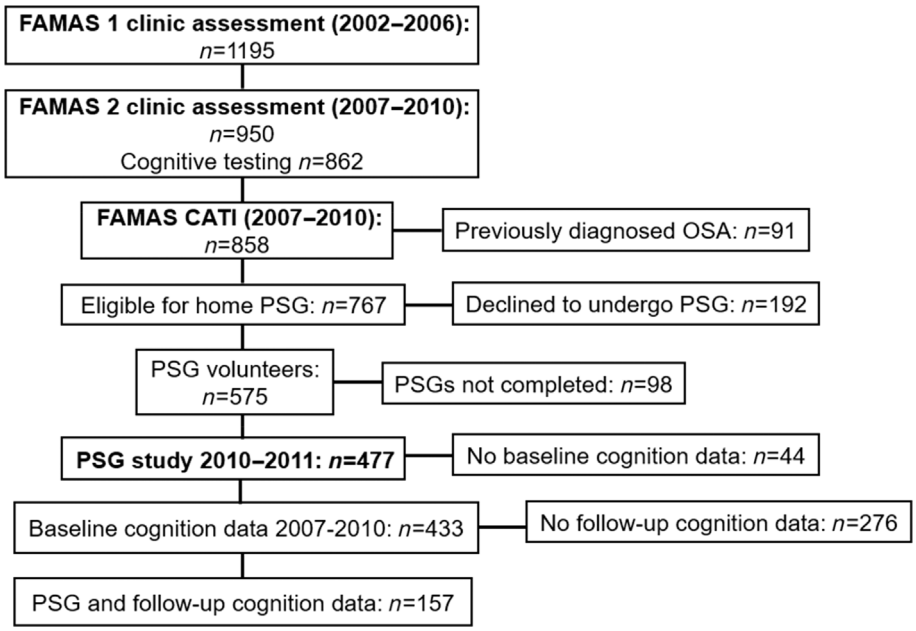

FIGURE 1 The Florey Adelaide Male Ageing Study (FAMAS) clinic and sleep study assessments and cognitive function testing. CATI, computer-assisted telephone interview; OSA, obstructive sleep apnea; PSG, polysomnography.

home-based eight-channel ambulatory PSG (Embletta X100, Embla Systems, Broomfield, Colorado, USA), which recorded electrical brain activity (electroencephalography [EEG], F4-M1) and left electro-oculography with 12-bit signal resolution, 200 Hz sampling rate, and band-pass filters (0.3–35 Hz) together with submental electromyography, nasal cannula pressure, thoracic and abdominal motion, finger pulse oximetry, and body position. Trained staff set-up and attached the PSG equipment and obtained anthropometric measures (height, weight, and body mass index [BMI, kg/m^2]).

A single experienced sleep technician manually scored all PSG measures from technically acceptable sleep studies according to the 2007 American Academy of Sleep Medicine (AASM) Alternative scoring criteria (Ruehland et al., 2009), recommended by an Australasian Sleep Association expert panel for use in prospective epidemiological studies (ASTA/ASA, 2010). The sleep technician participated in quarterly external Qsleep scoring concordance assessments, a national external proficiency testing programme (www.qsleep.com.au), where performance was consistently within two quartiles of national assessments. Acceptable sleep studies were those with ≥3.5 h of sleep and ≥5.5 h of total-recorded study time with good respiratory and EEG signal quality. Apnea was defined as complete or near-complete airflow cessation (≥90%) measured using nasal cannula pressure excursions lasting ≥10 s. Hypopnea was defined as a ≥50% decrease in nasal cannula pressure excursions and an associated ≥3% oxygen desaturation or EEG arousal (Ruehland et al., 2009).

Obstructive sleep apnea was identified by an AHI of ≥10 events/h and categorised as mild (10–19 events/h), moderate (20–29 events/h), or severe (≥30 events/h). An AHI of ≥5 events/h used to define sleep-disordered breathing by the AASM 2007 Recommended scoring criteria is approximately equivalent to ≥10 events/h using the Alternative and ≥15 events/h using the older 1999 Chicago criteria (Ruehland et al., 2009). Therefore, an AHI cut-off of 10 events/h was chosen to maintain comparability with previous work. Nocturnal hypoxaemia was assessed from the ODI 3% and percentage of TST with oxygen saturation (SaO_2) <90% (TST90). Sleep macroarchitecture parameters assessed included TST, arousal index (number of EEG events >3 s/h of sleep), and sleep stage (N1, N2, N3, and REM sleep) percentages.

2.3 | The HBI

The HBI (Chen et al., 2018) is calculated by dividing the total time-integrated area of SaO_2 <90% by TST using the equation presented below. Higher HBI values represent a higher hypoxic burden, and SaO_2 values <40% were excluded as artefacts.

$$\mathrm{HBI}\,(\%) = \frac{\sum_{t=t_0}^{t_n}(90 - \mathrm{SpO_{2t}})}{\mathrm{TST}}, \text{if } \mathrm{SpO_{2t}} < 90\%$$

2.4 | Baseline and follow-up cognitive assessments

Three standardised, validated, and well-established cognitive tests, described previously (Parker et al., 2022; Parker, Appleton, et al., 2021; Parker, Melaku, et al., 2021), were administered during the 2007–2010 follow-up and repeated at the 2018–2019 follow-up examination, including TMT-A and -B and the 30-point MMSE.

2.5 | The TMT

The TMT assesses visual search, processing speed, mental flexibility, visual attention, and executive function. Part A (TMT-A) assesses visual attention and processing speed and requires participants to connect encircled numbers (1–25) in sequence. Part B (TMT-B) assesses executive

function and requires participants to connect alternating encircled numbers and letters (1-A-2-B-3-C…12-L) (Salthouse, 2011). The time in seconds to complete each path is scored, with higher scores indicating inferior performance. The TMT-A and TMT-B were administered using a standardised, validated protocol by a trained health professional (Bowie & Harvey, 2006; Martin, Haren, Taylor, et al., 2007). TMT delta (TMT-B minus TMT-A) was also calculated as this is considered a more reliable measure of cognitive flexibility. Subtracting TMT-A completion time from TMT-B allows the assessment of visual search and psychomotor speed to be parsed from more complex executive functions, and the TMT difference score has been highly correlated with intelligence and severity of cognitive impairment (Corrigan & Hinkeldey, 1987).

2.6 | The MMSE

The MMSE is a quantitative measure of cognitive status consisting of a 30-point questionnaire designed to assess orientation, registration and recall, attention and calculation, language, and the ability to follow simple verbal and written commands (Arevalo-Rodriguez et al., 2021). The total score is used to scale an individual on cognitive ability. The maximum possible score is 30, with <24 indicating mild cognitive impairment and <18 indicating severe impairment (Pezzotti et al., 2008). As with the TMT, a trained health professional administered the MMSE using a standardised, validated protocol (Martin, Haren, Taylor, et al., 2007).

2.7 | Baseline covariate assessments

Self-completed questionnaires assessed chronic disease risk factors (smoking status, alcohol consumption, and physical activity) and demographic factors (age, financial stress, highest educational attainment, and marital status). Relative social disadvantage was determined using the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-Economic Disadvantage (IRSD) (Statistics ABo, 2016). Clinic assessments (2007–2010) included anthropometry, seated sphygmomanometer blood pressure, and a fasting morning blood sample to assess glucose and haemoglobin A1C (HbA1c) (Martin, Haren, Taylor, et al., 2007). Composite cardiovascular disease (self-reported, doctor-diagnosed myocardial infarction, angina, transient ischaemic attack, or stroke) and diabetes mellitus (self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L [126 mg/dL], HbA1c ≥6.5%, or reported antidiabetic medication use [oral hypoglycaemic agents and/or insulin]) were also determined. Men were classified as having insomnia symptoms if they reported difficulty initiating or maintaining sleep for ≥3 nights/week (Pittsburgh Sleep Quality Index dimensions) and significant daytime fatigue, defined as a score one standard deviation (SD) below the mean on the 36-item short-form survey instrument (SF-36) Vitality Scale (Lang et al., 2017). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use (Chobanian et al., 2003). BMI was categorised according to international criteria from the World Health Organization (<25 [underweight/normal], 25–29.9 [overweight], and ≥30 kg/m^2 [obese]) (Nuttall, 2015).

2.8 | Statistical analysis methodology

Data were analysed using the IBM Statistical Package for the Social Sciences (SPSS®) version 29.0 (IBM Corp., Armonk, NY, USA). Baseline participant characteristics are reported as mean (SD) for normally distributed continuous variables, median (interquartile range [IQR]) for skewed continuous variables, and percentage (frequency) for dichotomous and categorical variables. Baseline participant characteristics were stratified by follow-up cognitive examination participation and performance status to examine possible response bias.

Low TMT performance was defined as a ≥0.5 SD baseline to follow-up reduction in standardised (*z*-score) TMT completion time in line with previous literature used to classify as a minimal impairment that may be considered clinically meaningful based on a threshold of 0.5 to 2.0 SDs below the mean (Hochberger et al., 2018). In the present study, a cut-off of 0.5 SDs was used as the sample overall was not cognitively impaired, and few men recorded TMT scores of ≥1.0 SDs below the mean. Between-group differences were assessed using Pearson's chi-squared tests for dichotomous and categorical variables, independent *t* tests for normally distributed continuous variables, and non-parametric Mann–Whitney *U* tests for skewed continuous variables. Absolute baseline and follow-up cognitive task performance (TMT completion times) was compared to previously reported normative values based on age and highest educational attainment (Tombaugh, 2004).

Differences in cognitive performance across disease and chronic disease risk factor categories were assessed using non-parametric Mann–Whitney *U* tests and Kruskal–Wallis tests. Standardised scores were calculated using logarithmic base 10 test scores, subtracting the mean, and dividing by the sample SD to improve model interpretability, better define cognitive status, and facilitate comparison of findings with previous literature utilising similar statistical methodologies (Saint Martin et al., 2013). Standardised scores were calculated for the cognitive function outcomes as this approach has been deemed a more accurate method of minimising measurement error in an individual test (Martin et al., 2015). Differences in standardised scores were assessed using independent samples *t* tests and one-way analysis of variance (ANOVA) with Bonferroni correction for post hoc multiple comparisons.

Along with standardised scores, absolute cognitive test scores were also examined to compare differences in baseline performance between men who participated versus those who did not participate in the follow-up cognitive examination. To describe the sample characteristics, absolute cognitive test scores provide more direct insight into the level of cognitive impairment in the sample. One-way ANOVA with Bonferroni correction was also conducted to evaluate differences in absolute TMT-A and TMT-B performance at follow-up and performance change by OSA treatment status; (1) no self-report diagnosed OSA; (2) treated

with continuous positive airway pressure (CPAP; ≥4 h), mandibular advancement splint (MAS), or surgery; or (3) no treatment or CPAP <4 h.

Linear regression was conducted to examine associations of baseline PSG parameters (entered separately into models), including AHI, TST90, ODI 3%, ODI 4%, SaO_2 nadir, mean SaO_2, HBI, and sleep macroarchitecture (arousal index [*n*/h], N1, N2, N3, and REM sleep percentages, and hours of TST) parameters with standardised TMT-A, TMT-B, and TMT-B minus TMT-A performance after 8 years. Results are presented as unstandardised beta (*B*) coefficients (95% confidence intervals [CIs]). Three regression models were constructed, including (1) unadjusted, (2) adjusted for age, highest education, socioeconomic disadvantage, marital status, physical activity level, BMI, and cardio-metabolic conditions (one or more of hypertension, diabetes mellitus, or cardiovascular disease), and (3) additionally adjusted for baseline cognitive task performance (Tu & Gilthorpe, 2007). Sleep macroarchitecture models were additionally adjusted for the AHI and arousal index.

As a sensitivity analysis, associations of baseline OSA and sleep macroarchitecture parameters with baseline cognitive function in men who participated in the follow-up cognitive examination ($n = 157$) were examined. Utilising the purposeful covariate selection procedure ensured the retainment of robust covariates (Bursac et al., 2008; Parker et al., 2022). Covariates in multivariable adjustment are reported risk factors for cognitive decline (Legdeur et al., 2018). The principal assumptions of linear regression modelling were satisfied, including linearity, normality, and homoscedasticity. Multicollinearity among covariates was assessed by examining the tolerance and variance inflation factor for each covariate, which indicated an absence of multicollinearity (Table S1).

As a supplementary analysis, binary logistic regression models were constructed to examine associations of baseline OSA and sleep macroarchitecture parameters with odds of impairment (score <28/30) on the MMSE at follow-up ($n = 14$). Covariates included in multivariable adjustment were consistent with linear regression analyses. For all analyses, a two-sided $p < 0.05$ was considered statistically significant. Based on reported practical considerations (Marchi et al., 2020; Sangal & Sudan, 2020) and the exploratory nature of the analyses, multiple comparison adjustments were not performed.

3 | RESULTS

3.1 | Baseline participant characteristics stratified by follow-up status

Of the 433 men with baseline PSG and cognitive data, 36.3% ($n = 157$) participated in the follow-up cognitive examination. The baseline mean (SD, range) age of those who participated in follow-up was 58.9 (8.9, 41–81) years. The median (IQR) follow-up was 8.3 (7.9–8.6) years. Of the 276 men who did not participate in follow-up, 11.9% ($n = 33$) died. Compared to non-participants, follow-up participants more frequently reported being married or having a partner. However, there were no differences in OSA severity, oximetry, or sleep macroarchitecture (Table 1).

3.2 | Standardised cognitive test scores in relation to baseline participant characteristics

Men aged ≥70 years showed significantly worse standardised TMT-A performance and a greater reduction in TMT-A performance compared to men aged <50 and 50–59 years. Men aged ≥70 years also showed significantly worse standardised TMT-B performance at baseline relative to men aged <50 and 50–59 years, and a greater reduction in TMT-B performance relative to younger age groups (Table S2).

Men with severe OSA (AHI ≥30 events/h) showed significantly better standardised TMT-A performance at follow-up and less reduction in TMT-A performance relative to men with mild (AHI 10–19 events/h) and moderate (AHI 20–29 events/h) OSA. However, chronic disease risk factors and conditions were not associated with standardised or reduced TMT performance (Table S3).

3.3 | Level of cognitive impairment in the sample

At baseline, the sample was predominantly unimpaired on the TMT-A relative to normative values of age and highest educational attainment (Tombaugh, 2004). However, a considerable proportion showed impairment in the TMT-A at follow-up (Figure S1). Men showed worse TMT-B performance at baseline and follow-up than published normative values of age and highest educational attainment (Figure S2). However, no men showed mild cognitive impairment at baseline or follow-up. The lack of cognitive impairment in the cohort is also evidenced by only a small proportion of men showing a ≥0.5 SD baseline to follow-up reduction in standardised TMT-A ($n = 36$, 22.9%) and TMT-B ($n = 15$, 9.6%) performance. At baseline, 14.6% ($n = 23$) of men showed low MMSE performance (score <28/30), whereas at follow-up, 8.9% ($n = 14$) of men showed low MMSE performance.

3.4 | Associations of OSA and sleep macroarchitecture with future cognitive function

In unadjusted and adjusted models, a higher percentage of N1 sleep was associated with better standardised TMT-A performance at follow-up. Baseline OSA parameters were not associated with TMT-A performance at follow-up in unadjusted or adjusted models. However, after adjustment for baseline TMT-A performance, greater mean SaO_2 was associated with worse standardised TMT-A performance at follow-up (Table 2).

In unadjusted and adjusted models, baseline OSA and sleep macroarchitecture parameters were not associated with standardised TMT-B or TMT-B minus TMT-A performance at follow-up (Tables 3 and 4). Furthermore, the HBI was not associated with future TMT performance in unadjusted or adjusted models. Baseline mean SaO_2 and percentage of N1 sleep were not cross-sectionally associated with baseline TMT-A performance in men who participated in the follow-up examination (mean SaO_2, $B = -0.07$, 95% CI −0.18, 0.03, $p = 0.16$; percentage of N1 sleep, $B = 0.04$, 95% CI −0.11, 0.19, $p = 0.63$).

TABLE 1 Baseline participant characteristics stratified by participation in follow-up cognitive examination.

Baseline participant characteristics	Follow-up cognitive examination participation		
	Participants ($n = 157$)	Non-participants ($n = 276$)	p
Age, years, mean (SD)	58.9 (8.9)	59.4 (11.4)	0.66
SEIFA IRSD, % (*n*)			
Quintile 1 (most socioeconomic disadvantage)	21.0 (33)	23.6 (65)	0.93
Quintile 2	10.8 (17)	9.4 (26)	
Quintile 3	28.0 (44)	29.0 (80)	
Quintile 4	27.4 (43)	24.6 (68)	
Quintile 5 (least socioeconomic disadvantage)	12.7 (20)	13.4 (37)	
Married/partner, % (*n*)	89.8 (141)	80.4 (222)*	**0.012**
% (*n*)			
Cardiovascular disease	5.1 (8)	8.3 (23)	0.21
Diabetes mellitus	8.3 (13)	5.1 (14)	0.67
Insomnia	10.8 (17)	13.0 (36)	0.50
Hypertension	58.6 (92)	59.4 (164)	0.84
Cardio-metabolic conditions	61.1 (96)	62.0 (171)	0.87
Current smokers	14.6 (23)	19.9 (55)	0.15
Physical activity level: sedentary	18.5 (29)	25.0 (69)	0.086
Medium–very high alcohol risk	7.7 (12)	6.2 (17)	0.54
ESS score ≥11	16.2 (25)	12.5 (34)	0.30
Psychotropic medication(s)	8.9 (14)	8.3 (23)	0.84
AHI, events/h, mean (SD)	15.4 (16.1)	16.3 (14.4)	0.55
% (*n*)			
<10	47.1 (74)	44.6 (123)	0.31
10–19	30.6 (48)	25.4 (70)	
20–29	12.7 (20)	15.6 (43)	
≥30	9.6 (15)	14.5 (40)	
TST90 ≥4%, % (*n*)	28.0 (44)	26.9 (74)	0.80
ODI 3%, % (*n*)			
<15 events/h	14.6 (23)	13.8 (38)	0.92
≥15 to <30 events/h	18.5 (29)	17.4 (48)	
≥30 events/h	66.9 (105)	68.8 (190)	
ODI 4%, % (*n*)			
<15 events/h	86.0 (135)	83.0 (229)	
≥15 to <30 events/h	8.9 (14)	12.7 (35)	0.37
≥30/h	5.1 (8)	4.3 (12)	
Median (IQR)			
O_2 nadir, %	86.0 (81.5, 89.0)	86.0 (81.0, 88.0)	0.52
HBI, %	2.5 (0.2, 10.7)	2.0 (0.1, 11.6)	0.95
Mean (SD)			
SaO_2, %	93.7 (1.7)	93.7 (1.8)	0.91
Arousal index, *n*/h	18.5 (8.8)	18.3 (8.0)	0.58
Sleep macroarchitecture, mean (SD)			
N1 %	14.3 (6.7)	14.9 (6.7)	0.42
N2 %	54.0 (9.6)	54.9 (9.8)	0.36
N3 %	17.0 (8.8)	15.4 (8.6)	0.066
REM %	14.6 (5.3)	14.5 (5.7)	0.73

TABLE 1 (Continued)

Baseline participant characteristics	Follow-up cognitive examination participation		
	Participants ($n = 157$)	Non-participants ($n = 276$)	p
TST <360 min, % (*n*)	36.9 (58)	39.5 (109)	0.60
Cognitive baseline data, mean (SD)			
TMT-A, s	15.4 (5.2)	16.2 (7.1)	0.14
TMT-A z-score, s	0.1 (1.0)	0.2 (1.3)	0.17
TMT-B, s	75.3 (26.1)	80.0 (37.6)	0.12
TMT-B z-score, s	0.1 (1.1)	0.2 (1.3)	0.12
TMT-B minus TMT-A, s	59.9 (23.5)	63.9 (33.1)	0.15
TMT-B minus TMT-A z-scores, s	0.2 (1.2)	0.3 (1.2)	0.13

Note: Cardiovascular disease: self-reported, doctor-diagnosed myocardial infarction, angina, transient ischaemic attack, or stroke. Diabetes mellitus: self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), HbA1c ≥6.5%, or reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin). Insomnia: difficulty initiating or maintaining sleep occurring ≥3 nights/week (Pittsburgh Sleep Quality Index dimensions) and significant daytime fatigue defined as a score one standard deviation below the mean on the 36-item short-form survey instrument (SF-36) Vitality Scale. Hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use. Cardio-metabolic conditions: one or more of hypertension, diabetes mellitus, or cardiovascular disease. Psychotropic medication(s): reported use of one or more of opiates, antipsychotics, antiepileptics, antidepressants, or benzodiazepines.

Abbreviations: AHI, apnea–hypopnea index; AI, arousal index; CI, confidence interval; ESS, Epworth Sleepiness Scale; HBI, hypoxic burden index; IQR, interquartile range; N1, Stage 1 sleep; N2, Stage 2 sleep; N3, Stage 3 sleep; O_2, oxygen saturation; ODI 3%, oxygen desaturation index 3%; ODI 4%, oxygen desaturation index 4%; REM, rapid eye movement sleep; SaO_2, mean oxygen saturation; SD, standard deviation; SEIFA IRSD, Socio-Economic Indexes for Areas Index of Relative Socio-Economic Disadvantage; TMT-A, Trail-Making Test A; TMT-B, Trail-Making Test B; TST, total sleep time; TST90, percentage of total sleep time with oxygen saturation <90%.

Bold value statistically significant at $p < 0.05$.

TABLE 2 Unadjusted and adjusted associations of baseline, obstructive sleep apnea and sleep macroarchitecture parameters with standardised (z-score) Trail-Making Test A (TMT-A) performance at follow-up.

	Unadjusted model		Adjusted Model 1		Adjusted Model 2	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
AHI (event/h)	0.002 (−0.008, 0.01)	0.65	−0.0002 (−0.01, 0.009)	0.96	0.0004 (−0.008, 0.009)	0.99
TST90 (%)	0.003 (−0.02, 0.02)	0.75	−0.002 (−0.02, 0.02)	0.85	−0.003 (−0.02, 0.01)	0.65
ODI 3% (%)	−0.0002 (−0.002, 0.001)	0.84	−0.0003 (−0.002, 0.001)	0.67	−0.0001 (−0.001, 0.001)	0.88
ODI 4% (%)	−0.0003 (−0.01, 0.01)	0.97	−0.002 (−0.01, 0.01)	0.71	−0.001 (−0.01, 0.009)	0.79
O_2 nadir (%)	−0.008 (−0.02, 0.003)	0.15	−0.005 (−0.02, 0.006)	0.35	−0.004 (−0.01, 0.006)	0.40
SaO_2 (%)	−0.005 (−0.10, 0.09)	0.92	0.08 (−0.01, 0.17)	0.093	0.11 (0.02, 0.19)	**0.012**
AI (*n*/h)	0.0003 (−0.003, 0.003)	0.83	−0.0004 (−0.003, 0.002)	0.75	−0.0004 (−0.003, 0.002)	0.73
HBI (%)	0.001 (−0.01, 0.01)	0.91	−0.007 (−0.02, 0.006)	0.28	−0.007 (−0.02, 0.004)	0.23
N1 (%)	−0.02 (−0.05, −0.001)	**0.043**	−0.03 (−0.06, −0.006)	**0.014**	−0.04 (−0.06, −0.01)	**0.003**
N2 (%)	0.001 (−0.02, 0.02)	0.91	0.005 (−0.01, 0.02)	0.52	0.003 (−0.01, 0.02)	0.70
N3 (%)	0.01 (−0.004, 0.03)	0.12	0.009 (−0.009, 0.03)	0.34	0.02 (−0.001, 0.03)	0.073
REM (%)	−0.004 (−0.03, 0.03)	0.79	−0.002 (−0.03, 0.03)	0.91	−0.004 (−0.03, 0.02)	0.73
TST (h)	−0.0001 (−0.17, 0.17)	0.99	0.04 (−0.12, 0.21)	0.59	0.10 (−0.04, 0.25)	0.17

Note: Coefficients: unstandardised beta (*B*) coefficients (95% CI) from uni- and multivariable linear regression models are reported. Estimates: represent the change in TMT-A scores at follow-up corresponding to a 1-unit increase in the obstructive sleep apnea or sleep macroarchitecture parameter at baseline. Adjusted Model 1 (AHI, events/h; TST90, %; ODI 3%, %; ODI 4%, %; O_2 nadir, %, SaO_2, %; AI, *n*/h; and HBI, %): adjusted for baseline age, highest educational attainment, socioeconomic disadvantage, marital status, physical activity level, body mass index, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes mellitus, or hypertension). Sleep macroarchitecture models were additionally adjusted for the AHI and AI. Adjusted Model 2: additionally adjusted for baseline TMT performance.

Abbreviations: AHI, apnea–hypopnea index; AI, arousal index; CI, confidence interval; HBI, hypoxic burden index; N1, Stage 1 sleep; N2, Stage 2 sleep; N3, Stage 3 sleep; O_2, oxygen saturation; ODI 3%, oxygen desaturation index 3%; ODI 4%, oxygen desaturation index 4%; REM, rapid eye movement sleep; SaO_2, mean oxygen saturation; TST, total sleep time; TST90, percentage of total sleep time with oxygen saturation <90%.

Bold values statistically significant at $p < 0.05$.

TABLE 3 Unadjusted and adjusted associations of baseline obstructive sleep apnea and sleep macroarchitecture parameters with standardised (z-score) Trail-Making Test B (TMT-B) performance at follow-up.

	Unadjusted model		Adjusted Model 1		Adjusted Model 2	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
AHI (events/h)	−0.003 (−0.01, 0.007)	0.58	−0.004 (−0.01, 0.005)	0.37	−0.004 (−0.01, 0.004)	0.34
TST90 (%)	0.001 (−0.02, 0.02)	0.89	−0.002 (−0.02, 0.02)	0.85	−0.004 (−0.02, 0.01)	0.56
ODI 3% (%)	−0.001 (−0.002, 0.001)	0.27	−0.001 (−0.002, 0.001)	0.22	−0.001 (−0.002, 0.001)	0.31
ODI 4% (%)	−0.006 (−0.02, 0.007)	0.37	−0.007 (−0.02, 0.006)	0.28	−0.006 (−0.02, 0.006)	0.29
O_2 nadir (%)	0.009 (−0.004, 0.02)	0.18	−0.01 (−0.002, 0.02)	0.092	0.005 (−0.006, 0.02)	0.33
SaO_2 (%)	−0.02 (−0.11, 0.08)	0.70	0.03 (−0.07, 0.13)	0.57	0.005 (−0.08, 0.09)	0.91
AI (*n*/h)	0.0005 (−0.002, 0.003)	0.75	−0.0002 (−0.003, 0.003)	0.88	−0.0003 (−0.003, 0.002)	0.77
HBI (%)	−0.003 (−0.02, 0.01)	0.71	−0.008 (−0.02, 0.005)	0.21	−0.008 (−0.02, 0.004)	0.19
N1 (%)	−0.01 (−0.04, 0.01)	0.33	−0.02 (−0.05, 0.007)	0.15	−0.01 (−0.03, 0.01)	0.33
N2 (%)	−0.005 (−0.02, 0.01)	0.51	−0.001 (−0.02, 0.01)	0.86	−0.002 (−0.02, 0.01)	0.78
N3 (%)	0.01 (−0.005, 0.03)	0.16	0.01 (−0.008, 0.03)	0.26	0.008 (−0.008, 0.02)	0.32
REM (%)	0.002 (−0.03, 0.03)	0.91	0.002 (−0.03, 0.03)	0.91	0.0001 (−0.02, 0.02)	0.99
TST (h)	0.004 (−0.17, 0.18)	0.96	0.03 (−0.14, 0.19)	0.77	0.04 (−0.10, 0.18)	0.55

Note: coefficients: unstandardised beta (*B*) coefficients (95% CI) from uni- and multivariable linear regression models are reported. Estimates: represent the change in TMT-B scores at follow-up corresponding to a 1-unit increase in the obstructive sleep apnea or sleep macroarchitecture parameter at baseline. Adjusted Model 1 (AHI, events/h; TST90, %; ODI 3%, %; ODI 4%, %; O_2 nadir, %; SaO_2, %; AI, *n*/h; and HBI, %): adjusted for baseline age, highest educational attainment, socioeconomic disadvantage, marital status, physical activity level, body mass index, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes mellitus, or hypertension). Sleep macroarchitecture models were additionally adjusted for the AHI and AI. Adjusted Model 2: additionally adjusted for baseline TMT performance.

Abbreviations: AHI, apnea–hypopnea index; AI, arousal index; CI, confidence interval; HBI, hypoxic burden index; N1, Stage 1 sleep; N2, Stage 2 sleep; N3, Stage 3 sleep; O_2, oxygen saturation; ODI 3%, oxygen desaturation index 3%; ODI 4%, oxygen desaturation index 4%; REM, rapid eye movement sleep; SaO_2, mean oxygen saturation; TST, total sleep time; TST90, percentage of total sleep time with oxygen saturation <90%.

In an adjusted model, a lower ODI 3% at baseline was associated with higher odds of declining on the MMSE. However, this association was no longer significant after adjusting for baseline MMSE performance (Table S4).

3.5 | Associations of OSA and sleep macroarchitecture with future cognitive function in men who did not self-report OSA treatment

To account for the potential influence of self-reported OSA treatment (CPAP >4 h/night, MAS, or surgery) on longitudinal associations between OSA, sleep macroarchitecture, and future cognitive function, supplementary analyses were performed excluding the 19 men (13.2%) who self-reported OSA treatment ($n = 19$) from the analysis. Excluding these men did not quantitatively influence the findings in adjusted regression models, including those adjusted for baseline cognition (Tables S5–S8). However, in an unadjusted model, a higher AHI at baseline was associated with worse TMT-A performance at follow-up (Table S5).

3.6 | Differences in cognitive function at follow-up by OSA treatment status

There was a significant difference in TMT-A ($F_{2,143} = 3.19$, $p = 0.044$), but not TMT-B, ($F_{2,142} = 2.51$, $p = 0.085$), performance at follow-up across OSA treatment categories, including no self-report diagnosed OSA, OSA-treated, and untreated/used CPAP <4 h/night. Bonferroni corrected post hoc tests demonstrated that OSA-treated men ($n = 19$) scored significantly better on TMT-A at follow-up compared to men who were untreated/used CPAP <4 h/night or had no self-report diagnosed OSA ($n = 125$; $p = 0.042$).

4 | DISCUSSION

This study is the first to examine associations of OSA and sleep macroarchitecture with future cognitive function and decline in community-dwelling men who were on average aged <60 years at baseline. Most PSG indices of OSA and sleep disruption were not associated with cognitive function or decline after 8 years. However, a higher percentage of N1 sleep was associated with better visual attention and processing speed, whereas higher mean SaO_2 was associated with worse performance. These associations may reflect self-selection bias and differences in OSA treatment uptake.

Seven prospective cohort studies (clinical and community-based) examined associations of OSA or sleep macroarchitecture with cognitive decline (Lutsey et al., 2016; Martin et al., 2015; Osorio et al., 2015; Pase et al., 2017; Ramos et al., 2020; Song et al., 2015; Yaffe et al., 2011). However, these studies primarily recruited participants aged ≥60 years at baseline, many with mild cognitive

TABLE 4 Unadjusted and adjusted associations of baseline obstructive sleep apnea and sleep macroarchitecture parameters with standardised (z-score) Trail-Making Test (TMT)-B minus TMT-A performance at follow-up.

	Unadjusted model		Adjusted Model 1		Adjusted Model 2	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
AHI (events/h)	−0.001 (−0.004, 0.001)	0.38	−0.002 (−0.004, 0.001)	0.26	−0.001 (−0.004, 0.001)	0.25
TST90 (%)	−0.001 (−0.005, 0.005)	0.99	−0.001 (−0.005, 0.004)	0.81	−0.001 (−0.005, 0.003)	0.65
ODI 3% (%)	−0.002 (−0.003, −0.001)	0.23	−0.002 (−0.003, −0.001)	0.20	−0.0002 (−0.001, 0.0002)	0.24
ODI 4% (%)	−0.002 (−0.003, 0.004)	0.17	−0.002 (−0.003, 0.004)	0.19	−0.003 (−0.003, 0.003)	0.20
O_2 nadir (%)	0.003 (0.001, 0.007)	0.076	0.003 (−0.0001, 0.007)	0.055	0.002 (−0.001, 0.006)	0.16
SaO_2 (%)	−0.007 (−0.03, 0.02)	0.55	−0.001 (−0.03, 0.03)	0.92	−0.008 (−0.03, 0.02)	0.52
AI (/h)	0.0004 (−0.001, 0.001)	0.85	0.0005 (−0.001, 0.001)	0.84	0.0004 (−0.001, 0.001)	0.86
HBI (%)	−0.002 (−0.02, 0.03)	0.81	−0.001 (−0.003, 0.001)	0.86	−0.001 (−0.001, 0.001)	0.88
N1 (%)	−0.001 (−0.008, 0.005)	0.64	−0.003 (−0.01, 0.004)	0.38	−0.002 (−0.009, 0.005)	0.64
N2 (%)	−0.001 (−0.006, 0.003)	0.51	−0.001 (−0.005, 0.004)	0.77	−0.001 (−0.005, 0.003)	0.74
N3 (%)	0.002 (−0.003, 0.007)	0.45	0.009 (−0.009, 0.03)	0.34	0.001 (−0.004, 0.006)	0.71
REM (%)	0.002 (−0.006, 0.01)	0.58	0.002 (−0.006, 0.01)	0.61	0.002 (−0.006, 0.009)	0.60
TST (h)	0.009 (−0.04, 0.06)	0.70	0.01 (−0.04, 0.06)	0.65	0.01 (−0.03, 0.06)	0.56

Note: coefficients: unstandardised beta (*B*) coefficients (95% CI) from uni- and multivariable linear regression models are reported. Estimates: represent the change in TMT-B minus TMT-A scores at follow-up corresponding to a 1-unit increase in the obstructive sleep apnea or sleep macroarchitecture parameter at baseline. Adjusted Model 1 (AHI, events/h; TST90, %; ODI 3%, %; ODI 4%, %; O_2 nadir, %; SaO_2, %; AI, *n*/h; and HBI, %): adjusted for baseline age, highest educational attainment, socioeconomic disadvantage, marital status, physical activity level, body mass index, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes mellitus, or hypertension). Sleep macroarchitecture models were additionally adjusted for the AHI and AI. Adjusted Model 2: additionally adjusted for baseline TMT performance.

Abbreviations: AHI, apnea–hypopnea index; AI, arousal index; CI, confidence interval; HBI, hypoxic burden index; N1, Stage 1 sleep; N2, Stage 2 sleep; N3, Stage 3 sleep; O_2, oxygen saturation; ODI 3%, oxygen desaturation index 3%; ODI 4%, oxygen desaturation index 4%; REM, rapid eye movement sleep; SaO_2, mean oxygen saturation; TST, total sleep time; TST90, percentage of total sleep time with oxygen saturation <90%.

impairment or Alzheimer's disease/dementia. Most studies also included a relatively short follow-up (4–6 years). Our study makes a novel contribution by including younger community-dwelling men at baseline compared to prior studies and a longer follow-up period more relevant to examining associations of OSA-related sleep deficits and sleep disruption with future cognitive decline.

Five studies that examined OSA or sleep macroarchitecture predictors of cognitive decline recruited men and women and did not consider sex differences or perform sex-stratified analysis (Lutsey et al., 2016; Martin et al., 2015; Osorio et al., 2015; Pase et al., 2017; Ramos et al., 2020). In a study of women without dementia ($n = 298$, mean [SD] age 82.3 [3.2] years) Yaffe et al. (2011) demonstrated that an AHI ≥15 events/h, ODI ≥15 events/h, and >7.0% sleep time in apnea or hypopnea were associated with earlier onset of mild cognitive impairment or dementia after a mean follow-up of 4.7 years. In contrast, our study in men did not show associations of the AHI with cognitive function or decline after 8 years. Although our study included a longer mean follow-up, the sample was considerably younger at baseline (mean [SD] age 58.9 [8.9] years), which could have influenced the findings.

In the Osteoporotic Fractures in Men (MrOS) Sleep Study of community-dwelling men aged ≥67 years, men in the lowest quartile of percentage of time in N1 sleep and men who recorded less REM sleep showed a greater decline on the Modified MMSE (3MS) after a mean follow-up of 3.7 years (Song et al., 2015). While it is unclear why the results of the MrOS study differ from our findings, differences in mean follow-up time and age of these men may have influenced the likelihood of sleep macroarchitecture showing associations with cognitive decline.

In prior studies, OSA (AHI ≥15 events/h) has been associated with an earlier onset of mild cognitive impairment or Alzheimer's disease and an increased risk of dementia (Osorio et al., 2015; Pase et al., 2017; Yaffe et al., 2011). Severe OSA (AHI ≥30 events/h) has also been associated with worse visual attention and processing speed (Martin et al., 2015). In contrast, in the Atherosclerosis Risk in Communities Study, Lutsey et al. (2016) did not report any associations of AHI, TST90, or hours of TST with cognitive decline (Delayed Word Recall and Digit Symbol Substitution) after 15 years in middle-aged and older men and women (mean age 61 years at baseline).

In our study, the only significant adjusted associations were a higher percentage of N1 sleep with better TMT-A performance and greater mean SaO_2 with worse TMT-A performance. These associations contrast with literature in patients with OSA showing worse cognitive function was associated with greater N1 sleep from frequent arousals and lower mean SaO_2 (Marchi et al., 2020; Sangal & Sudan, 2020; Shahveisi et al., 2018). Our association of a higher percentage of N1 sleep with better TMT-A performance also contrasts with the association in the older sample of men (aged ≥65 years) in our cross-sectional analysis, which suggested that greater light or fragmented sleep is associated with worse TMT-A performance (Parker, Appleton, et al., 2021).

Interestingly, when examining associations of baseline OSA parameters with future cognitive decline, a lower ODI 3% was associated with higher odds of declining on the MMSE. This association was only apparent after adjusting for age but did not persist after adjustment for baseline MMSE performance. Further studies are needed to expand our findings and determine if oxygen desaturation parameters are linked with future cognitive decline.

Some evidence suggests that a higher percentage of N1 sleep and frequency of arousals at baseline are associated with less sleepiness after treatment with CPAP (Su et al., 2016). The literature also suggests that CPAP improves performance across various cognitive function domains, including attention, vigilance, memory, and executive function (Seda et al., 2021). In our study, men treated with CPAP (≥4 h/night), MAS, or surgery ($n = 19$) showed significantly faster TMT-A completion times (better performance) at follow-up compared to men who were untreated or used CPAP for <4 h/night. However, our data cannot account for potential confounding by treatment adherence or other health and behavioural factors that may have influenced cognitive function in these men.

Given that men with mild OSA may have been less likely to seek treatment, potentially leading to worse OSA over time, this may explain why they were more likely to show a significant baseline to follow-up reduction in TMT performance. However, the associations with percentage of N1 sleep and mean SaO_2 were of small effect size and questionable clinical significance. Longer and sufficiently large prospective follow-up evaluations remain warranted to clarify the nature and strength of associations of sleep-related breathing disturbances with future cognitive function and the effects of CPAP or other treatments on these associations.

Our sensitivity analysis examining cross-sectional associations of baseline OSA and sleep macroarchitecture parameters with baseline TMT performance revealed that the percentage of N1 sleep was not associated with baseline TMT-A performance in men who participated in the follow-up cognitive examination ($n = 157$). These findings suggest potential self-selection bias in men who participated in follow-up. These men could have been more resilient to disrupted sleep, or OSA treatment might have influenced the associations between the percentage of N1 sleep and mean SaO_2 at baseline and TMT-A performance at follow-up.

Marital status may have also influenced the associations observed. A greater proportion of men who participated at follow-up were partnered/married (89.8%) compared to men who chose not to participate (80.4%). Liu et al. (2020) recently investigated marital status differences in future dementia risk in 15,379 men and women aged ≥52 years from the community-based Health and Retirement Study. Widowed, never-married, and divorced respondents showed the highest proportions of dementia over 14 years compared to their married counterparts. Thus, one or more factors that relationships bring, including health behaviours, healthcare seeking, medication adherence, diet, and exercise, may have influenced the longitudinal outcomes in our sample of men (Brown & Lin, 2012; Liu & Umberson, 2008).

The characteristics of uncaptured OSA and arousal events, including apneas versus hypopneas and their durations, flow limitation, and arousal thresholds, could have contributed to the associations observed. Moreover, hypoxic burden or total area under the oxygen desaturation curve has been associated with cardiovascular disease-related and all-cause mortality and incident heart failure (Azarbarzin et al., 2019; Azarbarzin et al., 2020; Trzepizur et al., 2022). Recent findings suggest that frequent cortical arousals may, over time, reduce hypoxia and arousal intensity (Ali Azarbarzin, 'personal communication', September 2, 2022). These findings may partly explain our contradictory associations of percentage of N1 sleep and mean SaO_2 with TMT-A performance at follow-up.

Extending beyond previous cohort literature, we computed the HBI by dividing the total desaturation area of SaO_2 <90% by TST to examine associations between hypoxic burden and future cognitive function and decline. While no significant associations were observed with this variation of hypoxic burden that was not respiratory event specific, further investigations in larger community cohorts, including treatment intervention trials, remain needed to clarify the role and predictive value of hypoxic burden as a determinant of long-term cognitive function and decline.

The strengths of our study include a comparatively younger, understudied community-based sample representative of an adult male population, assessment of cognitive function by standardised and validated tests, and the collection of extensive survey and biomedical data (Grant et al., 2014; Martin, Haren, Middleton, & Wittert, 2007; Martin, Haren, Taylor, et al., 2007) that provided the means to control for multiple relevant potential confounders. Along with these strengths, several study limitations need to be acknowledged. The sleep sub-study was performed exclusively on men, so the generalisability of the results to women remains unknown. The follow-up response rate over 8–10 years was low, possibly related to the cognitive tests attached to a follow-up sleep study that was not well received. However, the PSG cohort had a 75% response rate on survey work. Although this study adjusted for multiple potential confounders, residual and unknown factors could have affected the findings. Also, a limited number of cognitive function domains were assessed. Another limitation is the temporal lag of 1–4 years between clinics and sleep assessments, with potential changes in clinical measures and the development of OSA over that period. Lastly, while excluding men who self-reported OSA treatment did not quantitatively influence the findings in our study, obtaining OSA diagnosis and treatment data via self-report may have influenced the accuracy of the data in analyses that included OSA-treated men, given the previously reported poor correlation between objective and subjective CPAP use data (Rauscher et al., 1993).

In summary, in this sample of community-dwelling men, a higher percentage of N1 sleep at baseline was associated with better TMT-A performance after 8 years, whereas greater mean SaO_2 was associated with worse performance. Future prospective studies should examine performance across a more comprehensive range of cognitive function domains. Given that this study relied on conventional PSG indices of OSA and sleep disruption, future research should consider characteristics of OSA and arousal events and non-routine hypoxaemia measures, which may show associations with cognitive function and decline.

AUTHOR CONTRIBUTIONS

Jesse L. Parker: Writing – original draft; writing – review and editing; methodology; conceptualization; investigation; visualization. **Andrew Vakulin:** Supervision; writing – review and editing. **Ganesh Naik:** Data curation. **Yohannes Adama Melaku:** Methodology. **David Stevens:** Methodology; validation; conceptualization. **Gary A. Wittert:** Conceptualization; data curation; resources; investigation; methodology; validation; project administration. **Sean A. Martin:** Conceptualization; investigation; methodology; validation; data curation; resources; project administration. **Peter G. Catcheside:** Conceptualization; methodology; validation. **Barbara Toson:** Formal analysis. **Sarah L. Appleton:** Methodology; writing – review and editing; supervision; project administration; funding acquisition. **Robert J. Adams:** Funding acquisition; data curation; supervision; methodology; writing – review and editing.

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Jesse L. Parker performed all primary and secondary analyses and takes primary responsibility for the work presented in this manuscript; Andrew Vakulin, Robert J. Adams and Sarah L. Appleton assisted with manuscript drafting and revisions, Robert J. Adams, David Stevens, and Sarah L. Appleton were responsible for the conduct of sleep studies. Gary A. Wittert and Sean A. Martin initiated and lead the FAMAS cohort. Yohannes Adama Melaku, Barbara Toson, and Ganesh Naik assisted with the planning of data analysis approaches. All authors have read and approved the final version of the manuscript. Open access publishing facilitated by Flinders University, as part of the Wiley - Flinders University agreement via the Council of Australian University Librarians.

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CONFLICT OF INTEREST STATEMENT

Andrew Vakulin is currently receiving research funding from the National Health and Medical Research Council and has received research funding and equipment from the ResMed Foundation and Phillips Respironics for research unrelated to this manuscript. Robert J. Adams and Gary A. Wittert have received research funding from the ResMed Foundation. Sarah L. Appleton has received research funding from the National Health and Medical Research Council of Australia and Hospital Research Foundation Group. Sean A. Martin has received research funding from the National Health and Medical Research Council of Australia. David Stevens has received research grant funding from the Hospital Research Foundation Group for the collection of cohort data. Jesse L. Parker, Yohannes Adama Melaku, Ganesh Naik, and Barbara Toson have nothing to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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