INVESTIGATING OBSTRUCTIVE SLEEP APNEA, SLEEP MACROARCHITECTURE, AND QUANTITATIVE ELECTROENCEPHALOGRAPHIC MARKERS OF COGNITIVE FUNCTION

by

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ABSTRACT

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder characterised by repetitive pharyngeal collapse leading to intermittent nocturnal hypoxemia (oxyhemoglobin desaturation) and sleep fragmentation. Physiological and pathophysiological consequences of OSA significantly interfere with sleep homeostasis, potentially contributing to cognitive dysfunction and decline. Advancing age is another fundamental risk factor for cognitive dysfunction and decline. Advancing age results in cortical morphological alterations, including neuronal shrinkage, reduced thickness, and synaptic loss, accelerating cognitive impairment and restricting functionality.

OSA and advancing age are associated with disrupted sleep architecture. Sleep is a daily biological imperative that plays a vital role in maintaining normal brain function, including overnight memory consolidation, neuronal communication, and removal of neurotoxic proteins and metabolites that gradually accumulate during wakefulness. Conventional OSA disease severity parameters, including the apnea-hypopnea index (AHI) and oxygen desaturation index (ODI), in addition to sleep macroarchitecture (e.g., sleep stage durations and percentages, total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset) assessed manually through visual inspection of 30-second epochs of the electroencephalogram (EEG) may be associated with daytime cognitive function. However, existing evidence comes from small experimental laboratory studies, clinical cohort studies (previous OSA diagnosis or incident mild cognitive impairment) or select community-based cohort studies (populations classified as at heightened risk of OSA or older age [≥65 years]). The clinical and select community-based cohort samples potentially account for often weak and inconsistent associations between routine polysomnography (PSG)-derived parameters and cognitive function. Consequently, the scope, magnitude, and generalisability of OSA- and disrupted sleep macroarchitecture-associated cognitive dysfunction among the broader population remain uncertain.

The AHI, the standard PSG-derived parameter of OSA disease severity, has been inconsistently associated with daytime cognitive performance outcomes with a limited ability to predict OSA-associated cognitive dysfunction. Consequently,

assessing the prognostic value of emerging alternative PSG parameters for predicting cognitive function is important. Emerging evidence, predominantly from small experimental laboratory and case-controlled studies, suggests finer-grained sleep EEG microarchitecture parameters, including absolute and relative spectral power, EEG slowing ratio, and sleep spindle metrics assessed through quantitative electroencephalographic (qEEG) power spectral analysis (PSA), might represent valuable brain-specific cognitive function markers. However, evidence from community-based cohort studies remains limited and preliminary, leaving the prognostic value of qEEG markers of cognitive function unclear.

This doctoral research makes several significant original contributions to knowledge by utilising data from one of Australia's most comprehensive and longest-running community-based cohort studies to investigate objective independent cross-sectional and longitudinal associations between OSA, sleep macroarchitecture, and sleep microarchitecture parameters (sleep spindle metrics and qEEG markers) and daytime cognitive function outcomes among community-dwelling middle-aged and older men. Methodological problems and literature gaps that this thesis aims to address are highlighted below.

Evidence supporting cross-sectional associations between OSA sleep macroarchitecture parameters and cognitive function outcomes is derived from subjective sleep study data or clinical or select community-based cohorts. Longitudinal evidence is derived from studies with a relatively short duration of follow-up (4-8 years), which may be insufficient time for cognition to change.

Although sleep spindles are commonly impaired in patients with OSA, it remains unclear whether OSA severity is a moderator of associations between sleep spindle metrics and cognitive function outcomes.

The one community-based cohort study that examined cross-sectional associations between EEG spectral power during NREM and REM sleep and cognitive function outcomes recruited participants ≥54 years, leaving it unclear whether differences in associations between EEG spectral power and cognitive function differ between older versus younger community-dwelling participants.

Evidence supporting longitudinal associations between sleep microarchitecture and future cognitive function is derived from small prospective observational studies with predominantly older participants and short follow-up (1-2 years) and many with baseline cognitive impairment (MCI and AD).

The six experimental chapters presented in this doctoral thesis resolve the issues identified in previous studies and the literature gaps. Specifically, objective sleep study data is utilised from a sample of community-dwelling middle-aged and older men recruited from the general population, includes a longer follow-up duration between baseline PSG and follow-up cognition in the longitudinal analyses, and also performs age-stratified and moderator analyses.

The broad hypotheses tested in the work presented in this thesis were:

a) Parameters indicative of greater OSA disease severity and disrupted sleep macro and microarchitecture would show independent cross-sectional associations with cognitive dysfunction.
b) Parameters indicative of greater OSA disease severity and disrupted sleep macro and microarchitecture assessed at baseline would show independent longitudinal associations with cognitive dysfunction 8–10 years later.

Consequently, the broad aim of the thesis was:

> To investigate independent cross-sectional and longitudinal associations between OSA and sleep macro and microarchitecture parameters and cognitive function among community-dwelling middle-aged and older men.

CHAPTER 1 assesses extant literature on advancing age and OSA as fundamental risk factors for cognitive function decline before assessing available evidence for associations between OSA and sleep macro and microarchitecture parameters and cognitive function. **CHAPTER 1** concludes by summarising the aim(s) and hypothesis of each experimental chapter **(CHAPTERS 3–8)**.

Besides the specific methodology provided in each experimental chapter, **CHAPTER 2** provides additional general methodological information on the community-based cohort study utilised to address the broad aim of the thesis, the Men Androgen

Inflammation Lifestyle Environment and Stress (MAILES) Study, one of the most comprehensive and longest-running longitudinal community-based cohort studies of male health and wellbeing with ageing in Australia.

The work described in **Study 1 (CHAPTER 3)** investigated independent cross-sectional associations between OSA, sleep macroarchitecture, and cognitive function. Conventional OSA disease severity parameters were not independently associated with cognitive function. Nevertheless, in older (≥65 years) community-dwelling men, a higher percentage of light non-rapid eye movement (NREM) stage 1 (N1) sleep was independently associated with worse visual attention and processing speed (trail-making test A [TMT-A] performance). These findings extend clinical and select community-based cohort studies and support that disrupted sleep macroarchitecture, although not OSA, may be associated with impaired attentional performance among older community-dwelling men. However, the associations between OSA, sleep macroarchitecture, and future cognitive function remain unclear. Therefore, it remains essential to investigate and determine the prognostic value of conventional sleep measures for identifying prospective cognitive dysfunction.

The work described in **Study 2 (CHAPTER 4)** addressed the above research question by investigating OSA and sleep macroarchitecture parameters assessed during the baseline (2010–2011) home-based PSG as predictors of cognitive function 8–10 years later while controlling for baseline cognitive task performance (2007–2010). A higher percentage of N1 sleep was associated with better TMT-A performance at follow-up, whereas higher mean oxygen saturation was associated with worse TMT-A performance at follow-up, contrasting with the significant cross-sectional associations. These surprising, counterintuitive findings could relate to the smaller follow-up sample, baseline participant characteristics, the potential influence of OSA treatment, and the characteristics of uncaptured OSA and arousal events (e.g., apneas versus hypopneas and respective durations, flow limitation, arousal thresholds, and non-routine measures of hypoxemia [e.g., OSA-specific hypoxic burden]). Future longitudinal studies should closely consider these factors, examine performance across more comprehensive cognitive function domains, and investigate the prognostic value of finer-grained sleep EEG microarchitecture parameters for identifying individuals at risk of future cognitive dysfunction.

The work described in **Study 3 (CHAPTER 5)** investigated independent cross-sectional associations between conventional OSA disease severity parameters and sleep spindle metrics. Sleep spindles are small bursts of neuronal oscillatory activity generated by the interplay of thalamic and thalamocortical nuclei predominantly occurring during NREM stage 2 (N2) sleep and, to a lesser extent, during stage 3 (N3) sleep. Some evidence suggests that sleep spindles may represent important physiological markers of cortical reorganisation processes involved in learning capability and overnight declarative memory consolidation. Small laboratory studies suggest that sleep spindles are impaired in patients with OSA. This community-based cohort study is the first to report independent cross-sectional associations between OSA disease severity parameters (obstructive breathing events [apnea-hypopnea index; AHI] and intermittent hypoxemia [percentage of total sleep with oxygen saturation <90%; TST90]) and spindle metrics during N2 sleep. Interestingly, compared to associations observed for spindle metrics during N2 sleep, the results suggest differential novel independent associations between OSA severity and hypoxemia measures and spindle metrics during N3 sleep. Given that the majority of previous literature focused on spindles during N2 or NREM sleep overall (N2 plus N3 sleep), the findings of this community-based cohort study highlight the importance of investigating spindles during N3 sleep separately as these may represent a discrete association with sleep disruption in OSA and a unique functional relationship with cognitive function, which requires future investigation. Further studies remain warranted to determine if sleep spindle metrics are associated with future cognitive decline and other functional and health-related outcomes.

The work described in **Study 4** (**CHAPTER 6)** investigated independent cross-sectional associations between sleep spindle metrics and cognitive function outcomes and determined the moderating role of OSA. Lower N2 sleep spindle occurrence (11–16 Hz, count) was associated with worse visual processing speed (longer inspection times), whereas higher N3 sleep average spindle frequency (Hz, oscillations/second) and fast spindle density (13–16 Hz, number/minute) were independently associated with worse trail-making test B (TMT-B) performance. With a decrease in N2 sleep spindle frequency, there was an increase in TMT-A completion times in men with severe OSA (AHI ≥30/h). Furthermore, with an increase

in N3 sleep spindle occurrence, there was an improvement in episodic memory and learning performance (Fuld Object Memory Evaluation [FOME] test) in men with mild OSA (AHI ≥10/h) but a decline in men with moderate OSA (AHI 20–29/h). These significant cross-sectional associations suggest that sleep spindles may represent useful cortical markers of cognitive function and that OSA plays an important moderating role in the associations between sleep spindle metrics and cognitive function outcomes. Specific spindle metrics during N2 and N3 sleep were independently associated with different cognitive function domains. Consequently, spindles during N2 and N3 sleep are likely not equal and potentially represent distinct associations with different cognitive function domains. Associations between sleep spindle metrics and prospective cognitive function decline warrant further longitudinal investigation.

The work described in **Study 5 (CHAPTER 7)** investigated independent cross-sectional associations between sleep microarchitecture determined by qEEG PSA and cognitive dysfunction. Lower NREM sleep relative delta power (0.5–4.5 Hz) and higher rapid eye movement (REM) sleep relative theta (4.5–8 Hz) and alpha (8–12 Hz) power were independently associated with worse visual attention and processing speed (TMT-A performance) and executive function (TMT-B performance) in older (≥65 years) community-dwelling men. These significant cross-sectional associations extend the emerging community-based cohort literature and support that sleep microarchitecture parameters may represent valuable brain-specific cognitive function markers, particularly among older community-dwelling men. Nevertheless, it remains uncertain whether sleep microarchitecture parameters are independently associated with prospective cognitive dysfunction, an important clinical question requiring further longitudinal investigation.

The work described in **Study 6 (CHAPTER 8)** addressed the next logical research step by investigating whether sleep microarchitecture parameters, including relative EEG spectral power, EEG slowing ratio, and sleep spindle metrics (described in previous cross-sectional analyses) assessed during the 2010–2011 home-based PSG were predictive of cognitive function at 8–10 years follow-up while controlling for baseline cognitive task performance. Baseline sleep microarchitecture parameters were not independent predictors of cognitive function after 8–10 years.

A potential explanation for these findings is the significant number of participants lost to follow-up or who did not consent to follow-up assessments, which reduced the power to detect significant associations, likely of small effect size. Moreover, several characteristics of participants who completed follow-up cognitive assessments may have been subject to selection bias and uncontrollable factors (e.g., the impact of OSA treatment modality and adherence).

CHAPTER 9 summarises the overall original contribution of this thesis work to understanding the associations between OSA and sleep macro and microarchitecture parameters and cognitive function in the broader population, outlines key limitations of the work, and highlights recommended future research directions in large community-based cohort studies.

To summarise, specific sleep macro and microarchitecture parameters were cross-sectionally associated with several cognitive function outcomes. However, although conventional OSA and sleep macroarchitecture parameters showed contrasting, counterintuitive associations, baseline sleep microarchitecture was not prospectively associated with cognitive function assessed after 8–10 years. The prognostic value of qEEG as an early brain-specific cognitive impairment marker requires further prospective investigation in studies with longer follow-up durations to potentially capture greater cognitive decline and different and more extensive cognitive tests that may be more sensitive to change or more likely to be affected by nocturnal hypoxemia or sleep disruption.

LIST OF PUBLICATIONS

The following list of publications in peer-reviewed journals in which I was involved as a lead author during my PhD study period have arisen from work conducted towards (and are included in) this thesis:

Journal articles:

Parker JL, Appleton SL, Melaku YA, Stevens D, Wittert GA, Martin S, Adams RJ & Vakulin A. Sleep macroarchitecture but not obstructive sleep apnea is independently associated with cognitive function in only older men of a population-based cohort. J Sleep Res. 2021:e13370. **[CHAPTER 3]**

Parker JL, Melaku YA, D'Rozario AL, Wittert GA, Martin S, Catcheside PG, Lechat B, Teare AJ, Adams RJ, Appleton SL & Vakulin A. The association between obstructive sleep apnea and sleep spindles in middle-aged and older men: A community-based cohort study, *Sleep*. 10.1093/sleep/zsab282. **[CHAPTER 5]**

Parker JL, Appleton SL, Melaku YA, D'Rozario AL, Wittert GA, Martin SA, et al. The association between sleep microarchitecture and cognitive function in middle-aged and older men: a community-based cohort study. J Clin Sleep Med. 2022. **[CHAPTER 7]**

Published abstracts:

Parker JL, Adams RJ, Appleton SL, Melaku YA, Vakulin A. 0722 The Association Between Obstructive Sleep Apnea and Neurobehavioural Function in Men: A Large, Population-Based Cohort Study. *Sleep,* Volume 43, Issue Supplement_1, April 2020, Pages A274-A275.

Parker JL, Appleton SL, Melaku YA, D'Rozario AL, Wittert GA, Catcheside PG, Adams RJ, Vakulin A, Martin SM. 158 The Association Between Sleep Spindles and Cognitive Function in Middle-Aged and Older Men: A Population-Based Cohort Study. *Sleep*, Volume 44, Issue Supplement_2, May 2021, Pages A64-A65.

Parker JL, Melaku YA, D'Rozario AL, Wittert GA, Martin SM, Catcheside PG, Lechat B, Teare AJ, Appleton SL, Adams RJ, Vakulin A. P110 The association between sleep spindles and cognitive function in middle-aged and older men: A community-based study. *SLEEP Advances*, Volume 2, Issue Supplement_1, October 2021, Pages A56-A57.

Parker JL, Melaku YA, D'Rozario AL, Wittert GA, Martin SM, Catcheside PG, Lechat B, Teare AJ, Appleton SL, Adams RJ, Vakulin A. P109 The association between sleep microarchitecture and cognitive function in middle-aged and older men: A community-based study. *SLEEP Advances*, Volume 2, Issue Supplement_1, October 2021, Page A56.

Parker JL, A Vakulin, Y Melaku, G Wittert, S Martin, A D'Rozario, P Catcheside, B Lechat, A Teare, B Toson, S Appleton, R Adams. O003 Longitudinal association of obstructive sleep apnea and sleep macroarchitecture with future cognitive function in middle-aged and older men from a community-based cohort study. *SLEEP Advances*, Volume 3, Issue Supplement_1, October 2022, Pages A1-A2.

Parker JL, A Vakulin, Y Melaku, G Wittert, S Martin, A D'Rozario, P Catcheside, B Lechat, A Teare, B Toson, S Appleton, R Adams. O070 Longitudinal associations of sleep microarchitecture with future cognitive function in middle-aged and older men from a community-based cohort study. *SLEEP Advances*, Volume 3, Issue Supplement_1, October 2022, Pages A29-A30.

DECLARATION

I certify that this thesis:
1. does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and
2. to the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text.

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Date: February 20 2023

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GLOSSARY OF ABBREVIATIONS/ACRONYMS

AASM	American Academy of Sleep Medicine
AD	Alzheimer's disease
AHI	Apnea hypopnea index (events·hr^{-1} sleep)
aMCI	Amnestic MCI
APOE	Apolipoprotein E
APPLES	Apnea Positive Pressure Long-term Efficacy Study
ASAP	Akershus Sleep Apnea Project
BMI	Body mass index
CATI	Computer-assisted telephone interview
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CVD	Cardiovascular disease
DAG	Directed acyclic graph
df	Degrees of freedom
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
EMG	Electromyography
EOG	Electrooculography
ESS	Epworth sleepiness scale
FAMAS	Florey Adelaide Male Ageing Study
FFT	Fast Fourier Transform
FOME	Fuld object memory evaluation
h	Hour
/h	Per hour
Hz	Hertz, cycles per second
IQR	Interquartile range
k	Cohen's Kappa
KSS	Karolinska sleepiness scale
MAS	Mandibular advancement splint
MAILES	Men Androgen Inflammation Lifestyle Environment and Stress
MCI	Mild cognitive impairment
MESA	Multi-Ethnic Study of Atherosclerosis

MMSE	Mini-mental state examination
MoCA	Montreal cognitive assessment
MRI	Magnetic resonance imaging
MrOS	Osteoporotic Fractures in Men Study
MSLT	Multiple sleep latency test
ms	Millisecond
MVA	Motor vehicle accident
MWT	Maintenance of wakefulness test
NREM	Non-rapid eye movement sleep
NWAHS	North West Adelaide Health Study
N1	Stage 1 sleep
N2	Stage 2 sleep
N3	Stage 3 sleep
ODI	Oxygen desaturation index
O_2 Nadir	Oxygen saturation nadir
O_2	Oxygen
OSA	Obstructive sleep apnea
PFC	Prefrontal cortex
PVT	Psychomotor vigilance test
PSA	Power spectral analysis
PSG	Polysomnography
PUP	Phenotyping Using Polysomnography
qEEG	Quantitative EEG
QoL	Quality of life
RAVLT	Rey Auditory Verbal Learning Test
RCT	Randomised controlled trial
REM	Rapid eye movement sleep
SD	Standard deviation
s	Second
SHHS	Sleep Heart Health Study
SNS	Sympathetic nervous system
SWA	Slow-wave activity
SWS	Slow-wave sleep

SYNAPSE	Autonomic Nervous System Activity, Aging and Sleep Apnea/Hyponea Study
TMT-A	Trail-making test A
TMT-B	Trail-making test B
TMT	Trail-making test
TST	Total sleep time
TST90	Percentage of total sleep time with oxygen saturation <90%
μV^2	Microvolts squared (unit of absolute EEG power)
WAIS-IV	Wechsler Adult Intelligence Scale-Fourth Edition

CHAPTER 1. GENERAL INTRODUCTION AND LITERATURE REVIEW

1.1 General introduction – research problems

Advancing age is associated with cognitive function decline (1-4), disrupted conventional sleep electroencephalography (EEG) macroarchitecture (5-8), and an increased risk of obstructive sleep apnea (OSA) (9-11). OSA is the most common sleep-related breathing disorder (12) associated with daytime cognitive dysfunction, including attentional problems, vigilance failure, memory impairments, and executive dysfunction (13-17). These cognitive function deficits likely result from repetitive pharyngeal collapse leading to intermittent nocturnal hypoxemia (oxyhemoglobin desaturation) and sleep fragmentation.

Although multiple clinical and community-based cohort studies previously examined cross-sectional (18-25) and longitudinal (26-31) associations between conventional OSA and sleep EEG macroarchitecture parameters and daytime cognitive performance outcomes, specific methodological problems limit the generalisability of the results to the broader population. Cross-sectional studies recruited from clinical (previous OSA diagnosis or incident mild cognitive impairment [MCI]) or select (heightened risk of OSA [Berlin screening questionnaire] or older age [≥65 years]) community-based cohort studies. Longitudinal studies recruited from older populations (≥60 years at baseline), including many participants with baseline cognitive impairment (MCI or Alzheimer's disease [AD]) and a relatively short follow-up (4–8 years) between polysomnography (PSG) and cognitive assessment and thus insufficient time may have passed for cognition to change. Consequently, additional objective cross-sectional and longitudinal studies are necessary to address the issues outlined above through analysis of data from a younger cohort randomly selected from the community and with longer follow-up to clarify the scope, magnitude, and generalisability of OSA- and disrupted sleep macroarchitecture-associated cognitive dysfunction among the broader population, which are significant original contributions to knowledge arising from Chapters 3 and 4 of this thesis.

Clinically, OSA is diagnosed following a formal sleep study evaluation or nocturnal, laboratory-based PSG utilising manually scored measurements of electrical brain activity (EEG) and nocturnal respiratory disturbances (32, 33). Conventional clinical sleep macroarchitecture parameters (e.g., sleep stage durations and percentages, total sleep time, sleep efficiency, sleep onset latency, and wake after sleep onset) are assessed using manual sleep staging and scoring procedures. This traditional clinical approach of visual EEG inspection ignores rich electrophysiological data (e.g., quantitative EEG-derived sleep microarchitecture parameters) collected during overnight sleep studies, which could better relate to disease, health, and functional outcomes and provide useful phenotypic information (34). Quantitative EEG (qEEG) power spectral analysis (PSA) offers the opportunity to explore finer-grained sleep EEG microarchitecture parameters, including absolute and relative power of distinct EEG frequencies, EEG slowing ratio, and sleep spindle metrics. Emerging evidence, predominantly from small experimental laboratory (35-39) and case-controlled (40-43) studies, suggests qEEG may represent a valuable brain-specific cognitive function marker (44). However, the prognostic value of qEEG markers of cognitive function remains under-investigated among community-based cohort samples (45). Developing a robust brain-specific cognitive function marker remains important because conventional PSG-derived OSA disease severity and sleep macroarchitecture parameters are poorly and inconsistently associated with various daytime cognitive function outcomes.

Although qEEG may be a useful emerging brain-specific marker of disease, health, and functional outcomes, several literature gaps that need to be addressed in larger studies are evident. While sleep spindle metrics commonly display morphological changes in patients with OSA (decreased frequency, densities, and amplitude) (46-48), the generalisability of associations between OSA parameters (obstructive breathing episodes and intermittent hypoxemia) and sleep spindle abnormalities has not been confirmed in a community-based cohort study. Moreover, while preliminary evidence from small experimental laboratory studies suggests that sleep spindles are associated with memory performance and attention, vigilance, and verbal fluency (49-51), the potential moderating effect of OSA severity in these associations has not

been investigated. The one community-based cohort study that previously examined cross-sectional associations between EEG spectral power during rapid eye movement (REM) and non-REM (NREM) sleep recruited participants ≥54 years, leaving associations between EEG spectral power and cognitive function among younger community-dwelling participants unclear. Lastly, evidence supporting longitudinal associations between baseline sleep microarchitecture and future cognitive function is derived from small prospective observational studies (52-55) that recruited older age participants (≥60 years at baseline) or included a short follow-up (1-2 years) between PSG and cognitive assessment. Recruitment of older participants with cognitive impairment and the relatively short follow-up emphasises the importance of conducting longitudinal community-based cohort studies to provide more robust evidence on the prognostic value of qEEG as a valuable marker of future cognitive dysfunction and decline.

Chapters 5, 6, 7, and 8 of this thesis make significant original contributions to knowledge by utilising data from a community-based cohort study to analyse cross-sectional and longitudinal associations between sleep qEEG markers and cognitive function outcomes with specific attention to addressing the fundamental limitations and knowledge gaps of previous studies. The cross-sectional analyses address the limitations of small sample size (OSA and spindles), moderation effects (OSA, spindles, and cognition), and age stratification (EEG spectral power and cognition). The longitudinal analysis addresses the limitations of small sample size and length of follow-up by assessing associations between baseline sleep microarchitecture and cognition assessed 8-10 years later.

The literature review of this thesis begins by assessing extant literature on age-associated cognitive function decline and the specific domains most strongly affected by OSA. The review of this literature motivates the cognitive tests administered in the study cohort and analysed in this thesis. Next, evidence for cross-sectional and longitudinal associations between OSA, sleep macroarchitecture, and cognitive function is assessed, followed by emerging evidence on the associations between sleep microarchitecture and cognitive function. Lastly, this introductory chapter highlights the importance of conducting further community-based cohort studies to

extend the emerging literature and identify the prognostic value of qEEG as a useful brain-specific cognitive function marker.

1.2 Age-associated cognitive function decline

Advancing age is associated with a measurable decline in performance across multiple cognitive function domains, including attention/vigilance, memory, executive function, language, and visuospatial/psychomotor abilities (1, 3). Furthermore, with rising years of life expectancy, there is an increase in age-associated MCI (early loss of memory or other cognitive abilities while maintaining independent living) and an approximate 20–30% conversion rate to Alzheimer's disease (AD) and clinical dementia (56, 57). Dementia remains a significant disease burden and one of the largest health and social challenges facing Australia and the world (58). In 2018, the Australian Bureau of Statistics estimated that dementia was the leading cause of death in women, the second leading cause of death overall, and predicted to become the leading cause of death within the next five years (59). The National Centre for Social and Economic Modelling estimated that in 2018 >436,000 Australians were living with dementia, with approximately 1.5 million people involved in their care (60). In 2022, an estimated 487,500 Australians are living with dementia (60). It is predicted that by 2058 approximately 1.1 million Australians will be living with dementia, including 27,000 people with younger onset dementia developing before age 65 (60). The total cost of dementia to the community in 2018 was $15 billion and is predicted to reach $18.7 billion by 2025 and >$36.8 billion by 2056 (61). The magnitude of age-associated cognitive function decline across various domains will be assessed, with a specific focus on the cognitive tests investigated in the experimental chapters of this thesis and the rationale for why these tests were chosen.

1.2.1 Exploring sleep as an early marker of cognitive function decline

Importantly, there is a transition period where subtle deterioration in cognitive function and contributing risk profiles might be detectable at a younger age before significant decline becomes evident (62). Emerging evidence suggests that sleep could represent a valuable early cognitive function marker. Sleep is a daily biological

imperative that plays a vital role in removing neurotoxic waste by-products that typically accumulate in the central nervous system (CNS) during wakefulness, enhancing memory consolidation, metabolic regulation, and reducing mental fatigue (63, 64). Therefore, cognitive function decline can potentially be identified early and defined through sleep architecture and patterns of electrical brain activity. Exploring sleep macro (traditional clinical sleep staging and scoring) and micro (quantification of brain oscillations) architectural characteristics could provide valuable early markers of cognitive function decline. Moreover, if sleep markers are linked with cognitive function decline, appropriate sleep management might represent a modifiable risk factor among at-risk populations. Before assessing extant literature on associations between sleep macro and microarchitecture and cognitive function outcomes, the magnitude of age-associated cognitive function decline across various domains will be assessed, with a specific focus on the cognitive tests investigated in the experimental chapters of this thesis.

1.2.2 Age-associated decline in executive function, visual attention, and visual processing speed

A hallmark of advancing age is a decline in performance on executive function tasks (3). Executive function represents higher-order cognitive processing abilities, including decision-making, problem-solving, flexibility, planning, sequencing, response inhibition, and multitasking (1). Age-associated executive function decline is particularly prominent compared to simple visual attention and processing speed, wherein performance is typically maintained well into older adulthood (3). The trail-making test (TMT) is a standardised, validated, and well-established cognitive test that assesses executive function, visual attention, and processing speed (65, 66) (see section 2.4.2 for a detailed description). Along with becoming particularly prominent with advancing age, executive dysfunction (impaired TMT-B performance) has been reported in patients with obstructive sleep apnea (OSA), frequently persisting despite treatment with continuous positive airway pressure (CPAP) therapy (15). Consequently, it is important to conduct community-based cohort studies to investigate independent associations between OSA parameters and TMT-B performance, which motivates TMT as a cognitive function test included in the experimental chapters of this thesis.

The very short-term storage of sensory information, long enough for the information to be registered and transferred into short-term memory (sensory memory), short-term memory, and motor skills (procedural memory) remain relatively stable with advancing age (67). However, episodic memory (longer-term memory for events) typically declines with advancing age (3). The Fuld object memory evaluation (FOME) is a standardised, validated, and well-established test of episodic memory and learning requiring the engagement of multiple sensory pathways (tactile, visual, and verbal) (68) (see section 2.4.3 for a detailed description). Along with frequently becoming impaired with advancing age, meta-analytic evidence has reported that verbal episodic memory (immediate and delayed recall, learning, and recognition) and visuospatial episodic memory (immediate and delayed verbal recall) are also significantly impaired in patients with OSA, which is another fundamental risk factor for cognitive function decline (17). This meta-analytic evidence motivates the choice of the FOME test to assess episodic learning and memory in this thesis, specifically through immediate and delayed verbal recall.

Studies that investigated age-associated decline in visual processing speed primarily focused on performance on the inspection time task and associations with MCI (69, 70). The inspection time task is a standardised, validated, and well-established test of visual processing speed (71) (see section 2.4.1 for a detailed description). One small study comparing performance on the inspection time task between 28 patients with MCI and 28 healthy age, gender, and education-matched controls reported that patients with MCI showed significantly longer inspection times compared to healthy controls (69). A review article reported that inspection time typically decreases by approximately 0.02 standard deviations (*SD*) per year (72). Furthermore, Godefroy et al. (70) found a mean ± *SD* inspection time of 46.7 ± 7.5 milliseconds in young adults compared to older adults with an inspection time of 117.3 ± 81.5 milliseconds. Information processing speed has also been impaired in patients with OSA. Similar to TMT-B performance, these impairments often persist despite CPAP treatment (73). Accordingly, it is important to investigate associations between OSA parameters and information processing speed to provide further insight into whether OSA parameters can be used to identify impaired information processing speed in community-based samples. Glymphatic system dysfunction may be an important

contributor to cognitive dysfunction and decline in older age, which will now be assessed.

1.2.3 Glymphatic system dysfunction could be involved in age-associated cognitive function decline

The glymphatic system serves as the brain's waste drainage pathway and is vital for clearing potentially harmful proteins and metabolites from the CNS (74-77). Sleep is vital for adequate glymphatic transport and clearance of neurotoxic waste products from the brain parenchyma via aquaporin-4 water channels (74). The restorative functions of sleep may enhance the clearance of neurotoxic waste products that accumulate during wakefulness. Consequently, in common sleep disorders such as obstructive sleep apnea (OSA), frequent microarousals, and intermittent hypoxemia can promote the accumulation of neurotoxic proteins, particularly amyloid beta (Aβ) peptide and hyperphosphorylated tau, key biomarkers of cognitive decline and dementia (78).

Accumulation of Aβ and tau in older age is associated with decline in episodic memory and executive function. Two studies report evidence for a relationship between key biomarkers of cognitive decline and impaired performance in episodic memory and executive function in older adults (79, 80). Maass et al. (79) investigated regional tau, global Aβ, and medial temporal lobe (MTL) atrophy in cognitively normal older adults (age range, 60–93 years) and the relation between these biomarkers of cognitive decline and dementia and episodic memory (visual and verbal recall). Using positron emission tomography, the authors found that greater tau accumulation within temporal lobe subregions, particularly in the parahippocampal gyrus and posterior entorhinal cortex, significantly predicted episodic memory performance. In a cross-sectional study, Tideman et al. (80) showed that greater Aβ was associated with impaired executive function (TMT-B performance) but not with memory, verbal, and visuospatial function in older cognitively unimpaired adults (n=316). The findings from these studies further motivate the choice of the TMT and FOME tests in the experimental chapters of this thesis. Along with advancing age and glymphatic system dysfunction, OSA is another fundamental risk factor that could be driving cognitive impairment. The next section of this review will focus specifically on the literature that has investigated cognitive impairment in OSA.

1.3 Definition and diagnosis of OSA

OSA is characterised by recurrent pharyngeal collapse leading to airflow reduction (hypopnea) or cessation (apnea), with each episode lasting ≥10 seconds (81, 82). Recurrent pharyngeal collapse is accompanied by intermittent nocturnal hypoxemia (oxyhemoglobin desaturation) and hypercapnia (elevated arterial carbon dioxide), spontaneous respiratory-induced microarousals, and exaggerated negative intrathoracic pressure (82-84). Nocturnal physiological disturbances persist despite continued respiratory efforts (81). Nocturnal microarousals interrupt sleep macroarchitecture, producing fragmented sleep (84, 85).

Nocturnal, laboratory-based PSG is the gold-standard diagnostic test for OSA. This procedure is typically performed in the sleep laboratory to evaluate sleep depth, quality, and macroarchitecture and indicate sleep disorders (32, 33, 86, 87). PSG comprises the measurement of electrophysiological signals during sleep, providing potentially valuable insight into electrical brain activity (EEG), electrical muscle activity (submental electromyography), and eye movements (electrooculography) in conjunction with respiratory effort, nasal airflow, heart rate variability, oxygen saturation (finger pulse oximetry), thoracic and abdominal motion, and body position (33, 88). EEG is routinely utilised for traditional clinical sleep staging and arousal scoring (88).

1.3.1 Prevalence rates of OSA among prospective epidemiological studies

OSA is the most prevalent sleep-related breathing disorder (89-92). OSA is estimated to affect almost one billion adults worldwide (12), with the highest prevalence reported amongst middle-aged males (91). Prospective community-based cohort studies, notably the Wisconsin Sleep Cohort Study (90), Sleep Heart Health Study (SHHS) (10, 93), and Penn State sleep study (94, 95), highlight that several decades ago, <10% of general adult populations, on average, show signs and symptoms of OSA. Notably, over the previous 30 years, the prevalence of OSA has risen from 4–10% (96, 97) to now affecting 20–38% of middle-aged and older populations (92, 98-100). Epidemiological studies estimate that approximately 85%

of patients presenting with clinically significant OSA in the broader population remain undiagnosed (92, 101). The rising OSA prevalence could be attributed to the global obesity epidemic, underscoring the importance of further exploring this frequently under-recognised and under-diagnosed sleep-related breathing disorder to work towards effective diagnosis, treatment, and clinical management.

1.3.2 American Academy of Sleep Medicine respiratory scoring criteria

OSA diagnosis and disease severity classification are primarily based on the apnea-hypopnea index (AHI). The AHI reflects the number of obstructive breathing episodes (apneas or hypopneas) ≥10 seconds /h of sleep (32, 102). The American Academy of Sleep Medicine (AASM) has developed recommendations regarding standard definitions of abnormal sleep-related breathing events with criteria and severity ratings (103). While there is consensus among studies that apneas should be scored when there is complete or almost complete airflow cessation (≥90%) lasting ≥10 seconds (32, 104), considerable controversy has arisen concerning the scoring of hypopneas (105). Several AASM respiratory scoring criteria have evolved, including *Chicago* ($AASM_{1999}$), *Recommended* ($AASM_{Rec}$), and *Alternative* ($AASM_{Alt}$), with the alternative criterion recently updated to reflect more current guidelines (104, 106). To score a hypopnea, $AASM_{1999}$ requires either an apparent decrease (>50%) from baseline in the amplitude of a valid measure of breathing during sleep or an apparent reduction of a validated measure of breathing during sleep associated with an oxygen desaturation of >3% or an arousal lasting ≥10 seconds (103); and $AASM_{Rec}$ requires ≥30% airflow reduction and ≥4% oxygen desaturation, although arousal is optional (107). The more liberal and current 2012 ($AASM_{2012}$) scoring criteria defines hypopneas as a ≥30% drop of airflow lasting ≥10 seconds with either an arousal or ≥3% oxygen saturation drop (99, 107).

According to conventionally accepted AASM scoring criteria, <5/h apneas/hypopneas is considered normal sleep breathing; mild OSA is diagnosed with an AHI ≥5 <15/h; moderate with an AHI ≥15 <30/h; and an AHI ≥30/h is considered severe OSA (32). However, the experimental chapters of this thesis use the 2007 $AASM_{Alt}$ scoring criteria to identify the presence and severity of OSA. The

$AASM_{Alt}$ scoring criteria defines normal sleep breathing (no OSA) as an AHI <10/h; mild OSA as an AHI 10-19/h; moderate OSA as an AHI 20-29/h; and severe OSA as an AHI ≥30/h of sleep. Furthermore, the $AASM_{Alt}$ scoring criteria defines an apnea as a complete or near complete airflow cessation (≥90% airflow reduction) measured using nasal cannula pressure excursions with breathing lasting ≥10 seconds, whereas a hypopnea is defined as a ≥50% decrease in nasal cannula pressure excursions with breathing along with an associated ≥3% oxygen saturation drop or cortical arousal (32). The $AASM_{Alt}$ scoring criteria was chosen to maintain comparability with previous work. It has been reported that an AHI of 5/h of sleep used to identify OSA by the $AASM_{Rec}$ criteria is approximately equivalent to 10/h using the $AASM_{Alt}$ criteria and 15/h using the $AASM_{1999}$ criteria (32). Moreover, the $AASM_{Alt}$ scoring criteria was recommended by an expert panel of the Australasian Sleep Association for use in prospective epidemiological studies (108).

1.3.3 AASM respiratory scoring criteria – implications for abnormal sleep-related breathing events

Some evidence suggests that the AASM scoring criteria may have implications for the incidence of hypopneas and associations observed with sleep disruption and EEG signals. Duce et al. (109) investigated the effect of the $AASM_{2012}$ scoring criteria on the prevalence and severity of OSA relative to previous scoring criteria in 112 patients undertaking PSG for suspected OSA. The authors concluded that the median AHI across the night and during NREM and REM sleep was significantly higher when using the $AASM_{2012}$ scoring criteria compared to the $AASM_{1999}$, $AASM_{Rec}$, and $AASM_{Alt}$ scoring criteria. Similar to Duce et al. (109), BaHammam et al. (106) compared the AHI values obtained using hypopnea definitions according to three AASM scoring criteria ($AASM_{2012}$, $AASM_{Rec}$, and $AASM_{Alt}$) in 100 patients investigated for OSA using overnight PSG. The authors found that using the $AASM_{2012}$ scoring criteria resulted in significantly more hypopneic events being detected compared to the other scoring criteria. Therefore, previous studies suggest that the chosen scoring criteria may significantly influence the observation of sleep disruption and abnormal EEG signals.

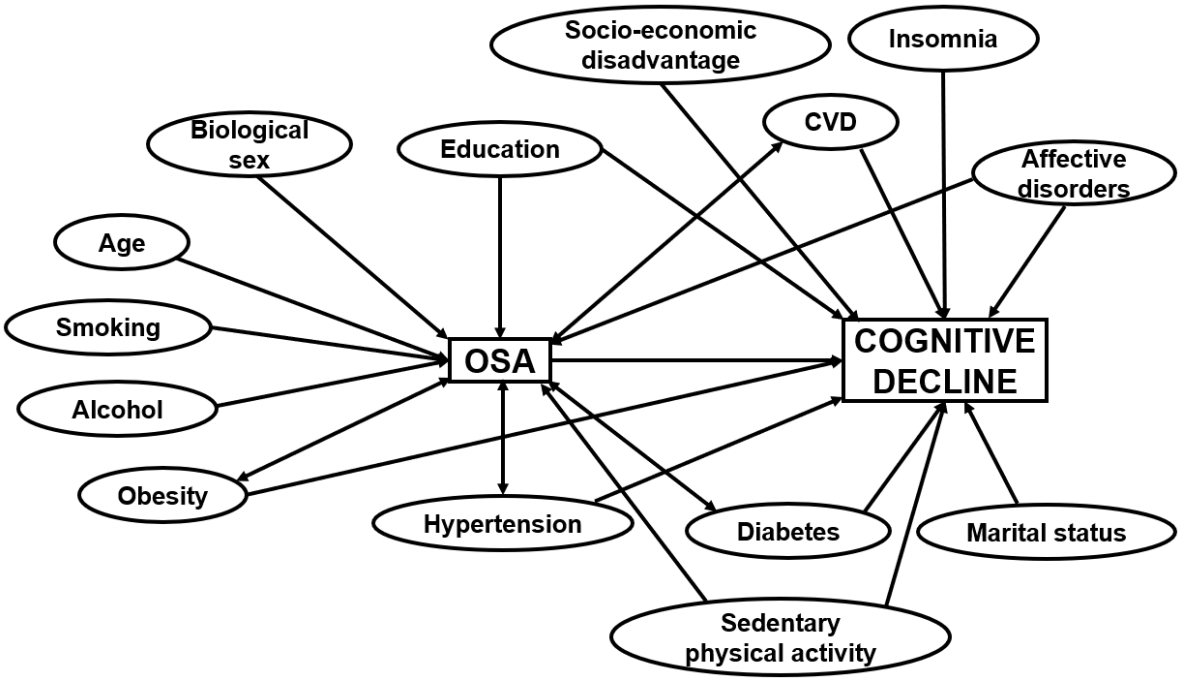
1.3.3.1 Respiratory scoring criteria – implications for cognitive function decline

The current updated $AASM_{2012}$ scoring criteria is only considered as a guideline. Therefore, it is perfectly acceptable for sleep laboratories to utilise alternative scoring criteria guidelines when defining abnormal sleep-related breathing events. However, the scoring criteria used to define abnormal sleep-related breathing events could have implications for associations observed or not observed with cognitive function decline. For example, intermittent hypoxemia and sleep fragmentation may be aspects of OSA associated with impaired performance across multiple cognitive function domains (110). Consequently, using the more liberal and current $AASM_{2012}$ scoring criteria may be more sensitive for identifying potential associations of OSA parameters with cognitive function outcomes, given that less airflow reduction or oxygen desaturation is necessary to score a hypopnea. Conversely, the $AASM_{Rec}$ and $AASM_{1999}$ scoring criteria could be less sensitive for identifying associations between OSA parameters and cognitive function outcomes. Specifically, the older 1999 Chicago criteria may be more sensitive than the AASM recommended criteria, given the 50% decrease in breathing during sleep necessary to score a hypopnea. Therefore, discrepancies in the scoring criteria used across studies could influence associations observed or not observed with various cognitive function outcomes.

1.3.4 Vulnerability risk factors for OSA – implications for cognitive function decline

Vulnerability risk factors for OSA include older age, obesity, and biological sex (81). Therefore, in prospective epidemiological studies, it is important to control for these potential confounders when exploring associations between OSA parameters and cognitive function decline (Figure 1.2). Vulnerability risk factors for OSA and implications for cognitive function decline will now be assessed.

Figure 1.1 Schema of factors associated with OSA and cognitive function decline and their respective interactions



1.3.4.1 OSA and advancing age – implications for cognitive function decline

Community-based studies demonstrate that adults ≥65 years have a ≥2-fold increased risk of OSA (10, 111, 112). Small studies indicate that ageing contributes to increased pharyngeal resistance and unfavourable morphology, including narrowing and lengthening (113-115). Along with physiological mechanisms, the increased risk of OSA with advancing age could be driven, at least in part, by metabolic and cardio-metabolic comorbidities, including obesity (body mass index [BMI] ≥30 kg/m^2), hypertension, cardiovascular disease (CVD), and diabetes mellitus, all of which are common in older age, and increasing globally (116). A recent community-based cohort study examined associations between OSA severity and metabolic and functional characteristics among a representative sample of older adults ≥60 years and reported a significant association between OSA and hypertension but not other metabolic and cardio-metabolic comorbidities (117). However, results have not always been consistent. For example, a systematic review of 68 studies, including a group of adults aged 30–60 and another group aged ≥60

years both with OSA, reported that adults aged ≥60 years showed cognitive function comparable to adults of the same age group without symptoms of OSA (118). Although there is generally an increased risk of OSA and cognitive decline with advancing age, inter-individual differences in the response to ageing may influence the extent of cognitive function decline. Therefore, age may moderate the relationship between sleep and cognitive function and higher age has been associated with cognitive function decline (3). These findings indicate that it is also important to treat age as a covariate and control for this variable when determining associations between OSA and cognitive function.

1.3.4.2 OSA and obesity – implications for cognitive function decline

The rising prevalence of OSA and its consequences are tied to the global obesity epidemic (119). Obesity (BMI ≥30 kg/m^2) is the strongest risk factor for OSA (119). Obesity extensively increases upper body adipose deposition and decreases pharyngeal size and patency (120). Moreover, extensive adipose deposition reduces thoracic compliance and increases oxygen demand (119, 121, 122). Similar to advancing age, obesity is associated with metabolic and cardio-metabolic comorbidities that could further exacerbate the association between OSA and cognitive decline (116, 123). However, despite increasing evidence suggesting the potential moderating role of obesity in the association between OSA and cognitive decline, few studies have adequately controlled for this potential confounder. Therefore, it will be important for future studies to account for the potential moderating influence of to control for obesity when examining the association between OSA and cognitive function decline. It is also important to acknowledge that there is evidence that obesity significantly affects performance across various cognitive function domains independent of OSA. A systematic review recently examined evidence for deficits across specific cognitive function domains in mid-life adults (18–65 years) (124). In obese mid-life adults, significant deficits have been reported in intellectual function, visual construction and memory (125), complex attention (126), verbal memory, psychomotor performance and speed (127), and decision making (128).

It is also important to acknowledge that there is evidence that obesity significantly affects performance across various cognitive function domains independent of OSA. A systematic review recently examined evidence for deficits across specific cognitive function domains in mid-life adults (18–65 years) (124). In obese mid-life adults, significant deficits have been reported in intellectual function, visual construction and memory (125), complex attention (126), verbal memory, psychomotor performance and speed (127), and decision making (128).

1.3.4.3 OSA and biological sex – implications for cognitive function decline

Biological sex is another vulnerability factor for OSA that may also have implications for cognitive function decline. In men, extensive adipose deposition in the upper body could interfere with breathing during sleep and increase susceptibility to hypoxia, which may lead to cognitive impairment (129, 130). With respect to women, OSA is frequently diagnosed post-menopause, suggesting that this period could result in heightened vulnerability to OSA and cognitive function decline, likely due to heightened inflammatory responses and decreased metabolic activity (116).. Recent data suggests that there are hormonal changes with age in men and women, which may indicate an interaction between age, biological sex, and OSA severity on cognitive function. For example, testosterone, the primary sex hormone in men, shows gradual decline with age, which has been reported to result in more disrupted and fragmented sleep, greater adipose deposition, and an increased risk of CVD, clinical dementia, and AD (131-134). In women, estrogen is the primary sex hormone, which, similar to men, declines during menopause and thus during the post-menopausal period may exacerbate the risk of OSA and cognitive decline (134). As such, women may be less likely to develop OSA and AD pre-menopause, which heightened vulnerability to OSA and AD post-menopause.

1.3.5 OSA and metabolic and cardio-metabolic comorbidities – implications for cognitive function decline

Along with age, obesity, and biological sex, metabolic and cardio-metabolic comorbidities, including diabetes mellitus, cardiovascular disease, and hypertension, could also influence associations between OSA and cognitive function decline and

should be controlled for in community-based cohort studies. Implications of metabolic and cardio-metabolic comorbidities for cognitive function decline in OSA will now be assessed.

1.3.5.1 OSA and diabetes mellitus – implications for cognitive function decline

Diabetes is a metabolic disease characterised by increased blood glucose levels as the body does not respond normally or use blood glucose effectively (135). Prevalence studies have consistently reported high prevalence rates of diabetes in patients with OSA (136-138). In a systematic review and meta-analysis of five studies, Fallahi et al. (136) reported an OSA prevalence rate of 54.5% in Iranian diabetic patients. Singh et al. (138) reported a similar OSA prevalence rate of 55% among 149 type 2 diabetic patients (age range 30–86 years). Furthermore, Schober et al. (137) reported an OSA prevalence rate of 35% among diabetic patients. Evidence suggests that metabolic disorders such as diabetes mellitus exacerbate the severity of OSA, which may indicate a potential bidirectional relationship between OSA and diabetes (116, 139). Issues with blood glucose regulation could lead to sleep difficulties and hypoxemia. In contrast, OSA could lead to issues with blood glucose regulation. Intermittent hypoxemia and sleep fragmentation commonly associated with OSA could potentially lead to alterations in glucose metabolism.

High prevalence rates of OSA in diabetes may also have implications for cognitive function decline. A pooled analysis of 2.3 million individuals, including >100,000 dementia cases, showed that diabetic patients had a 1.6-fold increased risk of developing dementia (140). Moreover, diabetes has been associated with an increase in tau protein and amyloid beta, potentially leading to neurodegeneration (141, 142). However, literature linking diabetes with cognitive impairment in patients with differing severities of OSA remains limited. A study investigating the association between sleep and cognitive function in diabetic patients found that although OSA itself was not associated with cognitive function, the presence of diabetes was associated with worse cognitive function (143). Consequently, diabetes is a potentially important confounder of cognitive function and should be controlled for when investigating associations between OSA and cognitive function.

1.3.5.2 OSA and hypertension – implications for cognitive function decline

OSA increases sympathetic nervous system (SNS) activity (144). Hypoxemia and hypercapnia act via chemoreceptors, resulting in SNS activation and hypertension due to the vasoconstriction response, which causes blood vessel narrowing (145). Nocturnal hypertension has been shown to persist during the daytime, accentuating the risk of further cardiometabolic comorbidities (146). Kim et al. (147) analysed blood pressure, sleep depth, and airflow limitation data in patients with OSA from the Multi-Ethnic Study of Atherosclerosis (MESA) Study, concluding that increased respiratory efforts were associated with elevated systolic and diastolic blood pressure. Likewise, a meta-analysis supports that increased respiratory efforts and the associated nocturnal hypertension are commonly observed in patients with OSA (148).

Along with associations with OSA, there is evidence supporting that hypertension may be associated with an increased risk of cognitive decline and vascular dementia (149-151). Increased SNS activity commonly observed in patients with OSA could be primarily responsible for cognitive decline by resulting in one or a combination of small vessel disease, large arterial atherosclerosis, and hypertension-associated cardiac dysfunction (152), OSA-associated intermittent hypoxemia, hypoxia, and sleep fragmentation could further exacerbate oxidative stress and inflammatory responses, which could, in turn, increase the risk of dementia (153).

1.3.5.3 OSA and cardiovascular disease – implications for cognitive function decline

The prevalence of CVD is estimated to be 2-3 times higher in patients with OSA compared to healthy controls (154). Punjabi et al. (155) analysed the prospective associations of OSA sequelae, including intermittent hypoxemia, repetitive arousals, and sleep fragmentation, with all-cause and cardiovascular mortality among 6,441 men and women from the SHHS cohort. The authors reported a significant independent association between OSA sequelae and all-cause and CVD-related mortality. However, along with CVD, other metabolic and cardio-metabolic comorbidities, including obesity, diabetes mellitus, and hypertension, can co-occur

in patients with OSA. Regarding cognitive function decline, dementia and CVD share common risk factors, including diabetes, smoking, and hypertension. Coronary artery disease, atrial fibrillation, and heart failure may also be linked with dementia (156). As such, it is important to control for this potential confounder when exploring associations between OSA and cognitive function.

1.3.6 OSA, chronic disease risk factors, and mental health outcomes – implications for cognitive function decline

Chronic disease risk factors, including smoking and excessive alcohol consumption, could interact with OSA to influence the association between OSA and cognitive function decline. Affective disorders could also influence the association between OSA and cognitive function decline. Chronic disease risk factors and mental health outcomes associated with OSA and implications for cognitive function decline will now be assessed.

1.3.6.1 OSA and smoking – implications for cognitive function decline

Several studies have investigated the impact of smoking on cognitive function decline in older age (157-159). Specifically, excessive smoking, particularly after age 50, significantly increases the risk of cognitive function decline. In one study, adults aged 50–60 were followed over 23 years, and smoking more than two packs of cigarettes a day at baseline was significantly associated with cognitive function decline at 23 years follow-up (157). However, only one study has examined the interaction effect of OSA and smoking on cognitive function decline (158). Lin et al. (158) reported a significant OSA-by-smoking interaction effect on performance on the Montreal Cognitive Assessment (MoCA) in 118 male patients with OSA. The literature reporting associations between smoking and cognitive function decline highlights the importance of controlling for this potential confounder when examining associations between OSA and cognitive function.

1.3.6.2 OSA and excessive alcohol consumption – implications for cognitive function decline

Regarding links with OSA, excessive alcohol consumption has been reported to increase pharyngeal collapsibility (160, 161). Regarding links with OSA, excessive alcohol consumption has been reported to increase pharyngeal collapsibility (160, 161). Excessive alcohol consumption has also been associated with an increased risk of cognitive function decline, as evidenced by findings from a systematic review (162). The association between excessive alcohol consumption and an increased risk of cognitive function decline is believed to stem predominantly from the neurotoxic effects of alcohol on cortical structure and function (163). Several studies have investigated the impact of alcohol on brain health (164, 165), with findings suggesting that alcohol could have deleterious effects on brain function. Specifically, excessive alcohol consumption has been reported to result in gradual white matter atrophy and vulnerability of astrocytes, oligodendrocytes, and synaptic terminals to the neurotoxic effects of alcohol (164). These previous findings highlight the importance of controlling for alcohol risk when examining associations between OSA and cognitive function.

1.3.7 OSA and excessive daytime sleepiness

One of the most common complaints of clinical concern in patients with OSA is excessive daytime sleepiness (EDS), with prevalence rates of approximately 50% among clinic samples, although less prevalent among community OSA samples (166). EDS is a clinically prominent symptom of OSA and can significantly interfere with daytime function, productivity, mood, and quality of life (167). Several scales are used to assess subjective daytime sleepiness and identify the presence of EDS. These include the Epworth Sleepiness Scale (EDS) (168, 169), Karolinska Sleepiness Scale (KSS), multiple sleep latency test (MSLT), and maintenance of wakefulness test (MWT). EDS is characterised by persistent sleepiness, a general lack of energy, and increased sleep propensity or pressure experienced during major waking episodes (110).

1.3.7.1 OSA severity markers and excessive daytime sleepiness

Previous literature has presented controversial findings regarding whether sleep fragmentation or hypoxemia is the primary determinant of EDS in OSA. Roure et al. (170) investigated sleep macroarchitecture in a large sample of patients with OSA, with and without EDS, and some patients presenting with EDS (ESS score ≥11) showed a higher sleep efficiency compared to those without EDS. However, other studies concluded that hypoxemia was strongly associated with EDS, whereas sleep fragmentation showed little or no association with EDS (171-176). Some findings suggest that sleep fragmentation and hypoxemia are equally important determinants of EDS (169, 177). A review concluded that disrupted sleep macroarchitecture and nocturnal hypoxemia equally contribute to EDS (110). Nocturnal hypercapnia has also been linked with EDS, particularly in hypercapnic patients with OSA (178-180). Accordingly, intermittent blood gas abnormalities and sleep fragmentation are likely, to varying degrees, important determinants of EDS in OSA.

1.3.7.2 OSA and excessive daytime sleepiness – implications for cognitive function decline

Although prevalence rates of EDS have been particularly low among community OSA samples and clinical samples, EDS has been associated with attentional and memory impairments and higher-order executive dysfunction (181). EDS has also been associated with a heightened risk of impaired work performance and motor vehicle accidents (110). Therefore, it is important to investigate associations of EDS with cognitive function in OSA and potential intervention opportunities to enhance quality of life (QoL) (110, 168, 169).

1.4 The effect of OSA on cognitive function

A significant proportion of patients with OSA demonstrate evidence of cognitive impairment. A systematic review (182) reported high prevalence rates of MCI in individuals with OSA. Along with a high prevalence of MCI in individuals with OSA, there is also evidence from systematic reviews and meta-analyses supporting that OSA is generally associated with poor cognitive performance (13, 14, 183, 184). The

high prevalence of cognitive function change or decline over time in OSA is likely exacerbated by cortical damage, particularly in the prefrontal cortex and hippocampal brain regions (14, 184). As mentioned in an earlier section of this literature review (see sections 1.2.2, 1.2.3, and 1.2.4), executive function or set-shifting abilities assessed by TMT-B, episodic memory and learning assessed by the FOME test, and attention and processing speed assessed by the inspection time task, respectively, have been documented to be significantly affected in patients with OSA, which has motivated the choice of these cognitive tests in the experimental chapters of this thesis.

Findings with previous studies suggest that OSA is associated with impaired cognitive function across multiple domains, including executive function, attention/vigilance, visual and long-term memory, and visuospatial/constructional abilities but not in language, delayed long-term visuospatial memory, and psychomotor function (13, 14). However, the results of previous studies have not always been consistent. Specifically, the effect of OSA on working memory, short-term memory, and global cognitive function remains unclear. The inconsistent findings emphasise the importance of conducting larger community-based cohort studies to examine the independent associations between OSA and various domains of cognitive function. However, before assessing the literature from larger studies, the studies that investigated the effect of OSA on cognitive function in smaller samples will be reviewed.

1.4.1 The effect of OSA on executive function

Reviews and a meta-analysis of small experimental laboratory studies have reported that executive function encompasses higher-order cognitive function, including processing, planning, and task execution (15, 16, 185). Moreover, executive function comprises six subcomponents: behavioural inhibition, set-shifting, self-regulation of affect-motivation-arousal, working memory, analysis/synthesis, and contextual memory (186, 187). Executive function enables individuals to maintain these skills in an organised manner in different external environments or under problem-solving conditions (188, 189). A review has reported that executive function is the most strongly affected cognitive domain in untreated OSA, primarily because it relies on

the PFC, which is thought to be particularly vulnerable to hypoxemia, as seen in OSA (185).

Considerable literature has investigated subcomponents of executive function and how these are affected in untreated OSA. Behavioural inhibition represents the ability to inhibit the initial response to an event, stop an ongoing response, and prevent a response from being influenced by other competing events (190). A task commonly used to test behavioural inhibition is the Stroop colour-word interference task. This task requires participants to inhibit their initial response to an event by naming the colour in which a word is printed but not the word itself (191). Untreated patients with OSA have shown little attempt to inhibit their initial response on this task (192, 193). Set-shifting represents the ability to shift attention between tasks (190). The most common set-shifting ability tests are the Wisconsin card sorting test (194) and trail-making test B (TMT-B) (195). On these tests, untreated patients with OSA have found it challenging to shift attention between tasks (193, 196). Self-regulation of affect-motivation-arousal is assessed by the internal motivation to achieve and sustain interest in a goal (190). It is commonly measured by continuous performance tests (CPTs) requiring participants to maintain task performance. Untreated patients with OSA repeatedly perform poorly on CPTs compared to matched controls, with poor performance becoming prominent towards the end of a task (196). Working memory is a temporary memory store that can be manipulated and updated consisting of a sketch pad for visual information and a phonological loop for auditory information (190). This memory system is capable of briefly holding onto recent (and predicting future) information (197). Untreated patients with OSA commonly perform poorly compared to matched controls on tasks requiring them to recall and repeat visual or verbal information (193, 196, 198). Analysis/synthesis represents the ability to recall and use information in a novel or interesting manner (190). Untreated patients with OSA often struggle to think laterally and innovatively and thus show poor analytic/synthetic skills (192, 193, 198). Finally, contextual memory represents the ability to place information into meaningful contexts (190). Contextual memory is linked with functions of the PFC, which are highly susceptible to hypoxemia and hypercapnia (196).

1.4.2 The effect of OSA on memory

A meta-analysis on memory in OSA has demonstrated that untreated patients with OSA show impaired verbal episodic memory (recall and recognition) and visuospatial episodic memory (immediate and delayed recall) (17). Salorio et al. (199) tested untreated patients with OSA and healthy matched controls on recall and recognition tasks. Untreated patients with OSA demonstrated impaired recall and recognition compared to controls. Naegele et al. (200) evaluated the effect of untreated OSA on episodic, procedural, and working memory, and episodic memory was impaired in untreated patients with OSA. As untreated patients with OSA improved their performance between successive trials on procedural and working memory tests, there were no significant differences in these memory domains between untreated patients with OSA and controls, suggesting a potential learning effect. Daurat et al. (201) evaluated verbal episodic memory in untreated patients with OSA and controls, and recognition was impaired only in untreated patients with OSA. The authors attributed these results to nocturnal arousals. A significant negative association was found between recognition and the number of arousals in the patient group, such that arousals were associated with worse recognition (201). In contrast, Twigg et al. (202) reported a negligible difference in verbal episodic memory between untreated patients with OSA and healthy controls.

1.4.3 The effect of OSA on attention and vigilance

Attention represents the ability to process information actively and select and concentrate on specific stimuli in the external environment for an extended duration without distraction (13). Meta-analyses have demonstrated that patients with OSA frequently experience attentional problems, predominantly responsible for impairments commonly observed in these patients, including performance errors and motor vehicle and workplace accidents (203, 204). In untreated patients with OSA, deficits have been identified in multiple attention subdomains, including alertness and sustained, focused, divided, and executive attention (203, 205).

Vigilance represents the ability to sustain attention over long periods (204). Mazza et al. (206) compared untreated patients with OSA and healthy controls on attentional tests measuring maintenance of wakefulness, sustained attention, and divided

attention. Untreated patients with OSA performed significantly worse compared to controls on each test, with approximately 95% of the patient group showing vigilance failure. The PVT is the most widely used essay of vigilance and alertness in sleep research and has been linked to real-world operational impairment (207). The PVT assesses vigilance based on how quickly participants respond to a visual stimulus. Furthermore, the PVT is a standardised and validated measure of total and partial sleep deprivation and objectively measures fatigue-associated changes in alertness with extended sleep loss (208). Sforza et al. (209) compared reaction time on the PVT between untreated patients with OSA and healthy controls and showed that reaction time was impaired in untreated patients with OSA compared to healthy controls. Sforza et al. (209) also showed that respiratory events, sleep fragmentation, and daytime sleepiness were also associated with worse reaction times in patients with OSA.

1.4.4 OSA severity markers may explain cognitive dysfunction

There are inconsistent findings across clinical studies regarding the nature and magnitude of OSA-related cognitive dysfunction. Notably, the extent of higher-order versus alertness-based cognitive dysfunction and nocturnal sleep or respiratory disturbances most strongly associated with cognitive dysfunction remains controversial (210-212). Several authors have attributed OSA-related cognitive dysfunction to sleep fragmentation (110, 213), whereas others have attributed this phenomenon to nocturnal hypoxemia (214). Some authors also suggested that nocturnal hypercapnia contributes to cognitive dysfunction (178, 179). These OSA disease severity markers are likely important for performance across different cognitive function domains, although this has not been fully delineated (14).

1.5 OSA treatments and benefits for cognitive function

1.5.1 Continuous positive airway pressure for treatment of OSA

Continuous positive airway pressure (CPAP) is the gold-standard first-line therapy for moderate-severe OSA (215). CPAP applies air pressure and acts as a pneumatic splint to hold the pharyngeal airway open during sleep (216). CPAP is highly effective

in increasing oxygen saturation and minimising microarousals (217). Nevertheless, roughly 50% of patients fail to adhere to CPAP long-term (218-221), limiting therapy effectiveness. Some evidence suggests the presence of residual daytime abnormalities after treatment with CPAP despite adequate adherence to therapy (222, 223). Adequate adherence is defined as using CPAP for >4 on >70% of nights (220). Studies that previously investigated the effect of CPAP on cognitive function predominantly utilised a randomised controlled trial (RCT) design (224), and evidence from large prospective studies is lacking. Importantly, previous studies have investigated the benefits of CPAP for executive function, attention/vigilance, and memory function and while some studies have shown significant improvements in performance in these cognitive function domains after CPAP treatment, other studies report that performance in these cognitive function domains may not significantly improve despite regular treatment with high adherence. The lack of improvement in performance across these cognitive function domains after treatment with CPAP motivates the choice of cognitive tests for this thesis. Studies that have investigated the effect of CPAP treatment on cognitive function will now be assessed.

1.5.1.1 Benefits of CPAP for executive function

Multiple studies have investigated the effect of CPAP on executive function (218, 225-228). Most studies have reported small-medium improvements in executive function after treatment with CPAP. Antic et al. (218) evaluated patients with moderate-severe OSA after 3 months of CPAP, and executive function improved from pre-treatment, which was reflected in improved scores on a maze learning task. Lau et al. (227) evaluated moderate-severe patients with OSA after 18 months of CPAP, and executive function deficits remained compared with matched controls, particularly in working memory. Consequently, although CPAP reduced pharyngeal obstruction and increased oxygen saturation levels, residual executive function deficits continued despite adequate therapy adherence. In contrast, Jurado-Gamez et al. (228) investigated the effect of 4 months of CPAP on executive function, reporting improved working memory post-treatment compared with pre-treatment status. Naegele et al. (226) recruited patients with OSA treated with CPAP over 4 months and evaluated performance improvement on frontal lobe-related tests involving planning, categorisation, and working memory. Compared with a well-

matched control group, all tested subcomponents of executive function had normalised post-treatment except for working memory. Kushida et al. (225) investigated the effect of CPAP on executive function after 2 and 6 months of follow-up, respectively, in 1,098 participants of the Apnea Positive Pressure Long-term Efficacy (APPLES) study with previously diagnosed OSA and found that CPAP improved performance on executive function tasks in men with severe OSA. However, this improvement did not persist at 6 months follow-up. In a cross-sectional, prospective, observational study of 126 patients with OSA, Dostalova et al. (229) evaluated the effect of short-term (3 months) CPAP on cognitive performance on the MoCA. The authors did not report any significant improvement in cognitive performance after treatment with CPAP. However, the sample size was relatively small, and participants were free of cognitive impairment.

It is difficult to make a strong conclusion regarding the efficacy of CPAP in improving executive function. Methodologic differences, patient populations studied, the types of executive function tests administered, and CPAP duration and adherence could have resulted in inconsistent findings (185). Also, the limited impairment sometimes seen in executive function after CPAP could represent higher-order processing being less prone to OSA-related hypoxemia and sleep fragmentation in some patients.

1.5.1.2 Benefits of CPAP for attention/vigilance

There are controversies regarding the efficacy of CPAP in improving attention and vigilance. Some studies report modest improvement in attention and vigilance after CPAP (230-233). Other studies report that attention and vigilance remained impaired despite adequate adherence to therapy (234-236). Ferini-Strambi et al. (236) investigated the effect of short- (15 days) and long-term (4 months) CPAP on attentional performance in patients with OSA compared with age- and education-matched controls. In this longitudinal study, after 15 days of CPAP, sustained and focused attention improved in patients with OSA, although there were no further improvements at 4 months. Bedard et al. (232) examined differences in vigilance between patients with OSA and matched controls after 6 months of CPAP. In patients with OSA, vigilance significantly improved from pre-treatment status such that performance was comparable to controls. These results are supported by a study that reported improved psychomotor vigilance in patients with OSA after 12 months

of CPAP (231). Furthermore, Wang et al. (230) reported that CPAP adherent participants with MCI showed improvement in psychomotor vigilance compared to the MCI group with nonadherence to CPAP. Similarly, in a quasi-experimental pilot study, Richards et al. (237) recruited CPAP-adherent patients with OSA and MCI and a non-adherent group and found that 1 year of CPAP adherence resulted in significant improvements in psychomotor/cognitive processing speed. Despite the finding that CPAP can improve psychomotor vigilance in patients with severe OSA, they may remain at high risk of motor vehicle accidents (MVAs). Vakulin et al. (235) investigated the effect of CPAP on driving performance in patients with severe OSA compared to healthy controls after 3 months of therapy. Although driving performance improved in patients with OSA after CPAP compared with pre-treatment status and the number of accidents was reduced, performance compared to the control group remained poor. Bhat et al. (234) examined the effect of CPAP on performance on the psychomotor vigilance test (PVT) in 182 patients with moderate-severe OSA and did not identify a predictive relationship between CPAP use and PVT performance.

The controversial results between studies that evaluated the effect of CPAP on attention and vigilance could reflect differences in CPAP duration and adherence and the patient populations studied. Thus, although CPAP modestly improved attention and vigilance in some studies, there is evidence that deficits can remain after therapy.

1.5.1.3 Benefits of CPAP for memory function

Several studies have investigated the effect of CPAP on memory function. Joyeux-Faure et al. (238) investigated improvements in verbal and procedural memory in patients with OSA after 6 weeks of CPAP versus sham therapy. At post-treatment, neither of these memory domains improved from pre-treatment status. Other studies that investigated the effect of CPAP on memory in patients with OSA focused on only one domain, with visuospatial memory being commonly investigated (239-241). Improvements in verbal episodic memory after CPAP have also been investigated. Barbe et al. (239) investigated the effect of 6 weeks of CPAP versus sham therapy on visuospatial memory in patients with severe OSA without daytime sleepiness and found that CPAP did not improve visuospatial memory compared with sham therapy. In contrast, Lee et al. (240) reported improved visuospatial memory after 3 weeks of

CPAP versus sham therapy. However, the authors did not investigate the effect of CPAP on other memory domains or the improvement in visuospatial memory at longer follow-up durations. Monasterio et al. (241) investigated the effect of CPAP on visuospatial memory in patients with mild OSA after 3 and 6 months of therapy. Visuospatial memory modestly improved at 3 months follow-up. However, there were no further improvements at 6 months follow-up. Improvements in verbal episodic memory after CPAP have also been investigated. Rosenzweig et al. (242) examined verbal episodic memory in patients with OSA after 1 month of CPAP. Verbal episodic memory improved, and the authors speculated that this might have occurred through partial neuronal recovery. In another study, Antic et al. (218) reported a significant improvement in verbal episodic memory after 3 months of CPAP. In the APPLES study, Quan et al. (243) examined scores on the Selective Reminding Test, a verbal episodic memory test, after 2 and 6 months of CPAP, reporting significant improvement in scores with treatment. Turner et al. (244) reported improvements in working memory, long-term verbal memory, and short-term visuospatial memory in 16 patients with moderate-severe OSA. In a large retrospective study, Dunietz et al. (245) examined odds of developing AD, MCI, and dementia in 53,321 beneficiaries ≥65 years based on CPAP use over 3 years and found that users of CPAP had significantly lower odds of AD and MCI.

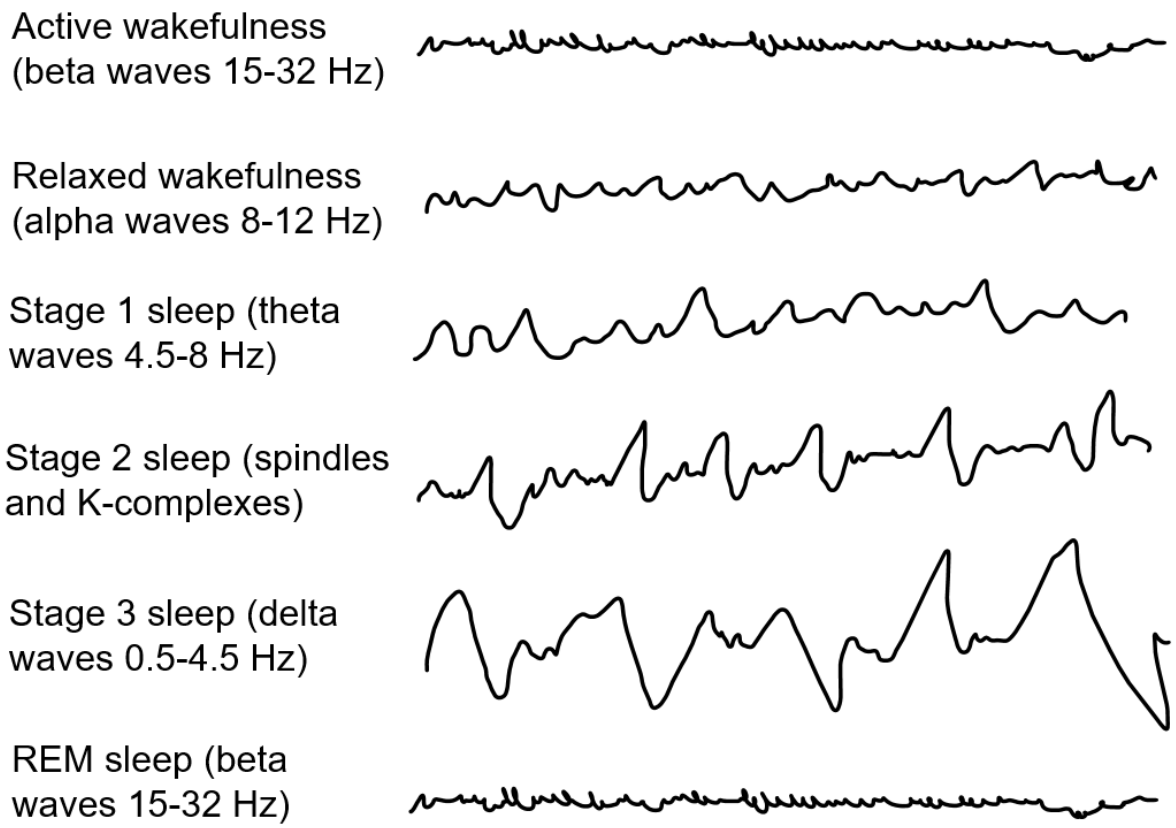
1.6 Quantifying wakefulness and sleep through EEG brain activity

Along with OSA, disrupted sleep macroarchitecture, conventional sleep staging and scoring through 30 second epochs of the EEG, could be associated with cognitive function. The next section of this review will introduce sleep macroarchitecture, assess the cross-sectional and longitudinal associations between OSA and sleep macroarchitecture parameters and cognitive function, and highlight the main issues and knowledge gaps to be addressed in Chapters 3 and 4 of this thesis.

EEG is a non-invasive electrophysiological monitoring technique that measures and detects abnormal electrical brain activity and differentiates awake and sleep states (246). EEG consists of brainwaves generated by thalamocortical networks and subthalamic structures decomposed into distinct sub-bands dependent on amplitude (μV) and frequency (Hz) (246). Brainwaves are divided into slow and fast electrical activity. Slow activity refers to high amplitude, low-frequency neuronal oscillations.

Conversely, fast activity refers to low amplitude, high-frequency neuronal oscillations (247). The distinct EEG frequencies include delta (0.5–4.5 Hz), theta (4.5–8 Hz), alpha (8–12 Hz), sigma (12–15 Hz), and beta (15–32 Hz) (248). Delta and theta are the slower brainwaves, whereas alpha, sigma, and beta represent faster electrical brain activity. During active wakefulness, the EEG predominantly displays low-voltage fast-frequency desynchronised (beta) activity associated with alertness. During relaxed wakefulness, the EEG predominantly displays alpha activity (249). Sleep is divided into rapid eye movement (REM) and non-REM (NREM) (stage 1 [N1], 2 [N2], and 3 [N3]) stages, which are mechanistically different. N1 sleep is typically characterised by alpha and theta activity, reduced muscle activity, slow heart rate, and slow breathing. During N2 sleep, heart rate, breathing, and muscle activity are slowed further, and the EEG predominantly displays theta activity associated with reduced consciousness. As the sleep cycle progresses, the sleeper enters N3 or slow-wave sleep (SWS), predominated by delta activity. Delta is the slowest frequency, representing deep sleep. In contrast to NREM sleep, REM sleep is characterised by rapid and random eye movements and muscle atonia. REM sleep is characterised by beta activity comparable to active wakefulness (246). An example of the EEG patterns observed during active and relaxed wakefulness and across the various stages of sleep is illustrated in Figure 1.1.

Figure 1.2 EEG patterns observed during active and relaxed wakefulness and across the various stages of sleep



1.7 Associations between OSA, sleep macroarchitecture, and cognitive function

Multiple cohort studies have examined associations between OSA, sleep macroarchitecture, and cognitive function. Although evidence suggests that OSA and disrupted sleep macroarchitecture may be associated with cognitive impairment, it remains important to examine which specific OSA and sleep macroarchitecture parameters are independently associated with performance across various cognitive function domains. Research in this area would provide clarity and insight into potential drivers of cognitive impairment. Presently, evidence for associations between OSA, sleep macroarchitecture, and cognitive function predominantly comes from clinical cohort studies (18, 24, 25, 182, 250) or community-based cohort studies in participants aged ≥65 years (19-21, 23) or at high risk of OSA (22). There have been inconsistencies in the associations reported between traditional OSA disease

severity metrics and cognitive function (251), which likely stems from discrepancies in respiratory scoring criteria, the cognitive outcomes assessed, study design, population characteristics, and follow-up duration in longitudinal studies (4). Inconsistences in these associations could also stem from the fact that the AHI collapses apneas and hypopneas, which may not be equally damaging to the brain. Therefore, further cohort studies remain warranted to clarify the associations between conventional OSA parameters and cognitive function outcomes.

1.7.1 Cross-sectional associations between OSA, sleep macroarchitecture, and cognitive function

Several clinical cohort studies have examined associations between OSA and/or sleep macroarchitecture parameters and cognitive function or decline (18, 24, 25, 182, 250). Along with OSA parameters, exploring the associations between NREM and REM sleep and TST and cognitive function may be useful because it is reported that levels of brain activity are altered in each stage of sleep, including both NREM and REM sleep, and evidence suggests that sleep enhances cognitive function. Moreover, both long and short TST has been associated with lower cognitive function, with further studies needed to confirm these findings. In the APPLES study, Quan et al. (18) recruited highly educated adults (n=1,204, mean age 50.7 years) with previously diagnosed OSA and found that greater oxygen desaturation was associated with worse visual attention and processing speed assessed by performance on the Pathfinder Number Test (computer analogue of trail-making test A [TMT-A]). However, sleep macroarchitecture parameters (percentages of NREM and REM sleep and total sleep time [TST]) were not associated with cognitive function (18). Although there were transient improvements in executive function after 2 months of CPAP, particularly in patients with severe OSA, these did not persist at 6 months of follow-up compared to those on sham CPAP therapy (225).

Other clinical cohort studies explicitly examined cross-sectional associations between OSA and cognitive decline. Beaudin et al. (24) recruited a large sleep-clinic population of adults with suspected OSA (n=1,084) and on the basis of OSA severity (AHI categories) examined the risk of MCI through performance on several measures of cognition, including the MoCA, Rey Auditory Verbal Learning Test (RAVLT), and the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV). The authors defined

MCI by a MoCA score <26/30 and reported that odds for MCI were >70% higher in patients with moderate or severe OSA groups compared to those without OSA. Tsai et al. (25) examined associations between spontaneous arousals during NREM and REM sleep and MCI. A higher spontaneous arousal index during NREM sleep was independently associated with greater MCI risk (25). Allen et al. (250) recruited Canadian patients with suspected OSA and identified four symptom subtypes of OSA, including excessively sleepy with disturbed sleep, excessively sleepy, minimally symptomatic, and disturbed sleep. However, these OSA symptom subtypes were not consistently associated with cognitive function, including performance on the MoCA, RAVLT, WAIS-IV, and Digit-Symbol Coding Subtest (250). The use of clinical cohorts to examine associations between OSA and/or sleep macroarchitecture parameters and cognitive function and/or decline limits the generalisability of the results to the broader population and there is a need for community-based cohort studies to resolve this literature gap.

Several community-based cohort studies have examined cross-sectional associations between OSA and/or sleep macroarchitecture parameters and cognitive function. However, participants were selected on the basis of age (≥65 years) or OSA risk (Berlin screening questionnaire). The Osteoporotic Fractures in Men (MrOS) Sleep Study of older (≥67 years) community-dwelling men found that greater light (N1) and less REM sleep were independently associated with worse executive function (TMT-B performance) (19, 20). Furthermore, the HypnoLaus Study of older (≥65 years) community-dwelling men and women identified that in adjusted analyses, the AHI and oxygen desaturation index (ODI) (>4% and >6%) were independently associated with worse memory, verbal fluency, and set-shifting ability (21). Hrubos-Strom et al. (22) found that mean oxygen saturation (SaO_2) was independently associated with worse verbal memory in younger (mean age 48 years) community-dwelling men and women from the Norwegian Akershus Sleep Apnea Project (ASAP) Study. However, all participants were recruited on the basis of being at high risk of OSA, as assessed by the Berlin screening questionnaire (22). As such, the cohort was likely enriched with participants at high risk of OSA, and the results may have been influenced by selection bias. In contrast to all other community-based cohort studies, Sforza et al. (23) reported no significant associations between AHI or ODI 3% and executive function (TMT-B performance) or verbal fluency in a healthy

older population (mean age 68 years) from the Autonomic Nervous System Activity, Aging and Sleep Apnea/Hypopnea (SYNAPSE) Study. Although there is evidence from community-based cohort studies suggesting that OSA and sleep macroarchitecture parameters are cross-sectionally associated with cognitive function outcomes, the recruitment of select samples (older age or at high risk of OSA) limits the generalisability of the results to the broader population. As such, there is a need for studies in unselected community-based cohort samples to increase generalisability of the results to the broader population.

Along with objective sleep studies, there is also limited evidence from subjective sleep studies reporting on cross-sectional associations between sleep EEG macroarchitecture and cognitive function in older (≥50 years) community-dwelling participants (252-255). Consistent findings include associations of short sleep duration (<6 hours), reduced sleep efficiency (total percentage of time asleep while in bed), and lower subjectively rated sleep satisfaction with worse performance across multiple tests of cognitive function (reasoning, vocabulary, semantic fluency, and memory) (252-256). However, cross-sectional studies did not specifically examine associations between objective measures of NREM and REM sleep and cognitive function. Studies of this nature would provide the opportunity to implicate the involvement of sleep macroarchitecture in cognitive function in older age. This thesis will investigate cross-sectional associations between objective measures of sleep macroarchitecture and cognitive function among an unselected community-based cohort to fill this literature gap.

1.7.2 Prospective associations between OSA and sleep macroarchitecture at baseline and future cognitive function

Several prospective clinical and community-based cohort studies have examined associations between OSA and sleep macroarchitecture parameters and future cognitive function at various durations of follow-up (26-31). Consistent findings include associations between OSA (AHI ≥15/h), intermittent hypoxemia, and a greater risk of cognitive decline (26, 27, 30). However, one study reported that OSA was not associated with a greater risk of cognitive decline (28). Regarding sleep macroarchitecture, one study reported that a reduced percentage of REM sleep was associated with an increased risk of cognitive decline (29). Another study reported

that greater TST (>9 h) was associated with an increased risk of cognitive decline (31). Prospective studies that have examined associations between OSA and sleep macroarchitecture at baseline and future cognitive function predominantly recruited older participants (≥60 years), many with baseline impairment. Moreover, most studies included a relatively short follow-up (4-8 years) between the baseline PSG assessment and future cognitive examination. Consequently, whether OSA and sleep macroarchitecture are associated with future cognitive function among a younger, unselected community-based cohort with a longer follow-up duration between the PSG and cognitive assessments remains unclear. Investigating these associations among a younger, unselected community-based cohort with a longer follow-up duration would provide evidence supporting OSA and sleep macroarchitecture as early markers of future cognitive impairment.

Along with objective sleep studies, there is also limited evidence from subjective sleep studies reporting on longitudinal associations between sleep EEG macroarchitecture parameters at baseline and future cognitive function in older (≥50 years) community-based populations. (257-260). These studies provide limited evidence suggesting that shorter sleep duration and reduced sleep quality may have prognostic value for identifying future cognitive dysfunction and incident MCI. However, these studies are limited by short follow-up times (1-2 years), which may be insufficient time for cognition to change. Consequently, further objective longitudinal studies with a longer duration between the baseline sleep and follow-up cognitive assessments warranted to capture greater cognitive decline and implicate the involvement of sleep macroarchitecture in cognitive impairment, which will be addressed in this thesis.

1.8 EEG markers of cognitive function

The AHI, the standard PSG-derived parameter of OSA disease severity has several methodologic problems that are widely recognised in the extant literature. Malhotra et al. (261) recently reviewed the weaknesses of utilising the AHI to predict clinically relevant correlates of OSA that may underlie the associated cognitive consequences. The authors highlighted that three problems limit the predictive value of the AHI, including 1) a lack of precision of identifying OSA-related exposures, 2) individual differences in the response to OSA, and 3) competing non-OSA causes of outcomes

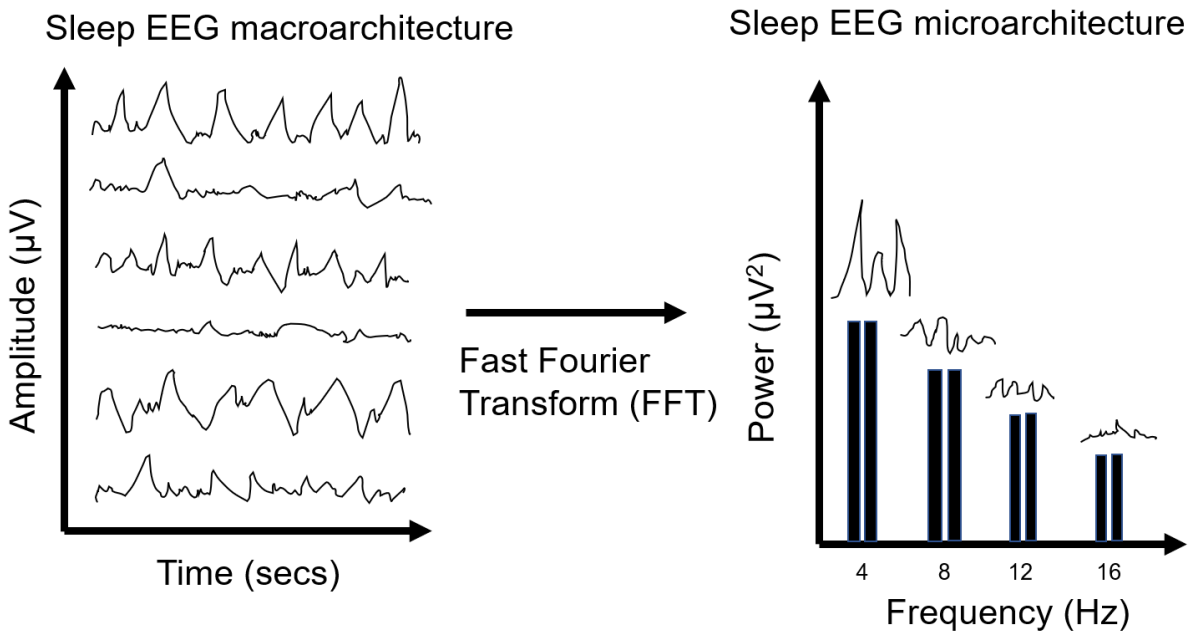
of interest (261). These problems with utilising the AHI to diagnose OSA, make decisions on treatment outcomes, and identify cognitive dysfunction have also been reported in other review articles (262, 263). Therefore, it is important for future research to examine the rich electrophysiological data that can be obtained from overnight PSG to determine if alternative emerging PSG parameters might be more predictive of daytime cognitive dysfunction.

Conventional sleep EEG macroarchitecture measured by visual inspection of 30-second epochs and manual sleep staging and scoring provides limited and superficial information as potentially useful phenotypic information that may provide valuable insight into disease, health, and functional outcomes can be easily missed. Consequently, this traditional approach does not provide the advantage of examining the rich electrophysiological data collected during formal overnight sleep studies (44, 264, 265). The below sections of this introduction will assess the literature on qEEG power spectral markers of cognitive function among healthy and disordered populations.

1.8.1 EEG power spectral analysis

Power spectral analysis (PSA) enables detailed investigation of EEG signals through conversion from the time to the frequency domain, most commonly using the quantitative fast Fourier transform (FFT) algorithm, which quantifies the power of EEG signals as a function of frequency content (Figure 1.3) (266). While considerable inter-individual variability exists in EEG composition between individuals, evidence of robust consistency and test-retest reliability of qEEG measures suggests a trait-like fingerprint of electrical brain activity (267). Therefore, the quantitative FFT algorithm provides the advantage of assessing subtle differences between EEG microarchitecture profiles through interventions or between populations and could enhance our understanding of associations between sleep microarchitecture and cognitive function (44, 268).

Figure 1.3 The quantitative FFT methodology



1.8.1 Associations between wake and sleep qEEG markers and cognitive function outcomes – evidence from small experimental laboratory studies

It remains challenging for sleep clinicians to identify which individuals are most at risk of cognitive dysfunction. Conventional clinical sleep metrics do not accurately explain the substantial heterogeneity in daytime performance. Emerging evidence suggests qEEG (sleep spindles, EEG spectral power, and EEG slowing) assessed using PSA may represent a novel brain-specific cognitive function marker. However, existing literature predominantly comes from small samples, with evidence from larger community-based cohorts remaining limited (45).

1.8.2 What are sleep spindles and how are they considered markers of learning and memory?

A sleep EEG microarchitecture parameter that may represent a valuable brain-specific cognitive function marker is the sleep spindle. Spindles are small bursts of oscillatory neural activity generated by the interplay of thalamic and thalamocortical nuclei (sigma frequency range [11–16 Hz]; duration threshold ≥0.5 ≤3 seconds) (269). Spindles are typically observed on the EEG waveform predominantly during

N2 and, to a lesser extent, during N3 sleep and are considered putative electrophysiological markers of thalamocortical network integrity (47, 48, 247, 270). Moreover, spindles are believed to play an important role in learning capability and overnight declarative memory consolidation (271, 272). Combined behavioural and EEG studies have shown that higher spindle frequency (Hz, oscillations/second) is associated with increased word-pair recall (273, 274) and improved motor learning (275).

1.8.3 Sleep spindle density in patients with OSA and healthy controls – evidence from small clinical studies

Sleep spindle density is an index derived by dividing the number of spindle events by minutes in a specific sleep stage (276). There are three measures of spindle density based on the number of spindle events per minute of sleep, including overall (11–16 Hz, number/minute), fast (13–16 Hz, number/minute), and slow (11–13 Hz, number/minute) spindle density. Spindle density has been reported to be abnormal in patients with OSA compared to healthy controls. Schonwald et al. (48) investigated differences in overall spindle density between patients with moderate OSA and controls. Compared to controls, patients with moderate OSA showed decreased frontal spindle density, which the authors attributed to diffuse, predominantly frontal thalamocortical dysfunction often seen in OSA (48). Hypoxemia is likely the primary mechanism contributing to OSA-related frontal thalamocortical dysfunction (46, 277).

1.8.4 Spindle frequency and occurrence in patients with OSA and healthy controls – evidence from small case-controlled studies

Differences in spindle frequency and occurrence (11–16 Hz, count) in patients with OSA relative to healthy controls have been reported in case-controlled studies (47, 278). Carvalho et al. (47) examined the regional distribution of fast (~13–16 Hz) and slow (~11–13 Hz) spindles in patients with OSA. In patients with OSA, greater frontal slow spindle activity was detected and attributed to diffuse, predominantly frontal thalamocortical dysfunction (47). Himanen et al. (278) also identified decreased frontal spindle frequency and occurrence in patients with OSA compared to controls. The greater number of slow frontal spindles commonly identified in patients with OSA

could reflect distributed sleep patterns and impaired neuronal function in frontal brain regions and partly explain the memory impairments and executive dysfunction.

1.8.5 Are OSA parameters independently associated with sleep spindle metrics in a community-based cohort?

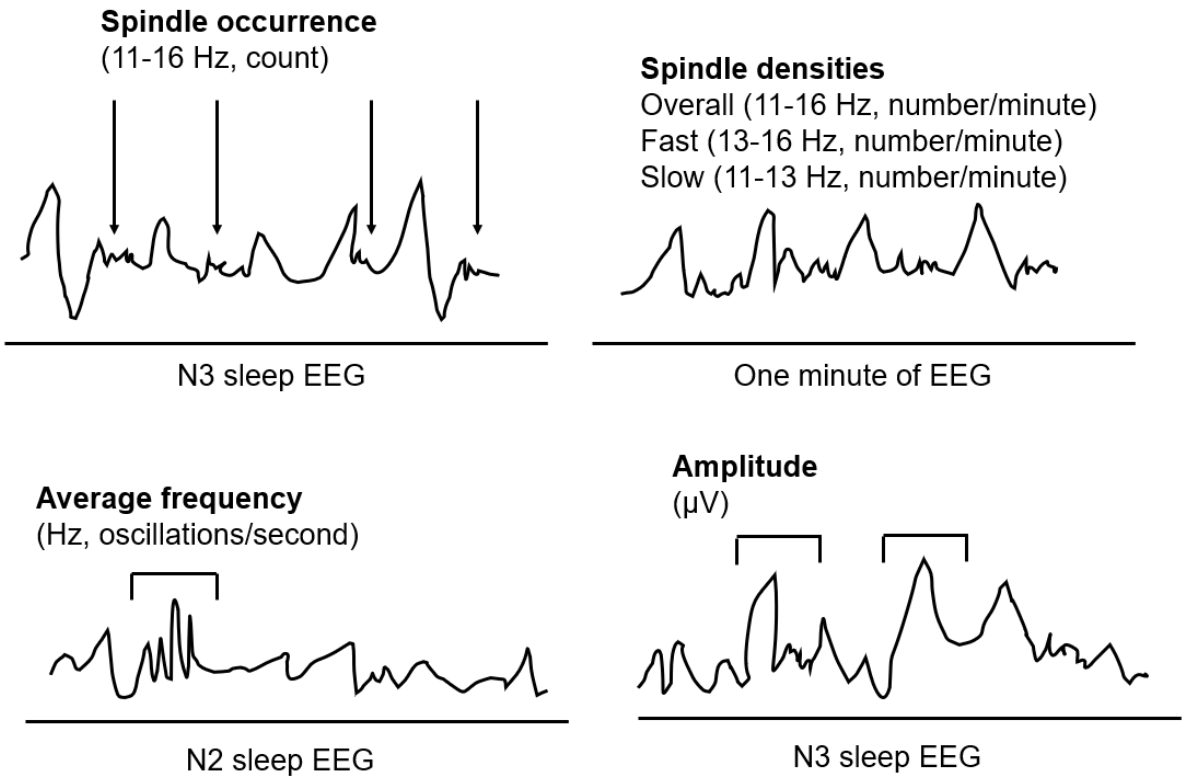
Although evidence from small studies supports sleep spindle abnormalities in patients with OSA relative to healthy controls, no community-based cohort studies are available to determine if OSA disease severity, including the number of obstructive breathing episodes (AHI) and intermittent hypoxemia (TST90), and sleep fragmentation (arousal index) parameters are independently associated with spindle metrics assessed during N2 and N3 sleep. Consequently, community-based cohort studies controlling for multiple potential confounders remain warranted to extend findings from smaller clinical and case-controlled studies and determine if OSA disease severity and sleep fragmentation parameters are independently associated with sleep spindle abnormalities.

1.8.6 Associations between sleep spindle metrics and cognitive function outcomes in healthy participants – evidence from small experimental laboratory studies

Evidence supporting an association between sleep spindle metrics and cognitive function outcomes predominantly comes from small experimental laboratory studies with an inability to control for potentially important confounding variables (49-51, 279). Greater spindle occurrence and densities have consistently been associated with better memory performance (50, 279, 280). Furthermore, greater spindle densities during N2 sleep have been associated with better selective attention and verbal fluency (51). The literature on the association between spindle amplitude (μV) and cognitive function remains limited. Taillard et al. (281) recruited people with subjective cognitive complaints (SCC) or mild cognitive impairment (MCI) (n=29, mean age 71 years) and cognitively normal controls (n=29, mean age 68 years) from the MEMENTO cohort, spindle maximal amplitude was significantly lower across non-rapid eye movement (NREM) sleep periods in patients with isolated SCC or MCI compared to cognitively normal controls A cross-sectional study (n=63) found that greater overall spindle density during N2 sleep was associated with better executive

function independent of age, OSA, BMI, and periodic limb movement index (282). Community-based cohort studies are needed to examine independent cross-sectional associations between spindle metrics during N3 sleep and cognitive function separately from N2 sleep. Currently, the literature on associations between sleep spindle metrics during N3 sleep and cognitive function outcomes is greatly limited, which likely reflect the limited number of spindle events observed during N3 sleep. Identifying associations between N3 sleep spindles and cognitive function would motivate the conduct of intervention studies to attempt to enhance slow-wave sleep and improve cognitive function. The sleep spindle metrics of interest during N2 and N3 sleep in the experimental chapters of this thesis, including occurrence, densities, average frequency, and amplitude, are illustrated below (Figure 1.4).

Figure 1.4 The sleep spindle metrics of interest during N2 and N3 sleep, including occurrence, densities, frequency, and amplitude



1.8.7 Does OSA severity modify the associations between sleep spindle metrics and cognitive function outcomes?

The literature examining associations between sleep spindle metrics and cognitive function outcomes in patients with OSA is limited. Only two small clinical studies (283, 284) and one community-based cohort study (45) have examined these associations. Mullins et al. (283) conducted a 40-h extended wakefulness experiment in which a small sample of male patients with OSA (n=8) completed the PVT and a driving simulator task. The authors examined associations of REM sleep EEG slowing and NREM sleep overall sleep spindle density with cognitive function after 24 h of extended wakefulness. Greater REM sleep EEG slowing was associated with slower PVT reaction times, more PVT lapses, and a greater number of driving simulator crashes, whereas lower overall NREM sleep spindle density was associated with slower PVT reaction times. Moreover, Stevens et al. (284) reported that greater fast spindle density in frontal and central brain regions was associated with better implicit statistical learning in male and female patients with OSA (n=47). In a community-based cohort study of 3,819 participants combined from two independent community-based cohorts, the MESA and MrOS studies, Djonlagic et al. (45) found that higher overall spindle occurrence and greater fast spindle density were associated with better executive function (TMT-B performance) while controlling for OSA (45). However, no additional community-based cohort studies are available to determine independent cross-sectional associations between spindle metrics and cognitive function. More importantly, given that spindle metrics are impaired in patients with OSA relative to matched controls, further community-based cohort studies remain warranted to determine if OSA severity plays a moderating role in associations between sleep spindle metrics and cognitive function outcomes. Community-based cohort studies of this nature would provide the means to determine if the association between sleep spindle metrics and cognitive function outcomes differs by OSA severity. These associations, if present, may be strongest in people with severe OSA but weaker in people with moderate or mild OSA. The potential moderating effect of OSA in the associations between sleep spindle metrics and cognitive function outcomes will be investigated in this thesis. If OSA has a moderating effect then additional studies should investigate if OSA treatment can reverse sleep spindle abnormalities, including reduced occurrence, density, frequency, and amplitude.

1.8.8 Differences in wake EEG spectral power and slowing ratio between patients with OSA and healthy controls

Evidence derived from clinical studies with small sample sizes postulates that EEG spectral power and slowing ratio differ significantly in patients with OSA relative to healthy matched controls. A review by D'Rozario et al. (44) outlined seven studies that analysed differences in wake EEG absolute spectral power (μV^2) between patients with OSA and controls (268, 285-290). Excluding one study (288), other studies reported that patients with OSA could be differentiated from controls by higher μV^2 within slower frequency bands (delta and theta), predominantly in frontal and central brain regions. Morisson et al. (285, 287) detected significant wake EEG slowing (a higher ratio of delta + theta frequencies to alpha + sigma + beta frequencies) in patients with OSA in frontal and central brain regions. Greneche et al. (290) compared wake EEG spectral power between patients with OSA and controls during 24 h of sustained wakefulness studied with the KDT. Wake delta power increased in both groups as time awake progressed; nevertheless, the increase was significantly more pronounced in the patient group compared to controls. Xiromeritis et al. (286) investigated wake microarchitecture parameters in patients with OSA and identified abnormally low fast (alpha and beta) and increased slow (delta and theta) EEG activity. In another study, during 40 h of sustained wakefulness, patients with OSA showed significantly higher wake delta power compared to controls (268). The findings support that patients with OSA often show EEG slowing during wakefulness. Accordingly, wake EEG slowing may help differentiate patients with OSA from healthy controls.

1.8.9 Differences in sleep sleep EEG spectral power and slowing ratio between patients with OSA and healthy controls

Multiple studies have presented evidence suggesting that compared to healthy controls, patients with OSA exhibit greater REM sleep EEG slowing and reduced SWA (delta power) and sleep spindle frequency (sigma power) during NREM sleep (44, 46, 178, 265, 270, 285, 291-293). Wang et al. (178) analysed sleep microarchitecture in severe OSA patients, and EEG was significantly slowed across the night. Morisson et al. (285) performed PSA of REM sleep EEG in patients with

OSA and detected significant EEG slowing over frontal, central, and parietal regions. Jones et al. (291) also observed REM sleep EEG slowing in patients with OSA, primarily in the parietal brain region. Guilleminault et al. (293) identified reduced SWA in patients with OSA compared with healthy controls across all NREM sleep cycles. Heinzer et al. (292) identified reduced SWA in patients with OSA compared to healthy controls, particularly during the first NREM sleep cycle. Ondze et al. (270) identified a gradual decrease in SWA from the first to the fourth cycle of NREM sleep and significantly lower sigma power in patients with OSA compared to healthy controls within each sleep cycle across the night. Interestingly, one study reported higher NREM sleep beta EEG in the OSA group relative to simple snorers (294). One large community-based cohort study has examined independent associations between OSA severity and sleep microarchitecture parameters among a large sample of community-dwelling middle-aged and older men while accounting for insomnia (34). Appleton et al. (34) reported that nocturnal hypoxemia was independently associated with greater REM sleep EEG slowing in the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study cohort. The results of this study suggest that qEEG may be a useful brain-specific cognitive function marker and should be further explored in community-based cohort studies. Therefore, sleep microarchitecture parameters may be more sensitive than standard PSG-derived OSA and sleep macroarchitecture parameters for predicting cognitive dysfunction (265).

1.8.10 Associations between wake EEG spectral power and cognitive function outcomes in healthy participants

In healthy participants, higher delta and theta and lower beta power during sustained wakefulness have been associated with poor attentional performance and vigilance failure (295-298). Makeig et al. (295) identified that poor visuospatial function during sleep deprivation was accompanied by higher power in the low theta frequency range. During 32 h of sustained wakefulness, Cajochen et al. (296) identified that frontal low-frequency theta activity increased with time awake and was associated with worse cognitive function. Belyavin et al. (297) examined the association between wake microarchitecture parameters and vigilance assessed using various digit vigilance tests and reported that lower beta power during wakefulness was a useful

marker of vigilance failure. Posada-Quintero et al. (298) examined the association between wake microarchitecture parameters and performance on an error awareness task during 24 h of sleep deprivation. Higher alpha and delta power in frontal regions was associated with worse error awareness, particularly after 18 h of sleep deprivation.

1.8.11 Associations between sleep EEG spectral power and cognitive function outcomes in healthy participants

Several studies have presented evidence that sleep qEEG markers may be associated with cognitive function in healthy young adults (35-37, 299). Goder et al. (36) reported that higher NREM sleep delta power was associated with better memory and attentional performance. Anderson et al. (299) found that higher NREM sleep delta power in the frontal brain regions was associated with better non-verbal planning and verbal fluency. Furthermore, higher NREM sleep sigma power has been associated with better learning and memory (35). Alternatively, reduced NREM sleep sigma power commonly observed in ageing has been associated with poorer learning and memory (37).

1.8.12 Associations between wake EEG spectral power and cognitive function outcomes in patients with OSA

Evidence for the prognostic value of wake qEEG markers of cognitive function in patients with OSA remains limited. Only three small clinical studies have examined this association with conflicting results (268, 289, 300). Mathieu et al. (289) found that wake EEG slowing in patients with OSA was not associated with performance on the four-choice reaction time test. Conversely, D'Rozario et al. (268) found that higher delta and theta power during sustained wakefulness were associated with poorer psychomotor vigilance. Furthermore, Wang et al. (300) found that higher delta and theta power during wakefulness were associated with poorer driving performance.

1.8.13 Associations between sleep EEG spectral power and cognitive function outcomes in patients with OSA

Despite a growing number of small experimental laboratory studies that have examined sleep microarchitecture parameters in patients with OSA (39, 44, 46, 178, 270, 283, 285, 287, 291, 292), only two have specifically examined the association with cognitive function (38, 39). Vakulin et al. (38) examined the association between sleep microarchitecture parameters and driving performance in patients with OSA. Higher REM sleep delta and NREM sleep beta power were associated with worse steering on a 30-minute driving simulator task. Importantly, OSA disease severity parameters (AHI, ODI, and percentage of total sleep time with oxygen saturation <90% [TST90]) and subjective daytime sleepiness (ESS) showed little or no association with driving simulator performance (44). These results imply that sleep microarchitecture parameters may provide more objective vigilance impairment markers compared to conventional OSA disease severity and subjective daytime sleepiness parameters. Parekh et al. (39) investigated whether sleep microarchitecture parameters, specifically during N2 sleep, were associated with psychomotor vigilance in patients with OSA. Reduced SWA was detected during N2 sleep and associated with poorer psychomotor vigilance.

1.8.14 Associations between sleep EEG spectral power and cognitive function outcomes – evidence from a community-based cohort study

Only one community-based cohort study has examined independent associations between sleep microarchitecture parameters and cognitive function. Djonlagic et al. (45) sought to determine associations between sleep microarchitecture parameters and cognitive function outcomes among 3,819 community-dwelling men and women recruited as part of two independent community-based cohorts, MESA and MrOS. Lower delta power during NREM sleep was associated with worse executive function (TMT-B performance) (45). Therefore, this community-based cohort study suggests that NREM sleep microarchitecture may represent a useful brain-specific cognitive function marker. Nevertheless, no additional community-based cohort studies are available to extend these findings and determine if other sleep microarchitecture parameters are independently associated with cognitive function. Specifically,

independent cross-sectional associations between sleep qEEG markers and cognitive function outcomes should be investigated in community-based cohort samples with a more comprehensive age range to better stratify by age. Age-stratification is particularly important as Djonlagic et al. (45) recruited participants ≥54 years, and it remains unclear whether associations between sleep microarchitecture and cognitive function differ dependent on age subgroups.

1.8.15 Differences between sleep qEEG markers in patients with MCI compared to healthy matched controls

Along with further examining cross-sectional associations between sleep microarchitecture parameters and cognitive function outcomes among community-based cohort samples, it is also important to consider associations between sleep microarchitecture parameters and cognitive decline. As recently reviewed by D'Rozario et al. (301), three small case-controlled studies (40-42) and one community-based case-controlled study (43) have investigated differences in sleep microarchitecture parameters between patients with MCI compared to age-matched controls. However, these studies only examined between-group differences in sleep microarchitecture and did not specifically examine if sleep microarchitecture parameters were associated with various cognitive function outcomes. Westerberg et al. (42) identified lower REM sleep theta activity and NREM sleep delta and theta activity in patients with amnestic MCI (aMCI) (n=18) compared to controls (n=10). Brayet et al. (40) identified greater REM sleep EEG slowing in patients with aMCI (n=22) compared to controls (n=33). Gorgoni et al. (41) identified lower NREM sleep fast spindle density in patients with aMCI (n=15) compared to controls (n=15) (41). In a community-based case-controlled study, the Study of Osteoporotic Fractures, Djonlagic et al. (43) identified higher baseline NREM sleep alpha and theta activity and REM sleep alpha and sigma activity in community-dwelling women ≥65 years who had developed MCI five years after the sleep study (n=85) compared to age-matched controls (n=85).

1.8.16 Longitudinal associations between wake EEG spectral power at baseline and future cognitive function decline

Small observational studies have reported that wake qEEG markers may have prognostic value for the longitudinal prediction of cognitive function decline (43, 52-55). Luckhaus et al. (52) recruited subjects with MCI and probable AD and examined associations between qEEG markers and cognitive decline at 1-year follow-up assessed by the Alzheimer's Disease Assessment Scale. Lower alpha power in posterior regions significantly predicted the transition from MCI to AD. In another study with a short follow-up duration (21 months), Jelic et al. (53) found that lower relative theta power was predictive of progression from MCI to AD. Prichep et al. (54) examined associations between wake qEEG markers and cognitive decline at 7–9 years of follow-up and found that higher theta power at baseline was significantly associated with greater cognitive decline at 7–9 years of follow-up in elderly participants without evidence of cognitive decline. Another study focused specifically on the distribution of alpha activity in patients with AD versus healthy older controls, identifying that patients with AD recorded a significantly lower alpha spectral peak at baseline (302). Associations between EEG slowing at baseline and future cognitive function decline have also been examined. Hamilton et al. (55) observed that greater EEG slowing assessed by the theta/alpha ratio was associated with a transition from MCI to AD after 1.5 years. Therefore, the small observational studies investigating wake qEEG in patients with AD versus matched controls suggest qEEG may represent a valuable early brain-specific marker of future cognitive function decline. However, further prospective studies are needed to determine the prognostic value of qEEG markers as predictors of future cognitive decline, specifically in younger, unselected community-based cohorts with a longer duration of follow-up and focusing on sleep qEEG markers, as these have not been investigated to date in longitudinal analyses.

1.9 Conclusions, future research recommendations, original contribution to knowledge, and study aims and hypotheses

Previous studies do not provide robust evidence supporting the prognostic value of conventional PSG parameters as cognitive function markers. Cross-sectional studies recruited from clinical or select community-based cohort samples or analysed associations of subjective sleep metrics with cognitive function. Furthermore, longitudinal studies recruited older (≥60 years) community-dwelling participants with many demonstrating evidence of cognitive impairment at baseline and most included a relatively short follow-up duration (4–8 years). Cross-sectional and longitudinal analyses of the potential associations between OSA, sleep macroarchitecture, and cognitive function are needed among an unselected community-based cohort sample to determine the scope, magnitude, and generalisability of findings from previous clinical and select community-based cohort studies to the broader population.

Although sleep microarchitecture parameters determined by qEEG PSA could represent novel brain-specific cognitive function markers, the evidence is preliminary and predominantly confined to small experimental laboratory, clinical, and case-controlled studies. Cross-sectional and longitudinal community-based cohort studies remain warranted to examine independent associations between sleep microarchitecture and cognitive function among the broader population. Cross-sectional studies are necessary to provide more robust evidence concerning whether qEEG represents a useful brain-specific cognitive function marker. Longitudinal studies are necessary to identify the prognostic value of qEEG as a brain-specific marker of future cognitive dysfunction and decline. Importantly, previous studies have not included rich data and sufficient participant numbers to adjust for multiple covariates and determine independent associations between sleep microarchitecture and cognitive function among an unselected community sample, which is a novel contribution that this thesis makes to the literature.

1.9.1 Original contribution to knowledge

The experimental chapters of this thesis collectively make a significant original contribution to knowledge by utilising data from one of Australia's most comprehensive and longest-running community-based cohort studies to investigate

objective independent cross-sectional and longitudinal associations between OSA, sleep macroarchitecture, and sleep microarchitecture parameters (sleep spindle metrics and qEEG markers) and daytime cognitive function outcomes among community-dwelling middle-aged and older men.

1.9.2 Aim and hypothesis of Study 1 (CHAPTER 3)

Evidence from objective sleep studies is required to provide greater insight into the cross-sectional associations between OSA, sleep macroarchitecture, and cognitive function. Therefore, the aim of the first study, presented in **Study 1 (CHAPTER 3)**, was to investigate independent cross-sectional associations between objectively measured OSA and sleep macroarchitecture parameters and cognitive function outcomes among a sample of unselected community-dwelling middle-aged and older men. It was hypothesised that parameters indicative of greater OSA disease severity and disrupted sleep macroarchitecture would show modest independent cross-sectional associations with worse cognitive function in the complete sample and men ≥65 years in age-stratified analysis based on previous reports.

1.9.3 Aim and hypothesis of Study 2 (CHAPTER 4)

Along with analysis of cross-sectional associations, objective sleep studies are also required to provide longitudinal evidence on the associations between OSA and sleep macroarchitecture at baseline and cognitive function at follow-up. Therefore, the primary aim of the second study, presented in **Study 2 (CHAPTER 4)**, was to investigate independent longitudinal associations between OSA and sleep macroarchitecture parameters at baseline and cognitive function (TMT performance) assessed 8–10 years later among a sample of community-dwelling men who were on average younger than 60 years at baseline. It was hypothesised that parameters indicative of more severe OSA, greater hypoxemia, and disrupted sleep macroarchitecture would predict cognitive decline over 8–10 years. After reporting on the associations between conventional PSG parameters and cognitive function, it is important to focus on finer-grained sleep EEG microarchitecture or quantitative EEG markers and the associations of these parameters with OSA disease severity and cognitive function.

1.9.4 Aim and hypothesis of Study 3 (CHAPTER 5)

Although sleep spindles are commonly impaired in patients with OSA, there are currently no community-based cohort studies available controlling for multiple confounders to determine if OSA parameters (obstructive breathing episodes and intermittent nocturnal hypoxemia) are independently associated with sleep spindle abnormalities. Therefore, the aim of the third study, presented in **Study 3 (CHAPTER 5)**, was to investigate independent cross-sectional associations between three OSA severity measures (AHI, TST90, and arousal index) and five spindle metrics (average frequency, amplitude, overall density, slow density, and fast density) among a large community-based sample of men. It was hypothesised that markers of more severe OSA would be independently associated with spindle metrics. Along with determining whether OSA parameters are independently associated with spindle abnormalities, it is important to investigate the potential moderating effect of OSA in associations between sleep spindle metrics and cognitive function outcomes.

1.9.5 Aims and hypothesis of Study 4 (CHAPTER 6)

Although sleep spindle metrics have been associated with cognitive function outcomes, the evidence predominantly comes from small experimental laboratory studies. Also, although sleep spindles are commonly impaired in patients with OSA, the potential moderating role of OSA in the associations between sleep spindle metrics and cognitive function outcomes has not been investigated. Therefore, the primary aim of the fourth study, presented in **Study 4 (CHAPTER 6)**, was to investigate independent cross-sectional associations between spindle sleep metrics and cognitive function outcomes. The secondary aim was to determine if OSA severity moderated associations between sleep spindle metrics and cognitive function outcomes to implicate spindle involvement in cognitive impairment in OSA. It was hypothesised that sleep spindle metrics would be independently associated with cognitive function outcomes, and OSA severity would moderate these associations.

1.9.6 Aims and hypothesis of Study 5 (CHAPTER 7)

Along with sleep spindle metrics, EEG spectral power and slowing ratio during NREM and REM sleep may be independently associated with cognitive function. However, further community-based cohort studies are required to extend the preliminary evidence in the literature and perform age-stratified analyses to determine if these associations, if present, differ between age groups. Therefore, the primary aim of the fifth study, presented in **Study 5 (CHAPTER 7)**, was to extend the emerging community-based cohort literature by investigating independent cross-sectional associations between sleep microarchitecture and cognitive dysfunction in community-dwelling men. A secondary aim was to investigate independent cross-sectional associations between sleep microarchitecture and cognitive dysfunction in early to middle-aged (<65 years) and older (≥65 years) men to determine whether sleep microarchitecture is differentially associated with cognitive dysfunction amongst early to middle-aged versus older community-dwelling men. It was hypothesised that lower NREM sleep delta power, higher power in faster-frequency EEG bands during NREM sleep, and greater EEG slowing during REM sleep would be independently associated with worse cognitive function.

1.9.7 Aim and hypothesis of Study 6 (CHAPTER 8)

After reporting on cross-sectional associations between sleep microarchitecture and cognitive function, the longitudinal associations need to be investigated. The literature in this area is currently confirmed to small prospective observational studies, with limited evidence from larger community-based cohort studies. Therefore, the aim of the sixth study, presented in **Study 6 (CHAPTER 8)**, was to investigate independent longitudinal associations between sleep microarchitecture parameters and cognitive function 8–10 years later among a sample of community-dwelling middle-aged and older men. It was hypothesised that sleep microarchitecture would be independently associated with cognitive function at 8–10 years follow-up after controlling for baseline obstructive sleep apnea and other relevant risk factors and cognitive task performance.

CHAPTER 2. GENERAL METHODOLOGY

2.1 Study cohort

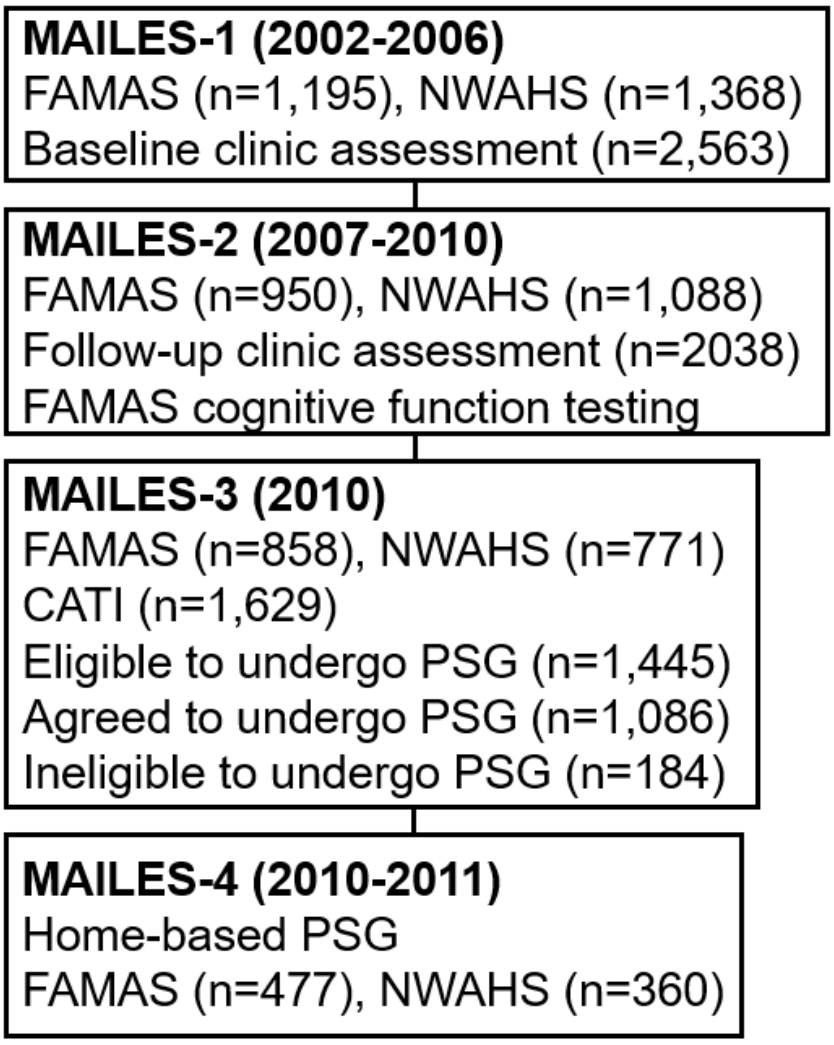
The experimental chapters of this thesis consist of analyses of data from the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study. The MAILES Study is one of the most comprehensive and longest-running longitudinal community-based cohort studies of male health and wellbeing with ageing in Australia (303). The MAILES Study includes 2,563 randomly selected, urban South Australian community-dwelling men aged ≥35 years at baseline, of predominantly Australian or European descent (96%), harmonised from two existing prospective cohort studies created using identical samples frames; all Florey Adelaide Male Ageing Study (FAMAS) and male North West Adelaide Health Study [NWAHS]) participants (303, 304).

2.2 MAILES Study clinic assessments

During the first MAILES Study follow-up (MAILES-1; 2002–2006), a baseline clinic assessment was performed with data collected on demographic, biomedical, and behavioural factors (303, 304). During the second follow-up (MAILES-2; 2007–2010), a follow-up clinic assessment was performed and FAMAS participants, comprising approximately half (46.6%) of the MAILES Study at baseline, completed cognitive assessments, including the inspection time task (n=435), TMT-A (n=433), TMT-B (n=430), FOME (n=433), and mini-mental state examination (MMSE) (n=399) (304). These administered cognitive tests are standardised and validated with well-established normative performance parameters (305-307). During a computer-assisted telephone interview (CATI) follow-up (MAILES-3; 2010), participants not reporting a previous OSA diagnosis were eligible and invited to undergo unattended eight-channel home-based PSG. During the fourth follow-up wave (MAILES-4; 2010–2011), 837 men underwent successful home-based PSG within time and budget constraints (Figure 2.1). Follow-up of these men from their original sleep study occurred approximately 8–10 years after the baseline PSG with data linkage, repeat cognitive tests, blood tests, and a second sleep study (NHMRC approval number:

1122342). Participant recruitment and cognitive testing, PSG scoring, coding, and data processing were performed by members of the team at Flinders Health and Medical Research Institute (FHMRI) Sleep Health before commencement of PhD candidature in 2019.

Figure 2.1 MAILES Study clinical and sleep study assessments and cognitive function testing



MAILES, Men Androgen Inflammation Lifestyle, Environment, and Stress. FAMAS, Florey Adelaide Male Ageing Study. NWAHS, North West Adelaide Health Study. CATI, computer-assisted telephone interview. PSG, polysomnography.

2.3 Covariate assessments

Utilising a community-based cohort provides the statistical advantage of investigating independent cross-sectional and prospective associations between OSA and sleep macro and microarchitecture parameters and daytime cognitive function outcomes controlled for potentially important demographic, biomedical, and behavioural confounders. Covariates used for statistical adjustment in multivariable regression models and their definitions are provided in Table 2.1.

Table 2.1 Covariates used for statistical adjustment in multivariable regression models and their definitions, dichotomisation, or categorisation

Covariate	Definition
Age	Years
Financial stress	Spends >earns versus saves a little/lot
Highest educational attainment	≥Diploma, Certificate, Trade versus ≤high school
Marital status	Married/partner versus other
Smoking status	Never/former versus current
Alcohol risk	Non-low vs med-very high
Physical activity level	Low/moderate/vigorous versus sedentary behaviour
Body mass index	<25 (underweight/normal), 25 to <30 (overweight), or ≥30 kg/m^2 (obese) (308)
Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-Economic Disadvantage (SEIFA IRSD)	Collapsed into quintiles (1 = most socio-economic disadvantage; 5 = least socio-economic disadvantage) (309)
Cardiovascular disease	Self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke
Diabetes mellitus	Self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) haemoglobin A1C ≥6.5%, or reported anti-diabetic medication use (oral hypoglycaemic agents and/or insulin)
Blood glucose level	The amount of glucose in the blood (mmol/L) during a fasting blood test
Insomnia	Difficulty initiating or maintaining sleep occurring at least three nights/week

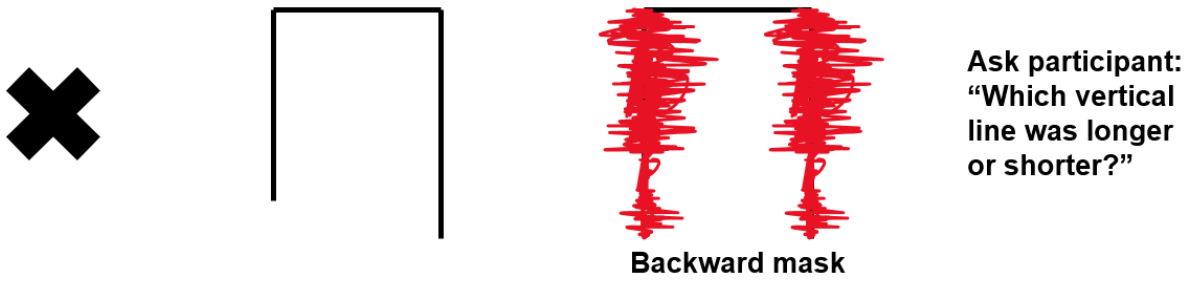
	(Pittsburgh Sleep Quality Index [PSQI] dimensions) and significant daytime fatigue (36-item short-form survey instrument [SF-36] score one standard deviation below the mean) (310)
Hypertension	Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use) (311)
Cardio-metabolic conditions	Combined variable including one or more of diabetes mellitus, hypertension, or cardiovascular disease
Psychotropic medication use	Reported use of one or more of opiates, antipsychotics, antiepileptics, antidepressants, or benzodiazepines

2.4 Cognitive assessments

2.4.1 Inspection time task

The inspection time task is a measure of visual processing speed whereby participants with normal vision are shown two vertical lines, each adjoined by one horizontal line in a figure called a pi figure (71). The presentation time of the pi figure ranges from <10 to >300 milliseconds and varies between trials. A backward mask is then presented for between 200 to 1000 milliseconds to mask the pi figure and disrupt visual processing. After the pi figure and backward mask are removed, the participant indicates which vertical line they perceived to be longer (Figure 2.2) (312). Reaction time is not an outcome measure, given that the participant is allowed as much time as needed to respond to the stimulus. The primary outcome measure is the duration the stimulus is presented to the participant before they achieve a preset accuracy, typically 75% correct responding (71). In Chapter 3, inspection time task scores were normalised using a logarithmic base 10 transformation to reduce skewness to ensure linear regression analyses could be performed.

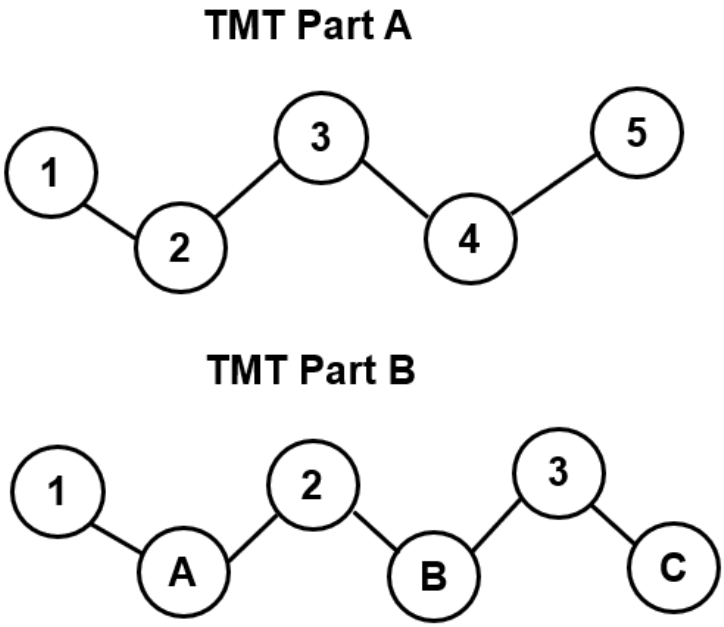
Figure 2.2 Inspection time task



2.4.2 Trail-making test

The TMT measures visual attention and task switching and assesses visual search, scanning, processing speed, mental flexibility, focused attention, and executive function (set-shifting ability) (65, 66). The test consists of two parts requiring the participant to map out a sequential path. The time needed to complete each path is scored. TMT-A is a measure of visual attention and processing speed requiring the participant to connect 25 encircled numbers (1–25) in sequence (Figure 2.3) (306). TMT-B is an executive function measure consisting of 24 circles, half containing numbers (1–12) and half letters (A–L). The participant is required to connect the circles by alternating drawing a line from circles containing numbers to those containing the corresponding letters in the appropriate sequence (1 – A, 2 – B, 3 – C, etc.) (Figure 2.3) (306). In Chapter 3, TMT scores were normalised using a logarithmic base 10 transformation to reduce skewness for use in linear regression analyses. In longitudinal analysis chapters (Chapters 4 and 8), TMT scores were converted to standardised z-scores to ensure a standardised cognitive outcome and is based on multiple previous studies utilising the same statistical approach (26, 31, 313, 314).

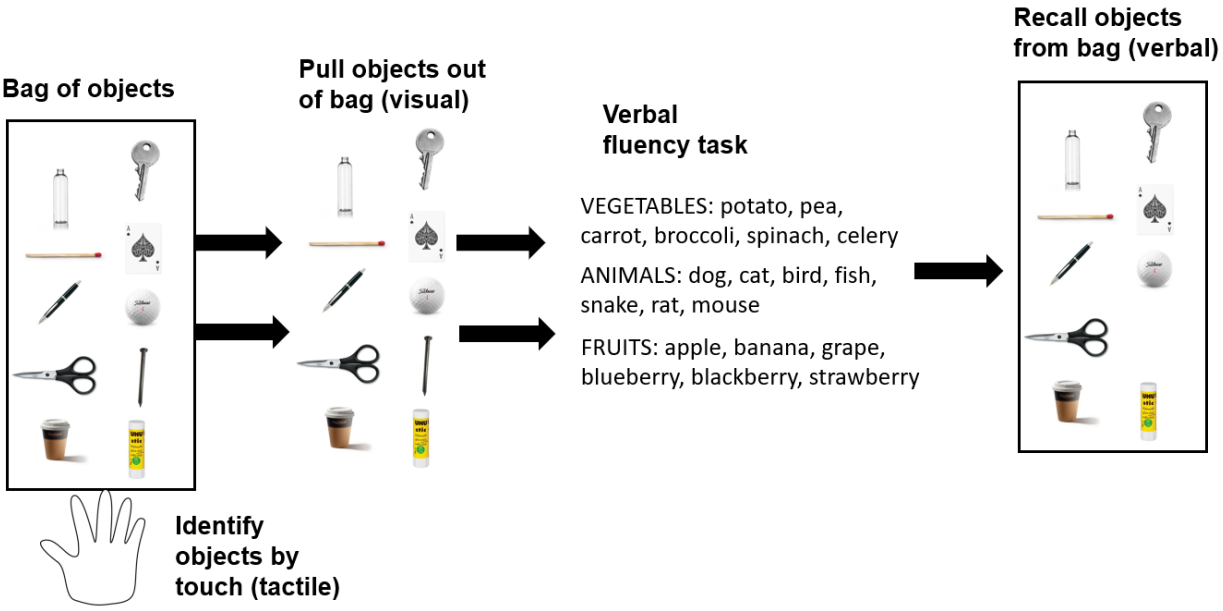
Figure 2.3 Trail-making test



2.4.3 Fuld object memory evaluation

The FOME test utilises multiple sensory pathways (tactile, visual, and verbal) to assess episodic memory and learning (Figure 2.4) (68). The participant is presented with a bag containing 10 unrelated objects identified by touch, sight, and verbally (307). The participant places their hand into the bag and attempts to identify an object by touch. The examiner corrects the participant if an object is misnamed after visual confirmation. The objects are then placed back in the bag, and the participant completes a distractor task in which they say words rapidly from a semantic category (e.g., animals, fruits, and vegetables). After the distractor task, the participant attempts to recall the objects in the bag verbally, and the number of objects correctly recalled is scored. The maximum possible score is 10, with higher scores representing intact memory and lower scores impaired episodic memory and learning. The FOME test helps identify memory decline in older adults, and low scores may indicate dementia (307). The experimental chapters of this thesis report on immediate verbal recall data as recall was recorded after a single trial without delay.

Figure 2.4 Fuld object memory evaluation test



2.4.4 Mini-mental state examination

The MMSE is a quantitative measure of cognitive status consisting of questions and problem-solving tasks that test orientation, registration and recall, attention and calculation, language, and the ability to follow verbal and written commands (315) (Table 2.1). The total score is used to scale an individual on cognitive ability, with a higher score indicating better cognitive ability. The maximum possible score is 30, with ≤27 indicating cognitive impairment classified as mild (22-27), moderate (17-21), or severe (<17) (316).

CHAPTER 3. SLEEP MACROARCHITECTURE BUT NOT OBSTRUCTIVE SLEEP APNEA IS INDEPENDENTLY ASSOCIATED WITH COGNITIVE FUNCTION IN ONLY OLDER MEN OF A POPULATION-BASED COHORT

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Author contributions: I undertook this work as the primary author and made the most significant contributions, from conceptualisation to realisation and documentation, with supervision from the co-senior authors. I undertook all analyses and was primarily responsible for research design (70%), data collection and analysis

(80%), and writing and editing (80%). My supervisors and the wider author group assisted with manuscript editing and revisions and all authors approved the final version.

3.1 Abstract

Evidence linking obstructive sleep apnea with cognitive dysfunction predominantly comes from clinical or select community samples. We investigated the independent cross-sectional association between obstructive sleep apnea and sleep macroarchitecture parameters with cognitive function in unselected community-dwelling middle-aged and older men. Four hundred and seventy-seven Florey Adelaide Male Ageing Study participants underwent successful home-based polysomnography. They also completed cognitive testing, including the inspection time task, Fuld object memory evaluation, trail-making test A and B, and mini-mental state examination. Multivariable regression models examined independent cross-sectional associations between obstructive sleep apnea and sleep macroarchitecture parameters with cognitive function. In univariable analyses, higher apnea-hypopnea index and percentage total sleep time with oxygen saturation <90% were associated with worse trail-making test A performance (both $p<0.05$). Higher apnea-hypopnea index was also associated with worse trail-making test B performance and slower inspection time (both $p<0.05$). In adjusted analyses, obstructive sleep apnea and sleep macroarchitecture parameters were not associated with cognitive function (all $p>0.05$). In age-stratified analysis in men ≥65 years, greater stage 1 sleep was independently associated with worse trail-making test A performance, while greater stage 3 sleep was independently associated with better trail-making test A performance (both $p<0.05$). Our findings suggest that obstructive sleep apnea is not independently associated with cognitive function. In older but not younger men, light sleep was associated with worse attention, while deep sleep was associated with better attention. Longitudinal population-based cohort studies are needed to determine if obstructive sleep apnea and disrupted sleep macroarchitecture independently predict prospective cognitive dysfunction and decline.

3.2 Introduction

Obstructive sleep apnea (OSA) is a highly prevalent sleep-related breathing disorder (99) that remains frequently under-recognised and under-diagnosed (317). OSA is characterised by recurrent pharyngeal collapse, leading to intermittent nocturnal hypoxemia (oxygen desaturation) and sleep fragmentation (81, 82). An association between OSA and daytime cognitive dysfunction, including attentional problems, vigilance failure, memory impairments, and executive dysfunction, has been reported in clinical samples (16, 17, 318, 319). However, inconsistencies remain regarding the scope, magnitude, and generalisability of these impairments (14, 319) and the extent to which demographic, biomedical, and behavioural risk factors that can impact cognitive function have been considered (110). Furthermore, the majority of studies that have previously investigated the effect of OSA disease severity and intermittent hypoxemia on daytime cognitive function recruited from small samples, underlining the need for larger community-based cohort studies to control for potentially important confounding variables and provide greater clarity on the associations between OSA and sleep macroarchitecture parameters and cognitive function outcomes.

As a means of seeking clarity on this issue, five cohort studies (one clinical and four community-based) previously investigated independent cross-sectional associations between OSA and/or sleep macroarchitecture parameters and cognitive function. (18-23). Community-based cohort studies recruited from select populations only (older age or at high risk of OSA). In the Osteoporotic Fractures in Men (MrOS) Sleep Study, reduced rapid eye movement (REM) and greater non-REM (NREM) stage 1 (N1) sleep was associated with impaired executive function independent of total sleep time and sleep-disordered breathing in cognitively intact community-dwelling men ≥67 years (n=2,601) (19). In contrast to the MrOS Sleep Study, in the HypnoLaus Study, conventional OSA severity parameters, including apnea-hypopnea index and oxygen desaturation index (>4% and >6%), were associated with impaired memory, verbal fluency, and set-shifting ability in community-dwelling men and women >65 years (n=580), including participants both with (global Clinical Dementia Rating [CDR] score of 0 [n=289]) and without (CDR score >0 [n=291]) cognitive impairment (21). The Akershus Sleep Apnea Project (ASAP) Study utilised

a different methodology by recruiting participants identified as at high risk of having OSA (n=290) and reported that average oxygen saturation was associated with worse verbal memory in a community-based cohort with a mean age of 48 years (22). In a community-based cohort of men and women with a mean age of 68 years from the Autonomic Nervous System Activity, Aging and Sleep Apnea/Hypopnea (SYNAPSE) Study (n=827), respiratory events and nocturnal hypoxemia were not associated with episodic and visual memory or executive function (23), contrasting with the findings of the HypnoLaus and ASAP studies (21, 22). In a clinical cohort of highly educated adults with a mean age of approximately 50 years from the Apnea Positive Pressure Long-term Efficacy Study (APPLES) (n=1,204), greater N1 sleep was associated with poorer attention and processing speed using the Pathfinder Number Test (18). The use of clinical or select community-based cohort studies does not provide robust evidence of associations between OSA, sleep macroarchitecture, and cognitive function, highlighting the need for studies in unselected populations.

Along with the rising prevalence of OSA, there is evidence that conventional sleep macroarchitecture parameters assessed utilising conventional visual inspection of 30 second epochs of the electroencephalogram (EEG) commonly becomes disrupted with advancing age. After age 60, the percentage of N3 sleep typically decreases by approximately 2% per decade, with an associated reduction in REM sleep and a net increase in N1 and N2 sleep (6). The aetiology and functional significance of changes in sleep macroarchitecture commonly observed with ageing are not fully understood but are thought to possibly reflect neuronal activity-dependent homeostatic sleep pressure build-up and/or circadian phase advances (5, 7, 8). The increased light (N1 and N2) sleep and reduction in REM and deep (N3) sleep may partly contribute to cognitive dysfunction in older adults. However, no community-based cohort studies have performed an age-stratified analysis to investigate independent associations between sleep macroarchitecture and cognitive function in older versus younger participants.

The occasionally disparate results obtained from previous cohort studies likely derive predominantly from the variable use of clinical or select community samples, the limited range of cognitive function outcomes assessed, inconsistencies in adjustment for potentially important confounders, or the large age differences (≥65 and ≤50

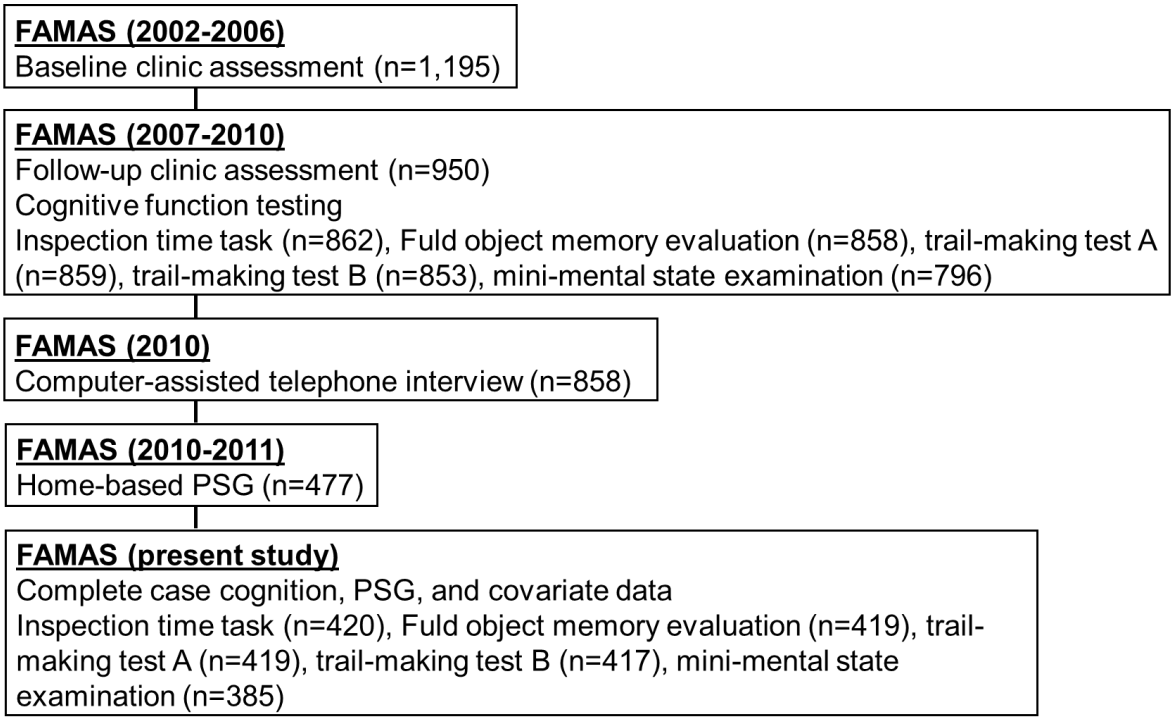
years). A community-based cohort study conducted in an unselected community sample would provide greater clarity regarding the scope, magnitude, and generalisability of OSA-related cognitive dysfunction. Therefore, the aim of this study was to investigate independent cross-sectional associations between objectively measured OSA and sleep macroarchitecture parameters and cognitive function outcomes among a sample of unselected community-dwelling middle-aged and older men. It was hypothesised that parameters indicative of greater OSA disease severity and disrupted sleep macroarchitecture would show modest independent cross-sectional associations with worse cognitive function in the complete sample and men ≥65 years in age-stratified analysis based on previous reports (6, 19-21).

3.3 Methods

3.3.1 Study participants

The Florey Adelaide Male Ageing Study (FAMAS) commenced in 2002 and is a multi-disciplinary community-based cohort study that includes unselected, urban community-dwelling men (n=1,195) aged between 35 and 80 years at baseline and living in the northern and western suburbs of Adelaide, South Australia (304, 320). The overarching aim of FAMAS is to investigate risk factors associated with physical and psychological disorders in a group of men representative of their target population (320). During a follow-up of the FAMAS cohort by computer-assisted telephone interview in 2010 (n=858), those participants reporting no previous clinical diagnosis of OSA were invited to undergo unattended eight-channel home-based polysomnography (PSG) between 2010–2011 as part of a sub-study of the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study (98, 303). Of these, 477 sleep studies were completed within time and budget constraints (Figure 3.1). FAMAS was conducted in accordance with the Declaration of Helsinki and approved by the Human Research Ethics Committees of the Royal Adelaide Hospital (approval number: 020305). All participants provided written informed consent before study commencement.

Figure 3.1 FAMAS clinical and sleep study assessments and cognitive function testing



FAMAS, Florey Adelaide Male Ageing Study. PSG, polysomnography.

3.3.2 Sleep study assessment

The PSG was conducted using an ambulatory system (Embletta X100, Embla Systems, Broomfield, Colorado, USA), which measured electrical brain activity (electroencephalography [EEG]), eye movements (electrooculography [EOG]), submental electromyography, nasal pressure, thoracic and abdominal effort, peripheral pulse oximetry, and body position. The EEG recording was obtained from one referential derivation (F4-M1) plus left EOG, with a sampling rate of 200 Hz. Before PSG set-up, trained staff obtained anthropometric measures, including height, weight, body mass index (BMI; weight in kilograms [kg] divided by height in metres squared [kg/m^2]), and waist and hip circumferences, and participants completed the Epworth Sleepiness Scale (ESS) and Pittsburgh Sleep Quality Index (PSQI). PSGs were timed to coincide with the habitual sleeping schedule of each participant.

A single experienced sleep technician manually scored all PSG measures in accordance with 2007 American Academy of Sleep Medicine (AASM) *Alternative* scoring criteria, which was recommended by the AASM and an expert panel of the Australasian Sleep Association for use in prospective epidemiological studies (321). OSA was identified by an apnea-hypopnea index (AHI) of ≥10/h and further categorised as mild (AHI 10–19/h), moderate (AHI 20–29/h), or severe (AHI ≥30/h). These cut-offs for classification were chosen because Ruehland et al. (32) have shown that an AHI of 5/h of sleep used to define sleep-disordered breathing by the *Recommended* criteria is equivalent to an AHI of 10/h using the *Alternative* criteria, and 15/h using the older 1999 *Chicago* criteria. To maintain comparability with previous work, an AHI cut-off of 10/h was chosen (322). Apnea was defined as complete or near-complete airflow cessation (≥90% airflow reduction), measured using nasal cannula pressure excursions from breathing, lasting ≥10 seconds. Hypopnea was defined as a ≥50% decrease in nasal cannula pressure with an associated ≥3% oxygen desaturation or EEG arousal. Nocturnal hypoxemia was identified by the oxygen desaturation index 3% (ODI 3%) and the percentage of total sleep time with oxygen saturation <90% (TST90). Sleep studies were considered acceptable with 3.5 h of sleep and 5.5 h of total-recorded study time with good respiratory and EEG signals for the recording duration. Failed sleep studies were repeated if possible, leading to a final failed study rate of 2.4%.

3.3.3 Cognitive assessments

Participants of the FAMAS cohort completed five standardised, validated, and well-established cognitive tests during the 2007–2010 follow-up, including the inspection time task, Fuld object memory evaluation (FOME), trail-making test A (TMT-A) and B (TMT-B), and mini-mental state examination (MMSE). These cognitive tests were chosen for inclusion in the present study as they were completed by the majority of FAMAS participants and attention and processing speed (inspection time and TMT-A), executive function or set-shifting ability (TMT-B), and episodic memory and learning (FOME test) are cognitive function domains have also been demonstrated to be affected in patients with OSA. Moreover, analysis of the MMSE provides the opportunity to examine OSA and sleep macroarchitecture parameters in relation to global cognitive impairment. Refer to Chapter 2 for a detailed description of the

cognitive tests. The final analysis included participants with complete case cognition, PSG, and covariate data.

3.3.4 Covariate assessments

Self-administered questionnaires determined demographic (age, financial stress, highest educational attainment, and marital status), biomedical (smoking status), and behavioural (alcohol intake placing participants at alcohol risk and physical activity) risk factors, and health-related quality of life (the 36-Item Short Form Survey Instrument [SF-36]). BMI was categorised according to international criteria (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 [obese]) (308). Relative social disadvantage, based upon participants' residential postcode, was determined with the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-Economic Disadvantage (IRSD) (309). Anthropometry (BMI and waist circumference), sphygmomanometery (seated blood pressure), and a fasting blood glucose sample were undertaken during clinic assessment (2007–2010) (304). Composite cardiovascular disease (CVD; self-reported, doctor-diagnosed, myocardial infarction, angina, transient ischemic attack, or stroke) and diabetes mellitus (self-reported, doctor-diagnosed, fasting plasma glucose [FPG] ≥7.0 mmol/L [126 mg/dL], haemoglobin A1C [HbA1C] ≥6.5%, or reported antidiabetic medication use [oral hypoglycaemic agents and/or insulin]) were also determined. Insomnia symptoms were classified on the basis of the participant reporting at least one difficulty initiating or maintaining sleep from the Pittsburgh Sleep Quality Index (PSQI) and significant daytime fatigue (SF-36 Vitality Scale score one standard deviation [*SD*] below the mean) (310). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use. Psychotropic medication included reported use of one or more of opiates, antipsychotics, antiepileptics, antidepressants, or benzodiazepines.

3.3.5 Statistical analysis methodology

Data were analysed using IBM SPSS version 25.0 (IBM Corporation, Armonk, New York, USA). Descriptive statistics are reported as mean (*SD*) for REM and NREM

stage N1, N2, and N3 sleep percentages and median (interquartile range [IQR]) for oxygen saturation nadir (O_2 nadir) and mean oxygen saturation (SaO_2). Descriptive statistics are reported as percentages (numbers) for categorical exposures and covariates. Descriptive statistics for inspection time, TMT-A, and TMT-B performance are reported as median (IQR) due to non-normality, whereas FOME performance is reported as mean (*SD*).

After visual inspection of residual distributions, inspection time, TMT-A, and TMT-B scores were normalised using a logarithmic$_{10}$ transformation, whereas MMSE scores were dichotomised (cognitive impairment: 17–27; not cognitively impaired: 28–30) (316). Inspection time, TMT-A, and TMT-B scores were logarithmically transformed to make the data as normal as possible. Due to non-normality, AHI, O_2 nadir, and mean SaO_2 were logarithmically transformed. TST90 was dichotomised (≤4%; >4%) based on previous literature reporting that a TST90 of >4% has demonstrated association with adverse cardiovascular outcomes (323). ODI 3% was categorised into <15, ≥15<30, or ≥30 oxygen desaturation episodes /h of sleep.

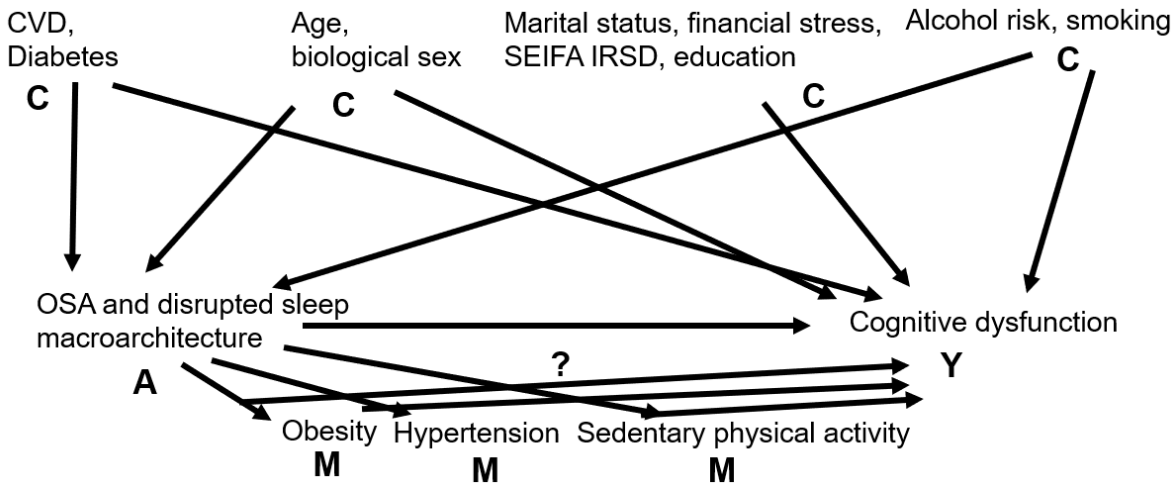
For univariable analyses of FOME performance in relation to categorical exposures and covariates, one-way analysis of variance and independent samples t-tests were performed. Kruskal-Wallis and Mann-Whitney U-tests were performed for univariable analyses of continuous cognitive outcomes with skewed distributions (inspection time, TMT-A, and TMT-B) in relation to categorical exposures and covariates. Pearson's chi-squared tests examined univariable differences in the distribution of MMSE dichotomised cognitive impairment.

Independent cross-sectional associations between OSA (AHI, TST90, ODI 3%, O_2 nadir, and mean SaO_2) and sleep macroarchitecture (REM and NREM stage N1, N2, and N3 sleep percentages; and total sleep time [TST; hours]) parameters and inspection time, TMT-A, TMT-B, and FOME performance were examined using multivariable linear regression models with results presented as unstandardised beta (*B*) coefficients (95% confidence interval [CI]). Multivariable binary logistic regressions were performed for the MMSE using clinical cut-off for mild cognitive impairment (≤27/30) (324), with results presented as odds ratios (95% CI). Model 1 was adjusted for age, while model 2 was additionally adjusted for demographic (financial stress, highest educational attainment, SEIFA IRSD, and marital status),

biomedical (BMI, smoking status, CVD, diabetes mellitus, insomnia, and hypertension), and behavioural (alcohol risk, physical activity, and psychotropic medication use) risk factors. Multivariable regression models were also performed after stratifying by age (<65 versus ≥65 years). These analyses were performed to investigate whether parameters indicative of greater OSA disease severity and disrupted sleep macroarchitecture would be independently associated with worse cognitive function in the complete and age-stratified samples. As a supplementary analysis, the purposeful covariate selection procedure (325) was utilised to reduce the number of covariates in model 2 and adjust for age, education, hypertension, and financial stress. Age was treated as a continuous covariate in multivariable linear regression to adjust for this potential confounder when examining cross-sectional associations between OSA, sleep macroarchitecture, and cognitive function in the complete study sample. Age stratification was then performed to examine differences in these associations in older versus younger community-dwelling men. The filter function in SPSS was used to ensure only participants with complete case cognition, PSG, and covariate data were included in the final analysis.

Moderator analysis was performed using BMI (obese [≥30 kg/m^2]), hypertension (≥140 mmHg systolic pressure and/or ≥90 mmHg diastolic pressure or treatment), and physical activity (sedentary) as interaction terms to further explore significant OSA, sleep macroarchitecture, and cognition associations in the complete and age-stratified samples. For all analyses, a two-sided $p<0.05$ was considered statistically significant.

Figure 3.2 Overview of relationships between variables



Legend: A=exposure/treatment/intervention/primary independent variable, C=confounder, M=mediator, Y=outcome variable.

3.4 Results

3.4.1 Participants' characteristics

Complete sample descriptive statistics of participant OSA and sleep macroarchitecture parameters and demographic, biomedical, and behavioural risk factors are reported in Table 3.1. The time lag between cognitive (2007–2010) and PSG (2010–2011) testing was mean (*SD*) 26.2 (11.8) (range: 3–51) months. The cohort analysed comprised 420 men with a mean age of roughly 60 years at the time of PSG testing. Of these, 55% were identified as having OSA (AHI ≥10/h); and 12.9% had severe OSA (AHI ≥30/h). Approximately one-third (33.8%) of men were obese (BMI ≥30 kg/m^2). Overall, the incidence of excessive daytime sleepiness (ESS ≥11) was low (13.8%). Men ≥65 years recorded significantly less TST and had a higher incidence of CVD and hypertension compared to men <65 years (Table 3.2). Higher age, lower education, diabetes, and hypertension were consistently associated with worse performance across the cognitive domains assessed (Table 3.3).

Table 3.1 Complete sample participant characteristics (OSA and sleep macroarchitecture and demographic, biomedical, and behavioural risk factors)

Participant characteristics	
Demographic risk factors	
Mean (*SD*)	
Age (years)	60.4 (10.6)
% (n)	
<50	23.6 (99)
50–59	31.2 (131)
60–69	25.5 (107)
>70	19.8 (83)
Financial stress	
Spends >earns	83.8 (352)
Saves a little/lot	16.2 (68)
Highest educational attainment	
≥Diploma, Certificate, Trade, Bachelor Degree or Higher	72.1 (303)
SEIFA IRSD	
Quintile 1 (most socio-economic disadvantage)	22.1 (93)
Quintile 2	10.5 (44)
Quintile 3	28.8 (121)
Quintile 4	25.5 (107)
Quintile 5 (least socio-economic disadvantage)	13.1 (55)
Married/partner	84 (353)
Sleep macroarchitecture	
Mean (*SD*)	
N1 (%)	14.8 (6.6)
N2 (%)	54.6 (9.4)
N3 (%)	16.0 (8.7)
N3 (mins)	60.0 (34)
REM (%)	14.6 (5.5)
% (n)	
TST (mins) <360	38.3 (161)
Mean (*SD*)	
OSA severity categories (AHI)	16.1 (15)
% (n)	
<10/h	36.1 (189)
10–19/h	22.1 (116)
20–29/h	14.5 (61)
≥30/h	10.3 (54)
TST90 ≥4%	27.4 (115)
ODI 3 (%)	
>15/h	13.6 (57)
≥15<30/h	17.6 (74)
≥30/h	68.8 (289)
Median (IQR)	
O_2 nadir	86.0 (81, 89)
SaO_2	93.7 (92.7, 94.9)
Biomedical risk factors	
Mean (*SD*)	
BMI (kg/m^2)	28.6 (3.4)
% (n)	
<25 (underweight/normal)	20.0 (84)

25 to <30 (overweight)	46.2 (194)
≥30 (obese)	33.8 (142)
Current smokers	18.1 (76)
Cardiovascular disease	7.1 (30)
Diabetes mellitus	18.6 (78)
Insomnia	12.4 (52)
Hypertension	59.3 (249)
Behavioural risk factors	
% (n)	
Low/moderate/vigorous physical activity	76.9 (323)
Medium–very high alcohol risk	6.7 (28)
Epworth Sleepiness Scale	
Mean (*SD*)	6.3 (4.0)
% (n)	
≥11 (excessive daytime sleepiness)	13.8 (57)
Psychotropic medication use	8.6 (36)

Abbreviations: REM, rapid eye movement sleep; TST, total sleep time; N1, stage 1 sleep; N2, stage 2 sleep; N3, stage 3 sleep; AHI, apnea-hypopnea index; TST90, percentage of total sleep time with oxygen saturation <90%; ODI 3, oxygen desaturation index 3%; SaO_2, mean oxygen saturation; BMI, body mass index; SEIFA IRSD, Socio-Economic Indexes for Areas Index of Relative Socio-Economic Disadvantage; *SD*, standard deviation; IQR, interquartile range.
BMI: body mass index categorised according to international criteria (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 [obese]).
Cardiovascular disease: self-reported, doctor-diagnosed, myocardial infarction, angina, transient ischemic attack, or stroke.
Diabetes mellitus: self-reported, doctor-diagnosed, FPG ≥7.0 mmol/L [126 mg/dL], HbA1C ≥6.5%, or self-reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).
Insomnia: at least one of two PSQI dimensions (difficulty initiating or maintaining sleep) and significant daytime fatigue defined as an SF-36 Vitality Scale score one *SD* below the mean.
Hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use.
Psychotropic medication use: self-reported use of one or more of opiates, antipsychotics, antiepileptics, antidepressants, or benzodiazepines.
Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

Table 3.2 Age-stratified sample participant characteristics (OSA and sleep macroarchitecture and demographic, biomedical, and behavioural risk factors)

Participant characteristics	<65 years (n=291)	≥65 years (n=129)
Demographic risk factors		
Mean (*SD*)		
Age (years)	53.4 (6.42)	71.9 (5.1) *
% (n)		
Financial stress		
Spends >earns	84.5 (246)	82.8 (106)
Saves a little/lot	15.5 (45)	17.2 (22)
Highest educational attainment		
≥Diploma, Certificate, Trade, Bachelor Degree or Higher	74.6 (217)	67.2 (86)
SEIFA IRSD		
Quintile 1 (most socio-economic disadvantage)	25.4 (74)	14.8 (19)
Quintile 2	11.0 (32)	9.4 (12)
Quintile 3	33.0 (96)	19.5 (25)
Quintile 4	22.0 (64)	33.6 (43)
Quintile 5 (least socio-economic disadvantage)	8.6 (25)	22.7 (29)
Married/partner	84.9 (247)	82.8 (108)
Sleep macroarchitecture		
Mean (*SD*)		
N1 (%)	14.9 (6.5)	14.5 (6.8)
N2 (%)	54.3 (9.0)	55.4 (10.1)
N3 (%)	15.9 (8.5)	16 (9.1)
N3 (mins)	60.2 (33.4)	59.2 (35.6)
REM (%)	14.9 (5.5)	14.1 (5.6)
% (n)		
TST (mins) <360	35.1 (102)	46.1 (59) *
Mean (*SD*)		
OSA severity categories (AHI)	15.3 (15.1)	17.8 (14.8)
% (n)		
<10/h	47.1 (137)	39.8 (51)
10–19/h	28.5 (83)	25.8 (33)
20–29/h	13.1 (38)	18 (23)
≥30/h	11.3 (33)	16.4 (21)
% (n)		
TST90 ≥4%	24.7 (72)	33.6 (43)
ODI 3%		
>15/h	14.8 (43)	10.9 (14)
≥15<30/h	17.2 (50	18.8 (24)
≥30/h	68.0 (198)	70.3 (91)
Median (IQR)		
O_2 nadir	86.0 (82.0, 89.0)	85.0 (80.0, 88.0)
SaO_2	93.9 (92.9, 95.0)	93.4 (92.2, 94.8)
Biomedical risk factors		

Mean (*SD*)		
BMI (kg/m^2)	28.7 (4.4)	28.22 (4.3)
% (n)		
<25 (underweight/normal)	20.6 (60)	18.8 (24)
25 to <30 (overweight)	45.0 (131)	49.2 (63)
≥30 (obese)	34.3 (100)	32.0 (41)
Current smokers	22.3 (65)	8.6 (11) *****
Cardiovascular disease	2.7 (8)	17.2 (22) *****
Diabetes mellitus	5.2 (15)	8.7 (11)
Insomnia	13.1 (38)	10.9 (14)
Hypertension	51.2 (149)	77.3 (99) *****
Behavioural risk factors		
Low/moderate/vigorous physical activity	71.6 (217)	82.0 (105)
Medium–very high alcohol risk	7.6 (22)	4.7 (6) *****
Mean (*SD*)		
Epworth Sleepiness Scale	6.6 (4.1)	5.7 (3.5)
% (n)		
≥11 (excessive daytime sleepiness)	15.0 (43)	11.2 (14)
Psychotropic medication use	6.5 (19)	13.3 (17)

Abbreviations: REM, rapid eye movement sleep; TST, total sleep time; N1, stage 1 sleep; N2, stage 2 sleep; N3, stage 3 sleep; AHI, apnea-hypopnea index; TST90, percentage of total sleep time with oxygen saturation <90%; ODI 3, oxygen desaturation index 3%; SaO_2, mean oxygen saturation; BMI, body mass index; SEIFA IRSD, Socio-Economic Indexes for Areas Index of Relative Socio-Economic Disadvantage; *SD*, standard deviation; IQR, interquartile range.

BMI: body mass index categorised according to international criteria (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 [obese]).

Cardiovascular disease: self-reported, doctor-diagnosed, myocardial infarction, angina, transient ischemic attack, or stroke.

Diabetes mellitus: self-reported, doctor-diagnosed, FPG ≥7.0 mmol/L (126 mg/dL), HbA1C ≥6.5%, or self-reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).

Insomnia: at least one of two PSQI dimensions (difficulty initiating or maintaining sleep) and significant daytime fatigue defined as an SF-36 Vitality Scale score one *SD* below the mean.

Hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use.

Psychotropic medication use: self-reported use of one or more of opiates, antipsychotics, antiepileptics, antidepressants, or benzodiazepines.

Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

Symbol legend: *****p<0.05 compared with <65 years.

Table 3.3 Cognitive function outcomes in relation to participant demographic, biomedical, and behavioural risk factors, and OSA and sleep macroarchitecture

	Inspection time (ms)	**TMT-A (sec)**	**TMT-B (sec)**	**FOME (n/10)**	**MMSE (n/30)**
	Median (IQR)	Median (IQR)	Median (IQR)	Mean (*SD*)	% (n) <28/30
	60 (52, 70)	15 (12, 18)	71 (56, 91)	6.3 (1.7)	17.1 (66)
Demographic risk factors					
Age (years)	Median (IQR)	Median (IQR)	Median (IQR)	Mean (*SD*)	% (n) <28/30
<50	54 (46, 64)	12 (10, 15)	59 (49, 72.5)	7.1 (1.5)	10.3 (10)
50–59	56 (48, 66)	14 (11, 17)	67 (51, 86)	6.6 (1.6)	12.8 (15)
60–69	64 (56, 76)	16 (13, 19)	77.5 (61.8, 94)	6.1 (1.7)	17.7 (17)
≥70	74 (62, 96)	20 (15, 25)	101 (77.5, 125)	5.3 (1.5)	32.0 (24)
p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Financial stress					
Spends more than earns	60 (50, 70)	16 (12, 21)	80 (60, 105)	6.2 (1.7)	18.5 (12)
Save a little/lot	60 (50, 72)	15 (12, 18)	69 (55, 90)	6.4 (1.7)	16.9 (54)
p	0.67	**0.016**	**0.022**	0.38	**<0.001**
Highest education					
>Diploma, Certificate, Trade, Bachelor Degree or Higher	60 (50, 72)	14 (11.8, 18)	72 (56.8, 91.3)	6.4 (1.7)	16.9 (39)
≤High school	62 (52, 74)	17 (13, 20)	80 (60, 105)	6 (1.6)	23.3 (24)
p	**0.037**	**0.006**	**0.002**	**0.025**	**<0.001**
SEIFA IRSD					
Quintile 1 (most socio-economic disadvantage)	60 (50, 70)	14 (12, 18)	70 (57.5, 90)	6 (5, 7)	19.0 (16)
Quintile 2	58 (46, 70)	15 (12, 18)	70 (55, 90)	6.5 (1.6)	14.3 (6)
Quintile 3	58 (52, 70)	15 (12, 19)	69 (55.5, 90)	6.6 (1.7)	18.4 (21)
Quintile 4	62 (50, 76)	15 (12, 18)	68 (55, 90)	6.2 (1.7)	15.5 (15)
Quintile 5 (least socio-economic disadvantage)	63 (51.5, 80)	16 (12, 21)	82.5 (60, 112)	6.2 (1.7)	16.7 (8)
p	0.37	0.46	0.084	0.15	**<0.001**
Married/partner					
No	58 (48, 72)	16 (12, 20)	74.5 (59.8, 99.3)	6.2 (1.9)	22.2 (14)
Yes	60 (50, 72)	15 (12, 18)	70 (55, 90)	6.4 (1.7)	16.1 (52)
p	0.76	**0.036**	0.14	0.42	**<0.001**
Biomedical risk factors					
BMI (kg/m^2)					
<25 (underweight/normal)	60 (50, 71)	15 (11, 20)	71.5 (55, 93.5)	6 (1.9)	19.7 (15)
25 to <30 (overweight)	61 (50, 72)	15 (12, 19)	72 (56, 91.3)	6.4 (1.5)	16.8 (30)
≥30 (obese)	60 (50, 71)	15 (12, 18)	69 (56, 91)	6.5 (1.8)	16.2 (21)
p	0.19	0.98	0.96	0.092	**<0.001**
Smoking status					
Never/former	60 (50, 72)	15 (12, 18)	70 (56, 93)	6.3 (1.7)	18.2 (58)
Current	57 (48, 68)	15 (12, 19.8)	72.5 (55.3, 90)	6.5 (1.6)	11.9 (8)
p	0.086	0.33	0.77	0.25	**<0.001**
Cardiovascular disease					
No	60 (50, 70)	15 (12, 18)	70 (55, 91)	6.4 (1.7)	17.5 (63)
Yes	71 (51.5, 86)	17 (14, 22.8)	88 (70.8, 110.3)	6 (1.7)	11.5 (3)
p	0.054	**0.008**	**0.002**	0.27	**<0.001**
Diabetes mellitus					
No	59.0 (50, 70)	15 (12, 18)	68 (55, 90)	6.4 (1.7)	16.6 (52)
Yes	64 (51, 84)	17 (13, 24)	85 (66.5, 111)	6.1 (1.6)	19.7 (14)
p	**0.004**	**0.001**	**<0.001**	0.16	**<0.001**
Insomnia					
No	60 (50, 70)	15 (12, 18)	70 (55, 91)	6.3 (1.7)	17.8 (60)
Yes	64 (52, 72)	15 (13, 19.5)	75 (60, 97)	6.7 (1.6)	12.8 (6)
p	0.27	0.21	0.17	0.11	**<0.001**
Hypertension					
No	58 (48, 68)	15 (11, 18)	67 (55, 85.3)	6.4 (1.7)	13.3 (19)

Yes	60 (52, 76)	15 (12, 19.5)	75 (58, 97)	6.3 (1.7)	18.0 (36)
p	**<0.001**	**0.033**	**0.004**	0.76	**<0.001**
Behavioural risk factors					
Alcohol risk					
Non–low risk	60 (50, 72)	15 (12, 18)	71 (56, 93)	6.3 (1.7)	17.8 (5)
Medium–very high risk	59 (52, 70)	13.5 (11.3, 18.5)	69.5 (52.3, 84.8)	6.9 (1.6)	17.1 (61)
p	0.99	0.49	0.65	0.069	**<0.001**
Physical activity					
Sedentary	58 (48, 68)	14 (11, 18)	73 (55, 95)	6.5 (1.7)	20.7 (18)
Low/moderate/vigorous	62 (50, 72)	15 (12, 19)	70 (57, 90.8)	6.3 (1.7)	16.1 (48)
p	0.095	0.15	0.86	0.36	**<0.001**
Psychotropic medication use					
No	60 (50, 70)	15 (12, 18)	70 (56, 91)	6.4 (1.7)	16.6 (59)
Yes	65 (46.5, 82)	17 (13, 22)	78 (57, 95)	5.9 (1.4)	23.3 (7)
p	0.48	0.066	0.48	0.13	**<0.001**
Epworth sleepiness scale (>11)					
No	60 (50, 72)	15 (12, 18)	70 (56, 91)	6 (5, 8)	10.8 (6)
Yes	62 (52, 70)	14 (12, 18)	78 (56, 92)	6.5 (5, 8)	18.5 (58)
p	0.72	0.72	0.99	0.54	**<0.001**
OSA and sleep macroarchitecture					
AHI (/h)					
<10/h	60 (50, 70)	15 (11, 18)	68 (55, 90)	6.4 (1.7)	19.6 (35)
10–19/h	60 (50, 72)	15 (12, 18)	75 (57.8, 95.5)	6.3 (1.7)	9.2 (10)
20–29/h	60 (52, 70)	15 (12, 20)	71 (57, 90)	6.3 (1.7)	27.6 (16)
≥30/h	62 (52, 82)	16 (12, 20)	75 (60, 99)	6.2 (1.9)	18.9 (10)
p	0.29	**0.020**	**0.002**	0.92	**<0.001**
TST90 (%)					
TST90 <4%	60 (50, 70)	14.5 (12, 18)	68 (55, 90)	6.3 (1.7)	16.0 (46)
TST90 >4%	62 (52, 74)	17 (12, 20)	77 (60, 96.3)	6.3 (1.8)	20.4 (20)
p	0.19	**0.012**	**0.024**	0.97	**<0.001**
ODI 3 (%)					
<15/h	56 (49, 67)	13.5 (11, 16.8)	67.5 (54, 94.8)	6.3 (1.5)	22.0 (11)
≥15<30/h	61 (50, 70)	15 (12, 19)	67 (55.8, 90)	6.6 (1.8)	16.2 (11)
≥30/h	60 (51, 72)	15 (12, 19)	73 (57, 94)	6.3 (1.7)	14.5 (44)
P	0.58	0.14	0.35	0.48	**<0.001**
TST (mins)					
<360	60 (50, 72)	15 (12, 20)	73 (58, 96)	6.3 (1.7)	18.6 (27)
>360	62 (50, 72.5)	14 (11.3, 18)	70 (55, 90)	6.3 (1.7)	16.4 (39)
p	0.96	**0.009**	0.28	0.88	**<0.001**

Abbreviations: REM, rapid eye movement sleep; NREM, non-rapid eye movement sleep; TST, total sleep time; AHI, apnea-hypopnea index; TST90, percentage of total sleep time with oxygen saturation <90%; ODI 3, oxygen desaturation index 3%; SaO_2, mean oxygen saturation; BMI, body mass index; SEIFA IRSD, Socio-Economic Indexes for Areas Index of Relative Socio-Economic Disadvantage; *SD*, standard deviation; IQR, interquartile range.

BMI: body mass index categorised according to international criteria (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 [obese]).

Cardiovascular disease: self-reported, doctor-diagnosed, myocardial infarction, angina, transient ischemic attack, or stroke.

Diabetes mellitus: self-reported, doctor-diagnosed, FPG ≥7.0 mmol/L [126 mg/dL], HbA1C ≥6.5%, or self-reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).

Insomnia: at least one of two PSQI dimensions (difficulty initiating or maintaining sleep) and significant daytime fatigue defined as an SF-36 Vitality Scale score one *SD* below the mean.

Hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use.

Psychotropic medication use: self-reported use of one or more of opiates, antipsychotics, antiepileptics, antidepressants, or benzodiazepines.

Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

Legend: p-values representing significant between-group differences boldfaced.

3.4.2 Complete sample associations between OSA and sleep macroarchitecture parameters and cognitive function outcomes

Complete sample univariable associations between OSA and sleep macroarchitecture parameters and cognitive function outcomes are reported in Table 3.4. In univariable analyses, greater TST was associated with better TMT-A performance, and higher mean SaO_2 was associated with better TMT-A and TMT-B performance. Moreover, higher AHI and TST90 were associated with worse TMT-A performance, and higher TST90 was associated with worse TMT-B performance. Higher AHI was also associated with slower inspection times. In adjusted analyses, OSA parameters were not associated with cognitive function outcomes. The lack of adjusted associations was also observed after utilising the purposeful covariate selection procedure to adjust for education, financial stress, and hypertension (Supplementary Table 3.1).

Table 3.4 Complete sample covariate unadjusted and adjusted linear and binary logistic regression estimated associations between OSA and sleep macroarchitecture parameters and cognitive function outcomes

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Inspection time						
AHI (/h)	1.14 (0.17, 2.12)	**0.022**	0.60 (-0.30, 1.49)	0.19	0.45 (-0.49, 1.39)	0.35
TST90 (%)	0.56 (-0.77, 1.88)	0.41	-0.46 (-1.68, 0.76)	0.46	-0.52 (-1.80, 0.76)	0.20
ODI 3 (%)	0.12 (-0.04, 0.27)	0.15	0.07 (-0.07, 0.22)	0.31	0.05 (-0.11, 0.20)	0.57
O_2 nadir (%)	-0.18 (-1.35, 0.97)	0.75	0.25 (-0.80, 1.30)	0.65	0.44 (-0.64, 1.53)	0.42
SaO_2 (%)	-4.95 (-13.5, 3.54)	0.25	4.07 (-3.83, 12.0)	0.31	5.62 (-3.37, 14.6)	0.22
TST (h)	2.04 (-13.2, 17.3)	0.79	11.0 (-2.84, 24.8)	0.12	7.36 (-7.00, 21.7)	0.31
N1 (%)	-0.81 (-3.03, 1.41)	0.47	-0.62 (-2.62, 1.39)	0.55	-1.04 (-3.11, 1.03)	0.32
N2 (%)	0.34 (-1.23, 1.91)	0.67	-0.02 (-1.44, 1.40)	0.98	-0.07 (-1.51, 1.37)	0.92
N3 (%)	0.05 (-1.64, 1.74)	0.95	-0.03 (-1.56, 1.50)	0.97	0.08 (-1.46, 1.62)	0.92
REM (%)	0.06 (-2.60, 2.72)	0.96	1.03 (-1.38, 3.44)	0.40	1.46 (-0.98, 3.91)	0.24
TMT-A						
AHI (/h)	1.03 (0.04, 2.01)	**0.041**	0.42 (-0.46, 1.30)	0.35	0.50 (-0.41, 1.41)	0.28
TST90 (%)	1.80 (0.48, 3.12)	**0.008**	0.71 (-0.49, 1.90)	0.25	0.59 (-0.64, 1.83)	0.35
ODI 3 (%)	0.04 (-0.12, 0.20)	0.63	-0.008 (-0.15, 0.13)	0.91	0.009 (-0.14, 0.16)	0.91
O_2 nadir (%)	-0.30 (-1.48, 0.87)	0.61	0.18 (-0.86, 1.21)	0.74	0.10 (-0.95, 1.15)	0.85
SaO_2 (%)	-13.2 (-21.7, -4.64)	**0.030**	-3.44 (-11.2, 4.36)	0.39	-2.11 (-10.8, 6.62)	0.64
TST (h)	-19.4 (-34.7, -4.04)	**0.013**	-9.58 (-23.2, 4.09)	0.17	-7.35 (-21.2, 6.53)	0.30
N1 (%)	1.24 (-1.00, 3.49)	0.28	1.47 (-0.50, 3.45)	0.14	1.40 (-0.60, 3.39)	0.17
N2 (%)	0.50 (-1.09, 2.09)	0.54	0.09 (-1.32, 1.49)	0.90	0.15 (-1.24, 1.54)	0.83
N3 (%)	-0.91 (-2.62, 0.80)	0.30	-0.98 (-2.49, 0.52)	0.20	-0.99 (-2.47, 0.50)	0.19
REM (%)	-0.97 (-3.67, 1.72)	0.48	0.06 (-2.32, 2.45)	0.96	0.10 (-2.27, 2.47)	0.93
TMT-B						
AHI (h)	0.88 (-0.15, 1.91)	0.094	0.22 (-0.70, 1.13)	0.64	0.38 (-0.56, 1.32)	0.43
TST90 (%)	2.00 (0.62, 3.38)	**0.005**	0.82 (-0.42, 2.06)	0.20	1.10 (-0.17, 2.38)	0.090
ODI 3 (%)	0.08 (-0.08, 0.25)	0.33	0.03 (-0.11, 0.18)	0.66	0.08 (-0.07, 0.23)	0.31
O_2 nadir (%)	-0.52 (-1.47, 0.71)	0.41	-0.003 (-1.08, 1.08)	0.99	-0.12 (-1.21, 0.97)	0.83
SaO_2 (%)	-10.30 (-19.2, -1.36)	**0.024**	-0.11 (-8.21, 7.98)	0.98	-3.19 (-12.3, 5.88)	0.49
TST (h)	-4.69 (-20.8, 11.4)	0.57	6.45 (-7.79, 20.7)	0.37	9.38 (-5.02, 23.8)	0.20
N1 (%)	-0.14 (-2.49, 2.22)	0.91	-0.04 (-2.10, 2.03)	0.97	-0.17 (-2.25, 1.91)	0.88
N2 (%)	0.30 (-1.36, 1.96)	0.72	-0.09 (-1.54, 1.37)	0.91	-0.26 (-1.70, 1.18)	0.73
N3 (%)	0.14 (-1.65, 1.93)	0.88	0.07 (-1.50, 1.64)	0.93	0.24 (-1.31, 1.78)	0.76
REM (%)	-1.06 (-3.95, 1.82)	0.47	0.13 (-2.41, 2.66)	0.92	0.40 (-2.12, 2.92)	0.76
FOME						
AHI (/h)	-0.14 (-0.55, 0.26)	0.49	0.12 (-0.26, 0.51)	0.54	-0.03 (-0.43, 0.38)	0.90
TST90 (%)	0.01 (-0.36, 0.38)	0.97	0.29 (-0.06, 0.63)	0.11	0.17 (-0.20, 0.53)	0.36
ODI (%)	-0.05 (-0.28, 0.18)	0.67	0.03 (-0.18, 0.25)	0.76	0.04 (-0.31, 0.38)	0.83
O_2 nadir (%)	-0.002 (-0.02, 0.01)	0.75	-0.006 (-0.02, 0.006)	0.30	-0.003 (-0.02, 0.01)	0.66
SaO_2 (%)	0.009 (-0.09, 0.10)	0.86	-0.08 (-0.17, 0.008)	0.074	-0.06 (-0.16, 0.04)	0.25
TST (h)	0.08 (-0.09, 0.25)	0.33	0.001 (-0.16, 0.16)	0.99	-0.02 (-0.18, 0.15)	0.85
N1 (%)	-0.001 (-0.03, 0.03)	0.99	-0.002 (-0.03, 0.02)	0.87	0.001 (-0.02, 0.03)	0.92
N2 (%)	-0.02 (-0.03, 0.002)	0.073	-0.01 (-0.03, 0.004)	0.13	-0.01 (-0.03, 0.002)	0.085
N3 (%)	0.01 (-0.006, 0.03)	0.19	0.01 (-0.004, 0.03)	0.14	0.01 (-0.005, 0.03)	0.15
REM (%)	0.01 (-0.02, 0.04)	0.35	0.01 (-0.02, 0.03)	0.71	0.007 (-0.02, 0.04)	0.60
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
MMSE						
AHI (/h)	0.76 (0.39, 1.47)	0.41	0.60 (0.30, 1.19)	0.14	0.52 (0.25, 1.09)	0.084
TST90 (%)	1.34 (0.75, 2.41)	0.32	1.16 (0.64, 2.12)	0.63	1.20 (0.63, 2.31)	0.58
ODI (%)	0.86 (0.60, 1.24)	0.43	0.81 (0.56, 1.17)	0.26	0.70 (0.38, 1.29)	0.25
O_2 nadir (%)	1.003 (0.98, 1.03)	0.79	1.01 (0.98, 1.03)	0.61	1.01 (0.98, 1.03)	0.61
SaO_2 (%)	0.42 (0.23, 0.87)	0.34	0.63 (0.41, 1.03)	0.48	0.69 (0.34, 1.14)	0.61
TST (h)	1.03 (0.78, 1.35)	0.85	1.10 (0.82, 1.45)	0.51	1.14 (0.83, 1.56)	0.41
N1 (%)	0.99 (0.95, 1.03)	0.48	0.99 (0.95, 1.03)	0.50	0.98 (0.94, 1.02)	0.28
N2 (%)	0.99 (0.97, 1.02)	0.64	0.99 (0.96, 1.02)	0.53	0.99 (0.96, 1.02)	0.36
N3 (%)	1.01 (0.98, 1.04)	0.46	1.01 (0.98, 1.04)	0.48	1.02 (0.99, 1.05)	0.32
REM (%)	1.01 (0.97, 1.06)	0.62	1.02 (0.97, 1.07)	0.42	1.03 (0.98, 1.09)	0.20

Abbreviations: TMT-A, trail-making test A; TMT-B, trail-making test B; FOME, Fuld object memory evaluation; MMSE, mini-mental state examination; AHI, apnea-hypopnea index; TST90, percentage total sleep time with oxygen saturation <90%; ODI 3, oxygen desaturation index 3%; O_2 nadir, oxygen saturation nadir; SaO_2, mean oxygen saturation; TST, total sleep time; N1, stage 1 sleep; N2, stage 2 sleep; N3, stage 3 sleep; REM, rapid eye movement sleep; CI, confidence interval; OR, odds ratio.
Estimates (inspection time, TMT-A, TMT-B, and FOME): Unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates (MMSE): Odds ratios (95% CI) from univariable and multivariable binary logistic regression models are reported. MMSE dichotomised cognitive impairment ≤27/30.
Adjusted Model 1: adjusted for age.
Adjusted Model 2: adjusted for age, financial stress, highest educational attainment, socio-economic disadvantage, marital status, alcohol risk, physical activity, BMI, smoking status, CVD, diabetes mellitus, insomnia, hypertension, and psychotropic medication use.
Legend: p-values representing significant associations boldfaced.
Notes: Multicollinearity tests displayed acceptable variance inflation factor for all covariates; AHI was scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

3.4.3 Age-stratified associations between OSA and sleep macroarchitecture parameters and cognitive function outcomes

Age-stratified univariable and adjusted associations between OSA and sleep macroarchitecture parameters and TMT-A performance are presented in Table 3.5. In univariable analyses in men ≥65 years, higher AHI was associated with worse TMT-A performance. In men ≥65 years, an increase of 1 percentage point (3.62 minutes) of N1 sleep was associated with an average increase of 4.7 seconds on the TMT-A test, whereas an increase of 1 percentage point (3.62 minutes) of N3 sleep was associated with an average decrease of 3.4 seconds on the TMT-A test. In adjusted analyses, associations between a higher percentage of N1 sleep and worse TMT-A performance and a higher percentage of N3 sleep and better TMT-A performance in men ≥65 years persisted, while the association with AHI did not persist. As reported in Supplementary Tables 3.1 and 3.2, there were no age-stratified univariable or adjusted associations between OSA and sleep macroarchitecture parameters and other cognitive function outcomes.

Table 3.5 Age-stratified covariate unadjusted and adjusted linear regression estimated associations between OSA and sleep macroarchitecture parameters and TMT-A performance

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
			Age-stratified sample (<65 years)			
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
TMT-A						
AHI (/h)	0.29 (-0.76, 1.34)	0.59	0.02 (-0.99, 1.04)	0.96	0.17 (-0.94, 1.27)	0.76
TST90 (%)	1.42 (-0.48, 3.32)	0.14	0.73 (-1.14, 2.60)	0.44	0.44 (-1.56, 2.43)	0.67
ODI 3 (%)	-0.02 (-0.18, 0.14)	0.78	-0.05 (-0.21, 0.11)	0.53	-0.04 (-0.21, 0.14)	0.68
O_2 nadir (%)	-0.70 (-2.02, 0.63)	0.30	-0.31 (-1.60, 0.98)	0.64	-0.29 (-1.63, 1.04)	0.67
SaO_2 (%)	-7.95 (-17.7, 1.76)	0.11	-2.34 (-12.1, 7.43)	0.64	-0.58 (-11.8, 10.7)	0.92
TST (h)	-9.99 (-26.0, 6.04)	0.22	-7.19 (-22.8, 8.37)	0.36	-5.28 (-21.5, 11.1)	0.53
N1 (%)	0.37 (-2.06, 2.80)	0.76	0.41 (-1.94, 2.76)	0.73	-0.05 (-2.50, 2.41)	0.97
N2 (%)	-0.81 (-2.56, 0.95)	0.37	-0.85 (-2.55, 0.84)	0.32	-0.65 (-2.40, 1.11)	0.47
N3 (%)	0.28 (-1.57, 2.14)	0.77	0.18 (-1.61, 1.98)	0.84	0.33 (-1.51, 2.17)	0.73
REM (%)	0.97 (-1.93, 3.86)	0.51	1.29 (-1.51, 4.09)	0.37	1.00 (-1.89, 3.90)	0.50
			Age-stratified sample (≥65 years)			
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
TMT-A						
AHI (/h)	1.79 (0.02, 3.58)	**0.048**	1.37 (-0.35, 3.09)	0.12	1.24 (-0.51, 2.99)	0.16
TST90 (%)	0.83 (-0.88, 2.54)	0.34	0.73 (-0.90, 2.36)	0.38	0.64 (-1.08, 2.37)	0.46
ODI 3 (%)	0.21 (-0.12, 0.55)	0.21	0.14 (-0.18, 0.47)	0.38	0.13 (-0.20, 0.46)	0.44
O_2 nadir (%)	0.94 (-0.93, 2.81)	0.32	0.68 (-1.11, 2.47)	0.45	0.84 (-1.01, 2.69)	0.37
SaO_2 (%)	-7.07 (-21.1, 6.96)	0.32	-6.29 (-19.6, 7.05)	0.35	-2.14 (-16.9, 12.6)	0.77
TST (h)	-25.9 (-55.1, 3.26)	0.081	-19.8 (-47.9, 8.26)	0.17	-17.0 (-46.2, 12.2)	0.25
N1 (%)	4.74 (0.93, 8.56)	**0.015**	4.00 (0.33, 7.66)	**0.033**	5.29 (1.63, 8.95)	**0.005**
N2 (%)	1.48 (-1.15, 4.11)	0.27	1.67 (-0.83, 4.17)	0.19	0.70 (-1.85, 3.25)	0.59
N3 (%)	-3.53 (-6.40, -0.66)	**0.016**	-3.33 (-6.06, -0.59)	**0.017**	-3.39 (-6.07, -0.72)	**0.013**
REM (%)	-2.56 (-7.27, 2.15)	0.28	-2.53 (-7.01, 1.95)	0.26	-0.57 (-5.22, 4.07)	0.81

Abbreviations: TMT-A, trail-making test A; AHI, apnea-hypopnea index; TST90, percentage total sleep time with oxygen saturation <90%; ODI 3, oxygen desaturation index 3%; O_2 nadir, oxygen saturation nadir; SaO_2, mean oxygen saturation; TST, total sleep time; N1, stage 1 sleep; N2, stage 2 sleep; N3, stage 3 sleep; REM, rapid eye movement sleep; CI, confidence interval; OR, odds ratio.
Estimates: Unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Adjusted Model 1: adjusted for age.
Adjusted Model 2: adjusted for age, financial stress, highest educational attainment, socio-economic disadvantage, marital status, alcohol risk, physical activity, BMI, smoking status, CVD, diabetes mellitus, insomnia, hypertension, and psychotropic medication use.
Legend: p-values representing significant associations boldfaced.
Notes: Multicollinearity tests displayed acceptable variance inflation factor for all covariates; AHI was scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

3.4.4 Effect moderator analysis

Hypertension significantly modified the univariable association between higher AHI and worse TMT-A performance (*B*=1.95, 95% CI [0.31, 3.60], p=0.020) and slower inspection times (*B*=2.45, 95% CI [0.83, 4.06], p=0.003). However, hypertension did not modify the association between AHI and cognitive function outcomes in age and fully adjusted models. Furthermore, there were no significant interactions of sleep macroarchitecture parameters with BMI and physical activity for any cognitive function outcomes in univariable or adjusted analyses.

3.5 Discussion

This community-based cohort study is the first to investigate independent cross-sectional associations between OSA and sleep macroarchitecture parameters and cognitive function outcomes among a sample of unselected community-dwelling middle-aged and older men. The primary complete sample analyses identified no significant independent cross-sectional associations between OSA and sleep macroarchitecture parameters and visual processing speed, executive function, memory performance, or broader cognitive status assessed by the MMSE. Although the main findings are broadly in disagreement with the majority of existing cohort literature, the secondary age-stratified analyses suggest that independent associations between sleep macroarchitecture and attention and processing speed are specific to men ≥65 years, partly supporting previous studies.

Previous clinical and select community cohort studies reported significant independent associations between OSA parameters and/or disrupted sleep macroarchitecture and cognitive dysfunction (18, 19, 21-23, 326). However, compared to the FAMAS cohort, previous studies have different sample characteristics. Previous studies recruited older (≥65 years) participants who may have had greater cognitive decline associated with poor sleep quality (19, 21, 23), middle-aged participants at high risk of having OSA based on the Berlin questionnaire (22), or participants diagnosed with OSA in sleep clinics (18), all potentially introducing selection bias. The present study attempted to address the contribution of referral bias within clinical studies and investigated the impact of OSA

and disrupted sleep macroarchitecture on cognitive function in older versus younger men.

The main finding of no independent cross-sectional associations between OSA parameters and cognitive function is in line with the SYNAPSE Study, which reported an absence of consistent independent associations between AHI and ODI 3% and cognitive function in healthy older men and women (23). The SYNAPSE Study, however, did not investigate independent associations between sleep macroarchitecture and cognitive function. There are also key differences between the SYNAPSE and FAMAS cohorts, making it difficult to compare findings. FAMAS comprised exclusively men aged (mean ± *SD*) 60 ± 10.6 years, while the SYNAPSE Study included almost 60% older women with a tighter age range (68 ± 1.8 years). The absence of independent associations between OSA parameters and cognitive function in the SYNAPSE Study despite a significantly older community sample may reflect shorter exposure to OSA, which in women increases in prevalence and severity post-menopause (327).

Partly consistent with the MrOS and HypnoLaus studies (20, 21), the present study showed that greater N1 sleep was independently associated with worse visual attention and processing speed in older men. Although the association between greater N1 sleep and worse cognitive function in the MrOS study was with TMT-B, a more complex component than the TMT-A that also assesses set-shifting ability (19), the findings broadly indicate that a higher percentage of light sleep in older men is associated worse visual attention. The HypnoLaus Study found, in univariable analyses, that greater N1 sleep, as well as less N3 and REM sleep, was associated with worse cognitive function, but in adjusted analyses, only the AHI and ODI remained statistically significant (21). These findings are difficult to compare given that the HypnoLaus Study associations were with a Clinical Dementia Rating Scale derived from a multi-test cognitive battery, while the association in the present study was with a single simple TMT-A test. Although the APPLES recruited a younger (average age 50.7 years) and more symptomatic (average ESS 10.15) clinical sample compared with the FAMAS cohort (average ESS 6.3), Quan et al. (18) also reported an independent association between greater N1 sleep and worse performance on the Pathfinder Number Test (computer analogue of the TMT-A). The

consistent independent associations observed across multiple clinical and select community cohorts and the FAMAS cohort suggest that lighter sleep contributes to impaired attention and processing speed, particularly in older adults.

Previous literature has reported that ageing is associated with increased light (N1 and N2) sleep and decreased REM and deep (N3) sleep (5-7, 328). The effect of ageing on sleep macroarchitecture has been found to be stronger in men than in women. In several studies investigating age-related changes in objective sleep patterns, older men were found to have decreased TST and percentage of REM and N3 sleep compared to age-matched women (329-331). Although the present study did not collect data on women, it reports significantly less TST in the older compared to the younger subgroup of men. Further community-based cohort studies are needed to investigate differences in sleep macroarchitecture between older men and women and whether gender differences in sleep macroarchitecture are independently associated with cognitive function.

Possible mechanisms driving the independent association between greater N1 sleep and worse visual attention and processing speed in the older subgroup of men include neurobiological changes reported to occur with ageing. The frontal cortex is the primary brain region studied in older adults in relation to visual attention and processing speed. One study examined age-related structural changes in the frontal cortex and the association with visual attention and processing speed in 42 healthy adults aged 19 to 79 years (332). A frontal pattern of gray and white matter variation was identified in older adults only and related to a decline in visual attention and processing speed. Loss of myelination within the frontal cortex associated with ageing has also been linked to worse visual attention and processing speed (333).

Another important factor to consider is genetics. The Wisconsin Sleep Cohort Study showed that in non-apolipoprotein-ε4 (APOE-ε4) allele carriers, higher NREM sleep AHI was associated with impaired psychomotor speed (326). This finding suggests that sleep state-specific (REM and NREM) OSA may be differentially associated with impaired psychomotor speed in middle-aged to older adults and is likely to be modified by APOE polymorphisms. Genetic data was unavailable in the FAMAS cohort but should be considered in future studies.

New respiratory event-related parameters may have greater utility over the AHI in predicting the risk of adverse health outcomes. For example, hypoxic burden and shorter respiratory event duration have been shown to be independently associated with CVD and all-cause mortality, respectively (334). Hypoxic burden encapsulates frequency, duration, and depth of respiratory events and can be used to quantify total ventilatory deficit (335). Therefore, hypoxic burden and shorter respiratory event duration may provide better insight into the association between OSA-related hypoxemia and cognitive function and should be explored in future studies.

The key strengths of the present study are 1) the relatively large unselected non-clinical community-based sample representative of an adult male population aged ≥40 years with objectively measured OSA and sleep macroarchitecture parameters; 2) assessment of cognitive function by multiple validated and widely utilised tests with well-established parameters, performance, and normative data (68, 306, 312); and 3) the extensive survey and biomedical data (304) allowing for control of numerous potentially important confounders. The main limitation is a cross-sectional association design from which causality is unable to be concluded. Another limitation is analysis reliant on PSG performed an average of 26 months after cognitive testing. Given that cognitive function has been shown to decline with age, this time lag may underestimate associations between OSA and cognitive function. Lastly, this sleep sub-study was performed as part of a specific men's health study, the MAILES Study, and thus, the results may not be generalisable to women.

In conclusion, the primary complete sample analysis identified no significant independent cross-sectional associations between OSA and sleep macroarchitecture parameters and visual processing speed, executive function, memory performance, or broader cognitive status assessed by the MMSE in unselected community-dwelling middle-aged and older men. However, the secondary age-stratified analysis identified that greater N1 sleep was independently associated with impaired visual attention and processing speed in older (≥65 years) men, while greater N3 sleep was protective. This novel finding suggests that the independent cross-sectional association between disrupted sleep macroarchitecture and impaired visual attention and processing speed is specific to older community-dwelling men. Longitudinal community-based cohort studies, ideally conducted in

large samples of unselected community-dwelling men and women, are needed to determine if parameters indicative of greater OSA disease severity and disrupted sleep macroarchitecture independently predict prospective cognitive dysfunction and decline.

3.6 Supplementary Tables

Supplementary Table 3.1 Covariate unadjusted and adjusted linear and binary logistic regression estimated associations between OSA and sleep macroarchitecture parameters and inspection time, TMT-B, FOME, and MMSE performance in the complete study sample (purposeful covariate selection).

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Inspection time						
AHI (/h)	1.14 (0.17, 2.12)	**0.022**	0.60 (-0.30, 1.49)	0.19	0.13 (-0.09, 0.35)	0.24
TST90 (%)	0.56 (-0.77, 1.88)	0.41	-0.46 (-1.68, 0.76)	0.46	-0.18 (-0.48, 0.11)	0.72
ODI 3 (%)	0.12 (-0.04, 0.27)	0.15	0.07 (-0.07, 0.22)	0.31	0.05 (-0.06, 0.16)	0.43
O_2 nadir (%)	-0.18 (-1.35, 0.97)	0.75	0.25 (-0.80, 1.30)	0.65	0.36 (-0.69, 1.43)	0.50
SaO_2 (%)	-4.95 (-13.5, 3.54)	0.25	4.07 (-3.83, 12.0)	0.31	4.36 (-3.57, 12.3)	0.28
TST (h)	2.04 (-13.2, 17.3)	0.79	11.0 (-2.84, 24.8)	0.12	8.73 (-5.19, 22.7)	0.22
N1 (%)	-0.81 (-3.03, 1.41)	0.47	-0.62 (-2.62, 1.39)	0.55	-1.18 (-3.21, 0.86)	0.26
N2 (%)	0.34 (-1.23, 1.91)	0.67	-0.02 (-1.44, 1.40)	0.98	-0.04 (-1.46, 1.38)	0.96
N3 (%)	0.05 (-1.64, 1.74)	0.95	-0.03 (-1.56, 1.50)	0.97	0.11 (-1.42, 1.64)	0.89
REM (%)	0.06 (-2.60, 2.72)	0.96	1.03 (-1.38, 3.44)	0.40	1.58 (-0.90, 4.06)	0.21
TMT-A						
AHI (/h)	1.03 (0.04, 2.01)	**0.041**	0.42 (-0.46, 1.30)	0.35	0.48 (-0.41, 1.37)	0.29
TST90 (%)	1.80 (0.48, 3.12)	**0.008**	0.71 (-0.49, 1.90)	0.25	0.67 (-0.52, 1.87)	0.21
ODI 3 (%)	0.04 (-0.12, 0.20)	0.63	-0.008 (-0.15, 0.13)	0.91	0.003 (-0.14, 0.15)	0.97
O_2 nadir (%)	-0.30 (-1.48, 0.87)	0.61	0.18 (-0.86, 1.21)	0.74	0.17 (-0.88, 1.21)	0.75
SaO_2 (%)	-13.2 (-21.7, -4.64)	**0.030**	-3.44 (-11.2, 4.36)	0.39	-3.61 (-11.4, 4.19)	0.36
TST (h)	-19.4 (-34.7, -4.04)	**0.013**	-9.58 (-23.2, 4.09)	0.17	-10.6 (-24.3, 3.10)	0.13
N1 (%)	1.24 (-1.00, 3.49)	0.28	1.47 (-0.50, 3.45)	0.14	1.52 (-0.48, 3.52)	0.14
N2 (%)	0.50 (-1.09, 2.09)	0.54	0.09 (-1.32, 1.49)	0.90	-0.03 (-1.42, 1.37)	0.97
N3 (%)	-0.91 (-2.62, 0.80)	0.30	-0.98 (-2.49, 0.52)	0.20	-0.91 (-2.42, 0.59)	0.23
REM (%)	-0.97 (-3.67, 1.72)	0.48	0.06 (-2.32, 2.45)	0.96	0.21 (-2.23, 2.66)	0.86
TMT-B						
AHI (h)	0.88 (-0.15, 1.91)	0.094	0.22 (-0.70, 1.13)	0.64	0.22 (-0.70, 1.14)	0.63
TST90 (%)	2.00 (0.62, 3.38)	**0.005**	0.82 (-0.42, 2.06)	0.20	0.74 (-0.49, 1.97)	0.24
ODI 3 (%)	0.08 (-0.08, 0.25)	0.33	0.03 (-0.11, 0.18)	0.66	0.04 (-0.11, 0.18)	0.63
O_2 nadir (%)	-0.52 (-1.47, 0.71)	0.41	-0.003 (-1.08, 1.08)	0.99	0.06 (-1.02, 1.14)	0.92
SaO_2 (%)	-10.30 (-19.2, -1.36)	**0.024**	-0.11 (-8.21, 7.98)	0.98	-0.41 (-8.50, 7.68)	0.92
TST (h)	-4.69 (-20.8, 11.4)	0.57	6.45 (-7.79, 20.7)	0.37	5.89 (-8.32, 20.1)	0.42
N1 (%)	-0.14 (-2.49, 2.22)	0.91	-0.04 (-2.10, 2.03)	0.97	-0.47 (-2.54, 1.61)	0.66
N2 (%)	0.30 (-1.36, 1.96)	0.72	-0.09 (-1.54, 1.37)	0.91	-0.16 (-1.60, 1.29)	0.83
N3 (%)	0.14 (-1.65, 1.93)	0.88	0.07 (-1.50, 1.64)	0.93	0.28 (-1.28, 1.84)	0.73
REM (%)	-1.06 (-3.95, 1.82)	0.47	0.13 (-2.41, 2.66)	0.92	0.44 (-2.10, 2.97)	0.73
FOME						
AHI (/h)	-0.14 (-0.55, 0.26)	0.49	0.12 (-0.26, 0.51)	0.54	0.07 (-0.32, 0.46)	0.73
TST90 (%)	0.01 (-0.36, 0.38)	0.97	0.29 (-0.06, 0.63)	0.11	0.29 (-0.06, 0.63)	0.11
ODI 3 (%)	-0.05 (-0.28, 0.18)	0.67	0.03 (-0.18, 0.25)	0.76	0.001 (-0.001, 0.003)	0.20
O_2 nadir (%)	-0.002 (-0.02, 0.01)	0.75	-0.006 (-0.02, 0.006)	0.30	-0.005 (-0.02, 0.007)	0.38
SaO_2 (%)	0.009 (-0.09, 0.10)	0.86	-0.08 (-0.17, 0.008)	0.074	-0.07 (-0.16, 0.02)	0.14
TST (h)	0.08 (-0.09, 0.25)	0.33	0.001 (-0.16, 0.16)	0.99	0.009 (-0.15, 0.17)	0.92
N1 (%)	-0.001 (-0.03, 0.03)	0.99	-0.002 (-0.03, 0.02)	0.87	-0.0003 (-0.02, 0.02)	0.98
N2 (%)	-0.02 (-0.03, 0.002)	0.073	-0.01 (-0.03, 0.004)	0.13	-0.01 (-0.03, 0.002)	0.093
N3 (%)	0.01 (-0.006, 0.03)	0.19	0.01 (-0.004, 0.03)	0.14	0.01 (-0.007, 0.03)	0.22
REM (%)	0.01 (-0.02, 0.04)	0.35	0.01 (-0.02, 0.03)	0.71	0.01 (-0.01, 0.04)	0.32
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
MMSE						
AHI (/h)	0.76 (0.39, 1.47)	0.41	0.60 (0.30, 1.19)	0.14	0.53 (0.26, 1.08)	0.080
TST90 (%)	1.34 (0.75, 2.41)	0.32	1.16 (0.64, 2.12)	0.63	1.07 (0.58, 1.98)	0.82
ODI 3 (%)	0.86 (0.60, 1.24)	0.43	0.81 (0.56, 1.17)	0.26	0.75 (0.51, 1.09)	0.13
O_2 nadir (%)	1.003 (0.98, 1.03)	0.79	1.01 (0.98, 1.03)	0.61	1.00 (0.99, 1.03)	0.49
SaO_2 (%)	0.42 (0.23, 0.87)	0.34	0.63 (0.41, 1.03)	0.48	0.99 (0.84, 1.16)	0.86

TST (h)	1.03 (0.78, 1.35)	0.85	1.10 (0.82, 1.45)	0.51	1.10 (0.82, 1.47)	0.54
N1 (%)	0.99 (0.95, 1.03)	0.48	0.99 (0.95, 1.03)	0.50	0.98 (0.94, 1.03)	0.36
N2 (%)	0.99 (0.97, 1.02)	0.64	0.99 (0.96, 1.02)	0.53	0.99 (0.96, 1.01)	0.46
N3 (%)	1.01 (0.98, 1.04)	0.46	1.01 (0.98, 1.04)	0.48	1.01 (0.98, 1.05)	0.37
REM (%)	1.01 (0.97, 1.06)	0.62	1.02 (0.97, 1.07)	0.42	1.03 (0.98, 1.08)	0.33

Abbreviations: TMT-A, trail-making test A; TMT-B, trail-making test B; FOME, Fuld object memory evaluation; MMSE, mini-mental state examination; AHI, apnea-hypopnea index; TST90, percentage total sleep time with oxygen saturation <90%; ODI 3, oxygen desaturation index 3%; O_2 nadir, oxygen saturation nadir; SaO_2, mean oxygen saturation; TST, total sleep time; N1, stage 1 sleep; N2, stage 2 sleep; N3, stage 3 sleep; REM, rapid eye movement sleep; CI, confidence interval; OR, odds ratio.
Estimates (inspection time, TMT-A, TMT-B, and FOME): Unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates (MMSE): Odds ratios (95% CI) from univariable and multivariable binary logistic regression models are reported. MMSE dichotomised cognitive impairment ≤27/30.
Adjusted Model 1: adjusted for age.
Adjusted Model 2: adjusted for age, financial stress, highest educational attainment, and hypertension.
Legend: p-values representing significant associations boldfaced.
Notes: Multicollinearity tests displayed acceptable variance inflation factor for all covariates; AHI was scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

Supplementary Table 3.2 Covariate unadjusted and adjusted linear and binary logistic regression estimated associations between OSA and sleep macroarchitecture parameters and inspection time, TMT-B, FOME, and MMSE performance in men <65 years

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Inspection time						
AHI (/h)	0.78 (-0.13, 1.69)	0.094	0.62 (-0.29, 1.53)	0.18	0.47 (-0.50, 1.44)	0.34
TST90 (%)	0.37 (-1.30, 2.05)	0.66	-0.07 (-1.74, 1.61)	0.94	-0.18 (-1.93, 1.57)	0.84
ODI 3 (%)	0.10 (-0.04, 0.24)	0.17	0.08 (-0.06, 0.22)	0.25	0.06 (-0.09, 0.21)	0.46
O_2 nadir (%)	-0.39 (-1.55, 0.77)	0.50	-0.14 (-1.30, 1.01)	0.80	-0.02 (-1.20, 1.16)	0.97
SaO_2 (%)	-1.96 (-10.5, 6.61)	0.65	1.70 (-7.04, 10.4)	0.70	1.20 (-8.71, 11.1)	0.81
TST (h)	8.12 (-5.96, 22.2)	0.26	9.89 (-3.99, 23.8)	0.16	7.08 (-7.28, 21.4)	0.33
N1 (%)	-0.33 (-2.46, 1.81)	0.76	-0.62 (-2.77, 1.54)	0.57	-0.90 (-3.05, 1.26)	0.41
N2 (%)	-0.67 (-2.21, 0.88)	0.40	-0.62 (-2.15, 0.90)	0.42	-0.92 (-2.46, 0.62)	0.24
N3 (%)	0.03 (-1.59, 1.66)	0.97	-0.04 (-1.64, 1.56)	0.96	0.44 (-1.17, 2.05)	0.59
REM (%)	2.18 (-0.34, 4.71)	0.090	2.40 (-0.09, 4.89)	0.085	2.64 (0.12, 5.16)	0.11
TMT-B						
AHI (/h)	0.64 (-0.42, 1.70)	0.24	0.32 (-0.69, 1.32)	0.53	0.72 (-0.37, 1.81)	0.19
TST90 (%)	1.78 (-0.14, 3.70)	0.069	0.88 (-0.96, 2.72)	0.35	1.23 (-0.72, 3.18)	0.22
ODI 3 (%)	0.07 (-0.09, 0.23)	0.40	0.04 (-0.12, 0.19)	0.64	0.11 (-0.06, 0.28)	0.21
O_2 nadir (%)	-0.24 (-1.59, 1.10)	0.72	0.25 (-1.02, 1.53)	0.70	0.25 (-1.07, 1.57)	0.71
SaO_2 (%)	-7.19 (-17.0, 2.64)	0.15	0.40 (-9.21, 10.0)	0.93	-3.47 (-14.6, 7.60)	0.54
TST (h)	1.29 (-15.0, 17.5)	0.88	5.22 (-10.1, 20.6)	0.50	5.58 (-10.5, 21.6)	0.49
N1 (%)	0.85 (-1.61, 3.31)	0.50	0.85 (-1.47, 3.17)	0.47	0.37 (-2.05, 2.79)	0.76
N2 (%)	-0.94 (-2.71, 0.84)	0.30	-1.01 (-2.68, 0.66)	0.23	-0.61 (-2.33, 1.11)	0.49
N3 (%)	0.55 (-1.33, 2.43)	0.57	0.37 (-1.41, 2.14)	0.69	0.40 (-1.41, 2.21)	0.66
REM (%)	0.02 (-3.02, 3.06)	0.99	0.73 (-2.14, 3.60)	0.62	0.17 (-2.78, 3.12)	0.91
FOME						
AHI (/h)	0.15 (-0.32, 0.62)	0.53	0.30 (-0.17, 0.76)	0.21	0.09 (-0.41, 0.58)	0.74
TST90 (%)	0.05 (-0.39, 0.50)	0.82	0.26 (-0.19, 0.70)	0.26	0.10 (-0.38, 0.57)	0.68
ODI 3 (%)	0.32 (-0.07, 0.71)	0.10	0.42 (0.04, 0.80)	0.16	0.22 (-0.21, 0.65)	0.32
O_2 nadir (%)	-0.006 (-0.02, 0.01)	0.47	-0.01 (-0.03, 0.006)	0.22	-0.005 (-0.02, 0.01)	0.54
SaO_2 (%)	-0.08 (-0.19, 0.04)	0.20	-0.09 (-0.15, -0.03	0.14	-0.09 (-0.22, 0.05)	0.21
TST (h)	0.02 (-0.17, 0.22)	0.83	-0.006 (-0.20, 0.19)	0.95	-0.02 (-0.22, 0.18)	0.84
N1 (%)	-0.002 (-0.03, 0.03)	0.88	-0.003 (-0.03, 0.03)	0.86	-0.001 (-0.03, 0.03)	0.94
N2 (%)	-0.02 (-0.04, 0.003)	0.10	-0.02 (-0.04, 0.003)	0.10	-0.02 (-0.04, -0.001)	0.13
N3 (%)	0.02 (-0.004, 0.04)	0.10	0.02 (-0.002, 0.04)	0.078	0.02 (0.00, 0.04)	0.16
REM (%)	0.006 (-0.03, 0.04)	0.75	0.003 (-0.03, 0.04)	0.88	0.007 (-0.03, 0.04)	0.69
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
MMSE						
AHI (/h)	0.54 (0.22, 1.32)	0.18	0.46 (0.18, 1.18)	0.11	0.43 (0.16, 1.21)	0.11
TST90 (%)	1.02 (0.99, 1.06)	0.21	1.02 (0.97, 1.09)	0.37	1.04 (1.00, 1.08)	0.081
ODI 3 (%)	0.66 (0.32, 1.39)	0.28	0.60 (0.28, 1.30)	0.20	0.63 (0.27, 1.47)	0.28
O_2 nadir (%)	0.99 (0.97, 1.01)	0.39	0.99 (0.97, 1.02)	0.48	0.99 (0.97, 1.02)	0.42
SaO_2 (%)	1.05 (0.85, 1.31)	0.64	0.89 (0.71, 1.12)	0.31	0.78 (0.59, 1.03)	0.081
TST (h)	1.34 (0.92, 1.96)	0.13	1.37 (0.93, 2.02)	0.11	1.52 (0.98, 2.34)	0.078
N1 (%)	0.99 (0.93, 1.04)	0.61	0.99 (0.93, 1.04)	0.62	0.98 (0.92, 1.04)	0.53
N2 (%)	0.98 (0.95, 1.03)	0.60	0.99 (0.95, 1.03)	0.60	0.99 (0.95, 1.03)	0.56
N3 (%)	0.99 (0.95, 1.04)	0.87	0.99 (0.95, 1.04)	0.84	0.99 (0.95, 1.04)	0.80
REM (%)	1.06 (0.99, 1.13)	0.091	1.06 (0.99, 1.13)	0.085	1.07 (1.00, 1.14)	0.076

Abbreviations: TMT-B, trail-making test B; FOME, Fuld object memory evaluation; MMSE, mini-mental state examination; AHI, apnea-hypopnea index; TST90, percentage total sleep time with oxygen saturation <90%; ODI 3, oxygen desaturation index 3%; O_2 nadir, oxygen saturation nadir; SaO_2, mean oxygen saturation; TST, total sleep time; N1, stage 1 sleep; N2, stage 2 sleep; N3, stage 3 sleep; REM, rapid eye movement sleep; CI, confidence interval; OR, odds ratio.
Estimates (inspection time, TMT-B, and FOME): Unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.

Estimates (MMSE): Odds ratios (95% CI) from univariable and multivariable binary logistic regression models are reported. MMSE dichotomised cognitive impairment ≤27/30.
Adjusted Model 1: adjusted for age.
Adjusted Model 2: adjusted for age, financial stress, highest educational attainment, socio-economic disadvantage, marital status, alcohol risk, physical activity, BMI, smoking status, CVD, diabetes mellitus, insomnia, hypertension, and psychotropic medication use.
Notes: Multicollinearity tests displayed acceptable variance inflation factor for all covariates; AHI was scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

Supplementary Table 3.3 Covariate unadjusted and adjusted linear and binary logistic regression estimated associations between OSA and sleep macroarchitecture parameters and inspection time, TMT-B, FOME, and MMSE performance in men ≥65 years

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Inspection time						
AHI (/h)	1.00 (-1.12, 3.11)	0.35	0.64 (-1.46, 2.73)	0.55	0.55 (-1.62, 2.72)	0.62
TST90 (%)	-0.57 (-2.58, 1.44)	0.58	-0.65 (-2.63, 1.32)	0.51	-0.26 (-2.38, 1.87)	0.81
ODI 3 (%)	0.14 (-0.26, 0.54)	0.50	0.08 (-0.31, 0.47)	0.69	0.06 (-0.35, 0.47)	0.79
O_2 nadir (%)	0.81 (-1.39, 3.01)	0.47	0.60 (-1.56, 2.77)	0.58	0.48 (-1.83, 2.80)	0.68
SaO_2 (%)	4.45 (-12.06, 21.0)	0.59	5.09 (-11.1, 21.3)	0.53	10.8 (-7.29, 29.0)	0.24
TST (h)	7.90 (-26.7, 42.5)	0.65	13.3 (-20.8, 47.4)	0.44	9.64 (-26.4, 45.7)	0.60
N1 (%)	-0.62 (-5.20, 3.96)	0.79	-2.19 (-7.07, 2.69)	0.38	-2.11 (-6.76, 2.53)	0.37
N2 (%)	0.96 (-2.14, 4.05)	0.54	1.30 (-1.78, 4.37)	0.41	0.84 (-2.30, 3.97)	0.60
N3 (%)	-0.06 (-3.51, 3.39)	0.97	0.11 (-3.27, 3.49)	0.95	0.47 (-2.91, 3.84)	0.79
REM (%)	-2.00 (-7.54, 3.55)	0.48	-1.97 (-7.40, 3.46)	0.47	-0.93 (-6.63, 4.78)	0.75
TMT-B						
AHI (/h)	0.37 (-1.68, 2.42)	0.72	-0.09 (-2.08, 1.90)	0.93	-0.24 (-2.21, 1.73)	0.81
TST90 (%)	0.90 (-1.04, 2.84)	0.36	0.80 (-1.07, 2.67)	0.40	1.21 (-0.70, 3.13)	0.21
ODI 3 (%)	2.19 (-62.2, 66.6)	0.95	0.07 (-0.37, 0.38)	0.97	0.01 (-0.36, 0.38)	0.95
O_2 nadir (%)	-0.23 (-2.36, 1.90)	0.83	-0.50 (-2.55, 1.55)	0.63	-0.45 (-2.56, 1.65)	0.67
SaO_2 (%)	-2.05 (-18.0, 13.9)	0.80	-1.26, (-16.6, 14.1)	0.87	-3.94 (-20.5, 12.6)	0.64
TST (h)	3.30 (-30.1, 36.7)	0.85	9.90 (-22.5, 42.3)	0.55	17.7 (-14.9, 50.2)	0.29
N1 (%)	-1.25 (-5.67, 3.16)	0.58	-2.08 (-6.34, 2.18)	0.34	-0.60 (-4.83, 3.63)	0.78
N2 (%)	1.48 (-1.50, 4.46)	0.33	1.67 (-1.20, 4.53)	0.25	0.48 (-2.37, 3.32)	0.74
N3 (%)	-0.67 (-3.99, 2.66)	0.69	-0.46 (-3.66, 2.74)	0.78	-0.63 (-3.70, 2.43)	0.68
REM (%)	-1.16 (-6.52, 4.20)	0.67	-1.13 (-6.28, 4.02)	0.67	1.13 (-4.04, 6.31)	0.67
FOME						
AHI (/h)	-0.36 (-1.07, 0.34)	0.31	-0.31 (-1.01, 0.38)	0.38	-0.25 (-1.03, 0.52)	0.52
TST90 (%)	0.25 (-0.32, 0.82)	0.38	0.33 (-0.24, 0.89)	0.25	0.39 (-0.24, 1.02)	0.22
ODI 3 (%)	-0.32 (-0.90, 0.25)	0.27	-0.33 (-0.89, 0.24)	0.26	-0.36 (-0.99, 0.28)	0.27
O_2 nadir (%)	-0.002 (-0.02, 0.02)	0.80	-0.001 (-0.02, 0.02)	0.92	0.005 (-0.02, 0.03)	0.63
SaO_2 (%)	0.02 (-0.12, 0.16)	0.77	0.02 (-0.12, 0.16)	0.82	-0.002 (-0.17, 0.17	0.99
TST (h)	0.03 (-0.27, 0.33)	0.83	-0.003 (-0.30, 0.29)	0.99	-0.02 (-0.35, 0.31)	0.90
N1 (%)	-0.003 (-0.04, 0.04)	0.87	0.001 (-0.04, 0.04)	0.95	0.01 (-0.03, 0.06)	0.53
N2 (%)	-0.003 (-0.03, 0.02)	0.83	-0.004 (-0.03, 0.02)	0.77	-0.006 (-0.04, 0.02)	0.67
N3 (%)	0.001 (-0.03, 0.03)	0.94	0.001 (-0.03, 0.03)	0.99	-0.003 (-0.03, 0.03)	0.87
REM (%)	0.01 (-0.04, 0.06)	0.65	0.01 (-0.04, 0.06)	0.65	0.008 (-0.04, 0.06)	0.77
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
MMSE						
AHI (/h)	0.87 (0.30, 2.50)	0.79	0.86 (0.30, 2.46)	0.78	0.82 (0.24, 2.80)	0.75
TST90 (%)	0.97 (0.93, 1.01)	0.19	0.97 (0.93, 1.01)	0.19	0.97 (0.93, 1.02)	0.21
ODI 3 (%)	0.97 (0.42, 2.27)	0.95	0.99 (0.43, 2.32)	0.99	1.06 (0.38, 2.93)	0.91
O_2 nadir (%)	1.04 (0.98, 1.11)	0.18	1.04 (0.98, 1.11)	0.21	1.04 (0.97, 1,11)	0.28
SaO_2 (%)	1.05 (0.85, 1.31)	0.64	1.05 (0.85, 1.31)	0.65	1.06 (0.82, 1.38)	0.64
TST (h)	0.80 (0.51, 1.25)	0.32	0.81 (0.51, 1.28)	0.36	0.85 (0.51, 1.43)	0.85
N1 (%)	0.99 (0.93, 1.05)	0.74	0.99 (0.93, 1.05)	0.64	0.96 (0.90, 1.03)	0.29
N2 (%)	0.99 (0.95, 1.03)	0.64	0.99 (0.95, 1.03)	0.68	0.98 (0.94, 1.03)	0.38
N3 (%)	1.03 (0.98, 1.07)	0.23	1.03 (0.98, 1.08)	0.22	1.05 (0.99, 1.10)	0.083
REM (%)	0.97 (0.90, 1.05)	0.46	0.97 (0.90, 1.05)	0.46	0.99 (0.91, 1.09)	0.89

Abbreviations: TMT-B, trail-making test B; FOME, Fuld object memory evaluation; MMSE, mini-mental state examination; AHI, apnea-hypopnea index; TST90, percentage total sleep time with oxygen saturation <90%; ODI 3, oxygen desaturation index 3%; O_2 nadir, oxygen saturation nadir; SaO_2, mean oxygen saturation; TST, total sleep time; N1, stage 1 sleep; N2, stage 2 sleep; N3, stage 3 sleep; REM, rapid eye movement sleep; CI, confidence interval; OR, odds ratio.
Estimates (inspection time, TMT-B, and FOME): Unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.

Estimates (MMSE): Odds ratios (95% CI) from univariable and multivariable binary logistic regression models are reported. MMSE dichotomised cognitive impairment ≤27/30.
Adjusted Model 1: adjusted for age.
Adjusted Model 2: adjusted for age, financial stress, highest educational attainment, socio-economic disadvantage, marital status, alcohol risk, physical activity, BMI, smoking status, CVD, diabetes mellitus, insomnia, hypertension, and psychotropic medication use.
Notes: Multicollinearity tests displayed acceptable variance inflation factor for all covariates; AHI was scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

CHAPTER 4. LONGITUDINAL ASSOCIATIONS OF OBSTRUCTIVE SLEEP APNEA AND SLEEP MACROARCHITECTURE WITH FUTURE COGNITIVE FUNCTION IN MIDDLE-AGED AND OLDER MEN FROM A COMMUNITY-BASED COHORT STUDY

4.1 Abstract

Study objectives: Prospective studies examining associations of obstructive sleep apnea (OSA) and sleep macroarchitecture with future cognitive function remain limited to older participants, many with baseline impairment. Therefore, this study examined OSA and sleep macroarchitecture predictors of cognitive function (visual attention, processing speed, and executive function) after 8–10 years in community-dwelling middle-aged and older men.

Methods: Of 477 Florey Adelaide Male Ageing Study participants who underwent home-based polysomnography (2010–2011), 157 completed baseline and follow-up cognitive testing. Trail-making tests A (TMT-A) and B (TMT-B) were administered at the baseline (2007–2010) and follow-up (2018–2019) examinations. Linear regression analyses examined associations of OSA and sleep macroarchitecture with cognitive task performance adjusted for baseline demographic, biomedical, and behavioural factors and cognition, with sleep macroarchitecture models adjusted for the apnea-hypopnea and arousal indices.

Results: At baseline, participants were mean (*SD*) aged 58.9 (8.9) years with normal cognitive function. OSA prevalence (AHI ≥10/h) was 52.9%, with severe OSA (AHI ≥30/h) in 9.6%. Following covariate adjustment, higher N1 sleep % was associated with better TMT-A performance at follow-up (*B*= -0.04, 95% CI [-0.06, -0.01], p=0.003), whereas higher mean oxygen saturation was associated with worse TMT-A performance at follow-up (*B*=0.11, 95% CI [0.02, 0.19], p=0.012).

Conclusions: In this sample of community-dwelling middle-aged and older men, N1 sleep % and mean oxygen saturation showed independent associations with visual attention and processing speed after 8–10 years. Further longitudinal studies remain warranted to determine whether finer-grained sleep microarchitecture parameters identify individuals at risk of future cognitive dysfunction.

4.2 Introduction

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder (12, 336) characterised by repetitive pharyngeal collapse leading to intermittent nocturnal hypoxemia (oxygen desaturation) and sleep fragmentation (81, 82). Furthermore, OSA is associated with disrupted conventional sleep electroencephalography (EEG) macroarchitecture, specifically reduced rapid eye movement (REM) and non-REM stage 3 (N3) sleep and greater stage 1 (N1) sleep compared to age- and gender-matched controls (292, 337). Chapter 3 of this thesis reported an independent cross-sectional association between a higher percentage (%) of N1 sleep and worse visual attention and processing speed (trail-making test A [TMT-A] performance) among older (≥65 years) community-dwelling men (338), with no independent associations observed between OSA parameters and cognitive function outcomes. Identifying longitudinal associations between conventional OSA and sleep macroarchitecture parameters at baseline and future TMT performance (TMT-A and executive function [trail-making test B, TMT-B]) would support these routine PSG parameters as important early impairment markers. To date, the literature is confined to clinical and community-based cohort studies with several key issues including 1) recruitment of predominantly older age (≥60 years) participants or 2) participants with evidence of cognitive impairment (mild cognitive impairment (MCI) or Alzheimer's disease (AD) at baseline or 3) relatively short follow-up (4–8) between polysomnography and cognitive assessment.

Six clinical and community-based cohort studies previously examined longitudinal associations between OSA disease severity (apnea-hypopnea index [AHI]) and intermittent nocturnal hypoxemia and/or sleep macroarchitecture parameters and future cognitive decline (26-31). In the Proof-Synapse Cohort of older community-dwelling men and women (67 years at study entry) (n=559), sleep-disordered breathing (SDB) (apnea-hypopnea index [AHI] ≥15/h) but not other OSA parameters,

was associated with attentional decline (worse TMT-A performance) over 8 years (26). Criteria of an older age for participant inclusion may have influenced the associations observed. Conversely, in the Hispanic Community Health Study/Study of Latinos (N=5,247), SDB (AHI ≥15/h) was not associated with cognitive decline over 7 years, whereas surprisingly, longer total sleep duration (>9 hours) was associated with worse episodic memory and learning, language, and processing speed (31). In the Framingham Heart Study (n=321), a lower % of REM sleep and higher REM sleep latency was associated with a higher risk of incident dementia at mean ± *SD* 12.5 years (maximum 19 years) follow-up (29). All recruited participants were aged over 60 years at the time of the sleep study assessment and thus may have already developed cognitive impairment at baseline. In the Alzheimer's Disease Neuroimaging Initiative (ADNI) cohort, participants with SDB showed a significantly earlier mean age of MCI onset (72 years) compared with participants without SDB (83 years), and treatment with continuous positive airway pressure (CPAP) delayed the age of MCI onset. (30) The ADNI Study, however, assessed a limited number of OSA parameters at baseline, meaning the associations between nocturnal hypoxemia parameters and future cognitive decline could not be determined. In older (mean age 82.3 years) community-dwelling women of the Study of Osteoporotic Fractures (n=298), women with SDB at baseline (n=105) had significantly higher odds of developing MCI or dementia (adjusted odds ratios of 1.71 and 2.04, respectively) compared to women without SDB at baseline (n=193) (27). However, as the Study of Osteoporotic Fractures was comprised of women, generalisability of the findings to men is not clear. Lastly, in the Atherosclerosis Risk in Communities Study (n=966), OSA and sleep macroarchitecture parameters at baseline were not associated with performance on the delayed word recall, word fluency, or digit symbol substitution tests at 15 years follow-up in men and women with a mean age of 61 years at baseline, contrasting with the findings of other studies.

Findings from previous longitudinal studies suggest OSA and sleep macroarchitecture parameters may have prognostic value for identifying individuals at risk of future cognitive impairment. However, longitudinal associations between OSA and sleep macroarchitecture and future cognitive function among younger community-dwelling participants remain uninvestigated. Identifying a link between baseline OSA and sleep macroarchitecture and future cognitive function among

comparatively younger community-dwelling participants would support these routine PSG parameters as important early impairment markers. Furthermore, given that one one longitudinal study previously investigated the effect of CPAP treatment on age of MCI onset, further studies are needed to confirm whether OSA treatment status significantly affects future cognitive function.

The primary aim of this study was to investigate independent longitudinal associations between OSA and sleep macroarchitecture parameters at baseline and cognitive function (TMT performance) assessed 8–10 years later among a sample of community-dwelling men who were on average younger than 60 years at baseline. It was hypothesised that parameters indicative of more severe OSA, greater hypoxemia, and disrupted sleep macroarchitecture would be associated with cognitive function over 8–10 years.

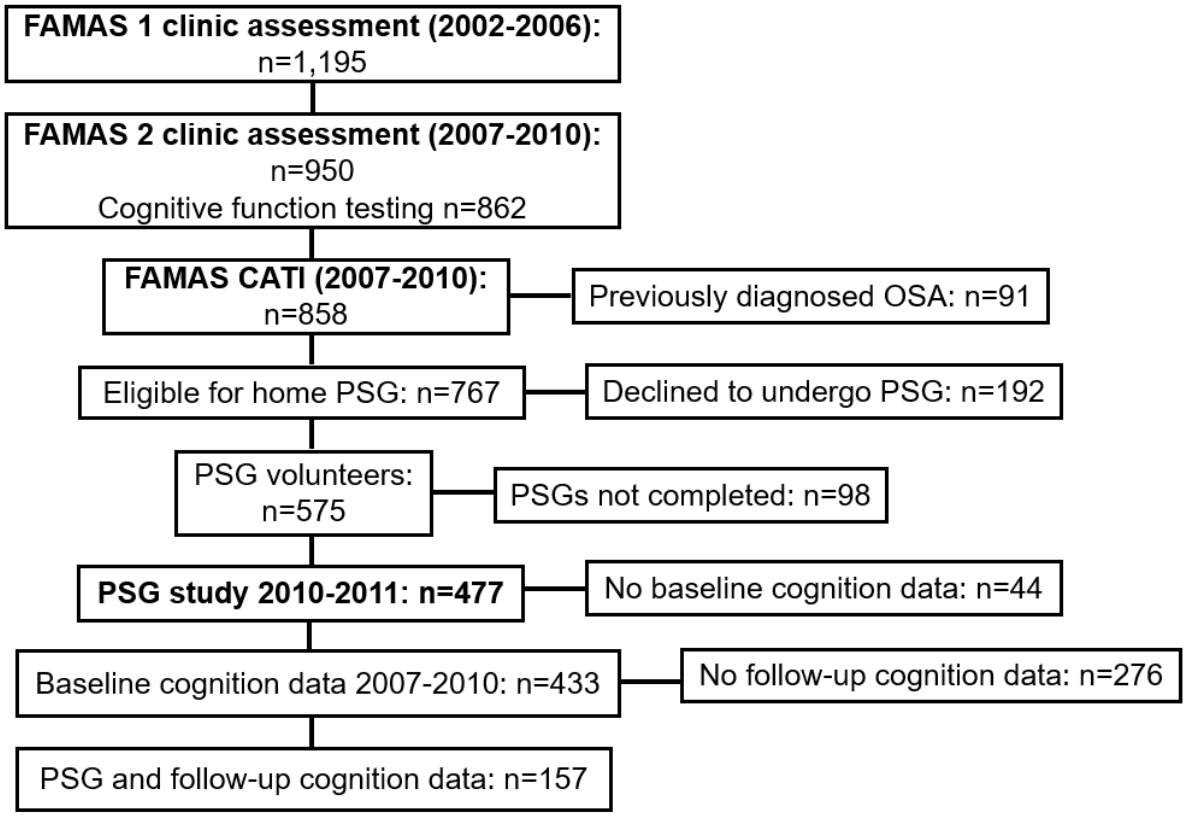
4.3 Methods

4.3.1 Study participants

The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study includes 2,569 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 longitudinal study includes FAMAS participants aged 35–80 years at baseline (2002–2006) residing in the north-west regions of Adelaide, South Australia (304, 320).

During a computer-assisted telephone interview follow-up in 2010 (n=858), FAMAS participants who reported no previous OSA diagnosis (n=767) were invited to undergo home-based PSG (2010–2011) as part of a sub-study of the MAILES Study (98, 303). Approximately 75% of eligible participants (n=575) agreed to participate, with time and budget constraints resulting in a final sample of n=477 (Figure 1). 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.

Figure 4.1 FAMAS clinical and sleep study assessments and cognitive function testing



FAMAS, Florey Adelaide Male Ageing Study. OSA, obstructive sleep apnea. CATI, computer-assisted telephone interview. PSG, polysomnography.

4.3.2 Baseline sleep study assessment

As previously described (338-340), participants underwent home-based eight-channel ambulatory PSG (Embletta X100, Embla Systems, Broomfield, Colorado, USA), which recorded electrical brain activity (EEG, F4-M1) and left electrooculography 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 height, weight, and body mass index (BMI, kg/m^2).

A single experienced sleep technician manually scored all PSG measures according to 2007 American Academy of Sleep Medicine (AASM) *Alternative* scoring criteria

(32), recommended by an expert panel of the Australasian Sleep Association for use in prospective epidemiological studies (321). OSA was identified by an AHI ≥10/h and further categorised as mild (10–19/h), moderate (20–29/h), or severe (≥30/h). An AHI ≥5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria is approximately equivalent to ≥10/h using the AASM 2007 *Alternative* and ≥15/h using the older 1999 *Chicago* scoring criteria (32). Therefore, an AHI cut-off of 10/h was chosen to maintain comparability with previous work. Apnea was defined as complete or near-complete airflow cessation (≥90%) measured using nasal cannula pressure excursions lasting ≥10 seconds. Hypopnea was defined as a ≥50% decrease in nasal cannula pressure excursions and an associated ≥3% oxygen desaturation or EEG arousal (32). Nocturnal hypoxemia was assessed from the oxygen desaturation index 3% (ODI 3%) and the percentage of total sleep time with oxygen saturation <90% (TST90). Acceptable sleep studies were those with ≥3.5 h of sleep and ≥5.5 h of total-recorded study time with technically acceptable respiratory and EEG signal quality.

4.3.3 Baseline and follow-up cognitive assessments

Three standardised, validated, and well-established cognitive tests, previously described in greater detail (65, 66, 306, 338), were administered during the 2007–2010 follow-up and repeated at the 2018–2019 follow-up examination, including trail-making tests A (TMT-A) and B (TMT-B) and the 30-point mini-mental state examination (MMSE). Refer to Chapter 2 for a detailed description of the cognitive tests. Although FAMAS participants also completed the inspection time task and Fuld object memory evaluation (FOME) test at baseline, these participants only completed TMT-A, TMT-B, and the MMSE at follow-up, and therefore the number of cognitive tests that could be examined was limited for the longitudinal analysis.

4.3.4 Baseline covariate assessments

Self-completed questionnaires assessed demographic factors (age, financial stress, highest educational attainment, and marital status). Relative social disadvantage, based on participants' residential postcode, was determined with the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA) Index of Relative

Socio-Economic Disadvantage (IRSD) (309). Clinic assessments (2007–2010) included anthropometry, seated sphygmomanometer blood pressure, and a fasting blood sample to assess blood glucose and haemoglobin A1C (304). Composite cardiovascular disease (self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke) and diabetes mellitus (self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L [126 mg/dL], haemoglobin A1C ≥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 at least three nights/week (Pittsburgh Sleep Quality Index [PSQI] 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 (310). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use (311). Self-completed questionnaires assessed chronic disease risk factors (smoking status, alcohol risk, and physical activity) and health-related quality of life (SF-36). BMI was categorised according to international criteria (308).

4.3.5 Statistical analysis methodology

Data were analysed using IBM SPSS version 25.0 (IBM Corporation, Armonk, New York, USA). Baseline participant characteristics are reported as mean (*SD*) for normally distributed continuous variables, median (interquartile range [IQR]) for skewed continuous variables, and percentages (frequencies) for dichotomous and categorical variables. Baseline participant characteristics are stratified by follow-up cognitive examination participation and performance status. As previously reported (313), impaired performance was defined as a ≥0.5 *SD* change in TMT score between the baseline and follow-up examinations. Between-group differences were assessed using Pearson's chi-squared tests for dichotomous and categorical variables, independent samples t-tests for normally distributed continuous variables, and Mann-Whitney U-tests for skewed continuous variables. Absolute cognitive task performance (TMT-A and TMT-B) a baseline and follow-up was compared to previously reported normative values based on age and highest educational attainment (306).

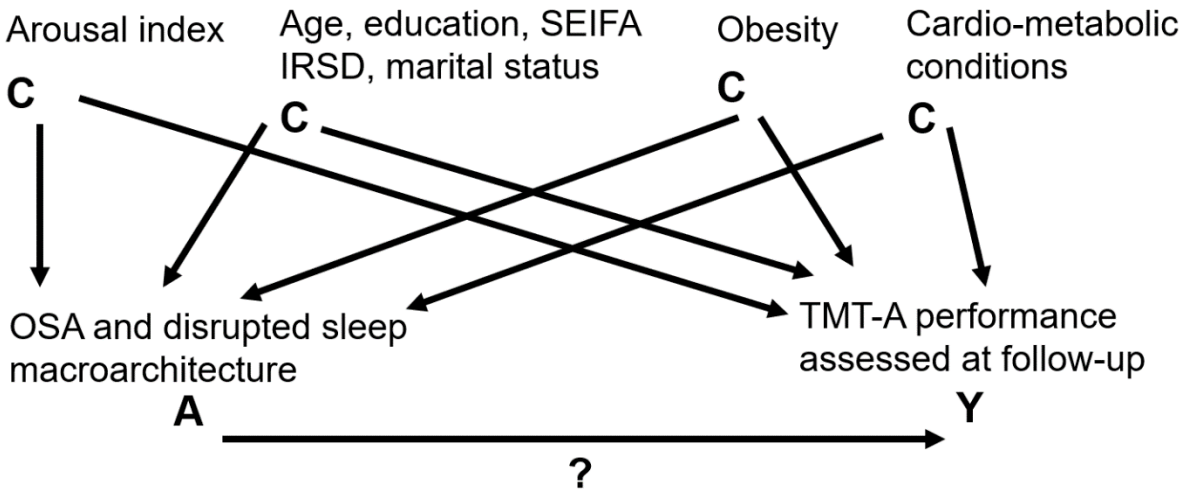
Mann-Whitney U and Kruskal-Wallis tests examined differences in cognitive performance across covariate dichotomies and categories. Standardised z-scores were calculated using logarithmic base 10 test scores, subtracting the mean, and dividing by the sample *SD* (26, 31, 313, 314). Differences in z-scores were assessed using independent samples t-tests and one-way analysis of variance (ANOVA) with Bonferroni correction for multiple comparisons. 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 hours), mandibular advancement splint (MAS), or surgery; or 3) OSA no treatment or CPAP <4 hours.

Linear regression models examined longitudinal associations between baseline OSA (AHI, TST90, ODI 3%, mean SaO_2, O_2 nadir) and sleep macroarchitecture (N1, N2, N3, and REM sleep % and TST [hours]) and standardised TMT-A and TMT-B performance at 8–10 years follow-up, with results presented as unstandardised beta (*B*) coefficients (95% confidence interval [CI]). Three regression models were constructed, including 1) unadjusted, 2) adjusted for age, highest educational attainment, socio-economic disadvantage, marital status, BMI, and cardio-metabolic conditions (one or more of hypertension, diabetes mellitus, or cardiovascular disease), and 3) additionally adjusted for baseline cognitive task performance (TMT performance) to predict the change in TMT time in relation to OSA and sleep macroarchitecture parameters at baseline. These linear regression analyses were performed to determined whether parameters of more severe OSA, greater hypoxemia, and disrupted sleep macroarchitecture would be independently associated with worse future cognitive function. Purposeful covariate selection (325, 339) ensured robust covariates were retained for adjustment. Furthermore, covariates in multivariable adjustment are previously reported risk factors for cognitive decline (306, 341-343). Sleep macroarchitecture models were additionally adjusted for the AHI and arousal index as these OSA severity parameters have been previously reported to impact sleep macroarchitecture (344, 345). The principal assumptions of linear regression modelling were satisfied, including linearity, normality, and homoscedasticity. Multicollinearity was assessed by examining the

variance inflation factor. As a sensitivity analysis, cross-sectional associations between OSA and sleep macroarchitecture and baseline cognitive function in men who participated in the follow-up examination (n=157) were examined. The filter function in SPSS was used to ensure only participants with complete case cognition, PSG, and covariate data were included in the final analysis. Based on previously reported practical considerations and given the exploratory nature of the analyses, multiple comparison adjustments were not performed (346, 347).

Binary logistic regression models examined associations between OSA and sleep macroarchitecture at baseline and dichotomised values of reduction in TMT times (standard deviation cut-offs for cognitive change; normal [≤0.5 *SD*] and impaired [>0.5 *SD*]) (313) and MMSE scores, with <28/30 at follow-up corresponding to cognitive impairment (316). Results are presented as odds ratios (OR) 95% CI. Covariates in multivariable adjustment were consistent with linear regression analyses. For all analyses, a two-sided p<0.05 was considered statistically significant.

Figure 4.2 Overview of relationships between variables



Legend: A=exposure/treatment/intervention/primary independent variable, C=confounder, Y=outcome variable.

4.4 Results

Of the 433 men with baseline PSG and cognitive data, 36.3% (n=157) participated in the 2018–2019 follow-up examination. The mean (*SD*) age at baseline of those who participated in the follow-up examination was 58.9 (8.9) (range, 41–81) years.

4.4.1 Baseline participant characteristics stratified by follow-up status

Relative to non-participants, of those who participated in the follow-up examination, more were partnered/married (Table 4.1). However, there were no differences in other risk factors (Table 4.1) and OSA or sleep macroarchitecture parameters (Table 4.2). Those who participated in the 2018-2019 follow-up cognitive examination did not differ in TMT performance at baseline compared to non-participants (Table 4.1).

Table 4.1 Baseline participant characteristics stratified by cognitive follow-up examination participation status

	Cognitive follow-up examination participation	
Baseline participant characteristics	**Participants (n=157)**	**Non-participants (n=276)**
Demographic risk factors		
Mean (*SD*)		
Age (years)	58.9 (8.9)	59.4 (11.4)
SEIFA IRSD		
Quintile 1 (most socio-economic disadvantage)	21.0 (33)	23.6 (65)
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 socio-economic disadvantage)	12.7 (20)	13.4 (37)
Married/partner	89.8 (141)	80.4 (222) *****
Biomedical risk factors		
Cardiovascular disease	5.1 (8)	8.3 (23)
Diabetes mellitus	8.3 (13)	5.1 (14)
Insomnia	10.8 (17)	13.0 (36)
Hypertension	58.6 (92)	59.4 (164)
Cardio-metabolic conditions	61.1 (96)	62.0 (171)
Behavioural risk factors		
Medium–very high alcohol risk	7.7 (12)	6.2 (17)
Mean (*SD*)		
Epworth Sleepiness Scale	6.9 (4.2)	6.0 (3.8)
% (n)		
Epworth Sleepiness Scale ≥11 (excessive daytime sleepiness)	16.2 (25)	12.5 (34)
Psychotropic medication(s)	8.9 (14)	8.3 (23)
Mean (*SD*)		
Cognitive baseline data		
TMT-A, secs	15.4 (5.2)	16.2 (7.1)
TMT-B, secs	75.3 (26.1)	80.0 (37.6)

Abbreviations: *SD*, standard deviation; IQR, interquartile range; 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.
Cardiovascular disease: self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke.
Diabetes mellitus: self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), haemoglobin A1C ≥6.5%, or reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).
Insomnia: difficulty initiating or maintaining sleep occurring at least three nights/week (PSQI dimensions) and significant daytime fatigue defined as a score one *SD* below the mean on the 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.
Symbol legend: *****p<0.05 compared with participants in the cognitive follow-up examination.

Table 4.2 Baseline OSA and sleep macroarchitecture stratified by cognitive follow-up examination participation status

	Cognitive follow-up examination participation	
Baseline OSA and sleep macroarchitecture	**Participants (n=157)**	**Non-participants (n=276)**
OSA parameters		
OSA severity categories (AHI)	15.4 (16.1)	16.3 (14.4)
% (n)		
<10/h	47.1 (74)	44.6 (123)
10–19/h	30.6 (48)	25.4 (70)
20–29/h	12.7 (20)	15.6 (43)
≥30/h	9.6 (15)	14.5 (40)
% (n)		
TST90 ≥4%	28.0 (44)	26.9 (74)
ODI 3%		
>15/h	14.6 (23)	13.8 (38)
≥15 <30/h	18.5 (29)	17.4 (48)
≥30/h	66.9 (105)	68.8 (190)
Median (IQR)		
O_2 nadir	86.0 (81.5, 89.0)	86.0 (81.0, 88.0)
Mean (*SD*)		
SaO_2	93.7 (1.7)	93.7 (1.8)
Sleep macroarchitecture		
Mean *(SD)*		
N1 %	14.3 (6.7)	14.9 (6.7)
N2 %	54.0 (9.6)	54.9 (9.8)
N3 %	17.0 (8.8)	15.4 (8.6)
REM %	14.6 (5.3)	14.5 (5.7)
TST, minutes	380.2 (55.1)	371.0 (59.7)
% (n)		
TST <360 minutes	36.9 (58)	39.5 (109)

Abbreviations: OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; TST90, percentage of total sleep time with oxygen saturation <90%; ODI 3%, oxygen desaturation index 3%; O_2 nadir, oxygen saturation nadir; SaO_2, mean oxygen saturation; N1, stage 1 sleep; N2, stage 2 sleep; N3, stage 3 sleep; REM, rapid eye movement sleep; TST, total sleep time, *SD*, standard deviation; IQR, interquartile range.
Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

4.4.2 Standardised cognitive test scores in relation to baseline participant characteristics

Higher age and mild and moderate OSA at baseline were associated with worse standardised TMT-A performance at follow-up and greater reduction in TMT-A performance from baseline to follow-up. Higher age at baseline was also associated with worse standardised TMT-B performance at follow-up and a greater reduction in TMT-B performance (Supplementary Table 4.1). However, chronic disease risk factors and conditions were not associated with standardised or reduced TMT performance (Supplementary Table 4.2).

4.4.3 TMT performance at baseline and follow-up relative to normative values of age and highest educational attainment

At baseline, the sample was predominantly non-impaired on TMT-A relative to previously published normative values of age and highest educational attainment. However, a considerable proportion showed impairment on TMT-A at follow-up (Supplementary Figure 4.1). Regarding TMT-B performance, most participants recorded worse at baseline and follow-up relative to previously published normative values of age and highest educational attainment (Supplementary Figure 4.2).

4.4.4 Baseline participant characteristics stratified by reduction in TMT performance

Of participants included in the final analytic sample, 17.8% (n=28) showed a ≥0.5 *SD* reduction on TMT-A and 28.7% (n=35) on TMT-B from baseline to follow-up (Table 4.3). Of participants who showed a ≥0.5 *SD* reduction on TMT-A and TMT-B, more had mild OSA (AHI 10–19/h) compared to participants who did not show a ≥0.5 *SD* reduction. Men who showed a ≥0.5 *SD* reduction on TMT-A recorded a lower % of N1 sleep but a greater % of N3 sleep at baseline.

Table 4.3 Baseline OSA and sleep macroarchitecture parameters stratified by standard deviation reduction in TMT performance from baseline to follow-up

	Cognitive follow-up examination			
Follow-up cognitive performance domains	**Visual attention and processing speed (TMT-A)**		**Executive function (TMT-B)**	
Cognitive performance subgroups	**<0.5 *SD* reduction (n=129)**	**≥0.5 *SD* reduction (n=28)**	**<0.5 *SD* reduction (n=122)**	**≥0.5 *SD* reduction (n=35)**
OSA parameters				
OSA severity categories (AHI) % (n)				
<10/h	54.3 (70)	25.0 (7) $	48.8 (63)	34.3 (12) $
10–19/h	26.2 (33)	46.4 (13) $	24.0 (28)	54.3 (19) $
20–29/h	10.3 (13)	25.0 (7)	13.2 (16)	8.6 (3)
≥30/h	10.3 (13)	3.6 (1)	11.6 (14)	2.9 (1)
% (n)				
TST90 ≥4% ODI 3%	25.6 (33)	35.7 (10)	27.0 (33)	28.6 (10)
>15/h	15.5 (20)	10.7 (3)	16.4 (20)	8.6 (3)
≥15 <30/h	20.2 (26)	10.7 (3)	20.5 (25)	11.4 (4)
≥30/h	64.3 (83)	78.6 (22)	63.1 (77)	80.0 (28)
Median (IQR)				
O_2 nadir	86.5 (82.0, 89.0)	85.0 (78.3, 87.8)	86.0 (82.0, 89.0)	86.0 (81.0, 88.0)
Mean (*SD*)				
SaO_2	93.8 (1.74)	93.4 (1.59)	93.8 (1.76)	93.5 (1.54)
% (n)				
OSA treatment status				
No self-report diagnosed OSA	74.1 (86)	60.7 (17)	73.5 (83)	57.1 (20)
CPAP ≥4 hours or MAS, surgery	17.2 (20)	10.7 (3)	12.3 (15)	11.4 (4)
No treatment or CPAP <4 hours	17.8 (23)	32.0 (8)	19.7 (24)	31.4 (11)
Sleep macroarchitecture				
Mean *(SD)*				
N1 %	14.9 (6.90)	12.1 (5.26) *	14.4 (6.93)	14.2 (5.89)
N2 %	54.0 (9.34)	52.9 (10.3)	54.5 (9.64)	52.3 (9.62)
N3 %	16.5 (8.94)	20.1 (7.23) *	16.8 (8.74)	18.1 (9.04)
REM %	14.7 (5.15)	14.9 (6.21)	14.4 (5.34)	15.4 (5.37)
TST, minutes	380.4 (55.7)	376.8 (53.9)	379.1 (54.9)	383.1 (57.0)
% (n)				
TST <360 minutes	34.9 (45)	42.9 (12)	37.7 (46)	34.3 (12)

Abbreviations: OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; TST90, percentage of total sleep time with oxygen saturation <90%; ODI 3%, oxygen desaturation index 3%; O_2 nadir, oxygen saturation nadir; SaO_2, mean oxygen saturation; CPAP, continuous positive airway pressure; MAS, mandibular advancement splint; N1, stage 1 sleep; N2, stage 2 sleep; N3, stage 3 sleep; TST, total sleep time, *SD*, standard deviation; IQR, interquartile range.
Symbol legends: *****independent samples t-test p<0.05 compared to men without follow-up cognition data.
$Pearson's chi-squared test p<0.05 compared to men without follow-up cognition data.

Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

4.4.5 Longitudinal associations between OSA and sleep macroarchitecture and future cognitive function

In unadjusted and adjusted models, a higher % of N1 sleep was associated with better standardised TMT-A performance at follow-up. After adjustment for baseline TMT-A performance, greater mean oxygen saturation (SaO_2) was associated with worse standardised TMT-A performance at follow-up. There were no unadjusted or adjusted associations between OSA or sleep macroarchitecture parameters and standardised TMT-B performance at follow-up (Table 4.4). Higher ODI 3% was associated with reduced odds of decline on the MMSE in an adjusted model, which was attenuated after adjustment for baseline MMSE performance (Table 4.5). Sensitivity analysis showed that, in adjusted models, mean SaO_2 and % of N1 sleep were not cross-sectionally associated with TMT-A performance at baseline in men who participated in the follow-up examination (mean SaO_2, *B*=-0.07, 95% CI [-0.18, 0.03], p=0.16; N1 sleep percentage, *B*=0.04, 95% CI [-0.11, 0.19], p=0.63).

Table 4.4 Covariate unadjusted and adjusted associations between baseline OSA and sleep macroarchitecture parameters and standardised (z-score) TMT-A and TMT-B performance at follow-up

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
			TMT-A			
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
AHI (/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
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**
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
			TMT-B			
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
AHI (/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
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
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

Abbreviations: TMT-A, trail-making test A; TMT-B, trail-making test B; AHI, apnea-hypopnea index; TST90, percentage total sleep time with oxygen saturation <90%; ODI 3%, oxygen desaturation index 3%; O_2 nadir, oxygen saturation nadir; SaO_2, average oxygen saturation; N1, percentage of stage 1 sleep; N2, percentage of stage 2 sleep; N3, percentage of stage 3 sleep; REM, rapid eye movement sleep; TST, total sleep time; CI, confidence interval.
Coefficients: Unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates: estimates represent the change in TMT-A and TMT-B scores at follow-up corresponding to a one-unit increase in the OSA or sleep macroarchitecture parameter at baseline.

Adjusted Model 1 (AHI /h, TST90 %, ODI 3%, O_2 nadir %, and SaO_2 %): adjusted for baseline age, highest educational attainment, socio-economic disadvantage, marital status, BMI, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes mellitus, or hypertension).
Adjusted Model 1 (N1 %, N2 %, N3 %, REM %, and TST h): adjusted for baseline age, AHI, arousal index, highest educational attainment, socio-economic disadvantage, marital status, BMI, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes mellitus, or hypertension).
Adjusted Model 2: additionally adjusted for baseline TMT performance.
Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

Table 4.5 Covariate unadjusted and adjusted associations between OSA and sleep macroarchitecture parameters at baseline and impaired MMSE performance at follow-up

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
AHI (/h)	0.98 (0.95, 1.02)	0.39	0.94 (0.89, 1.01)	0.082	0.96 (0.90, 1.03)	0.23
TST90 (%)	1.00 (0.95, 1.05)	0.97	1.01 (0.96, 1.07)	0.68	1.02 (0.96, 1.08)	0.61
ODI 3% (%)	0.99 (0.98, 1.00)	0.20	0.99 (0.98, 1.00)	**0.026**	0.99 (0.98, 1.00)	0.089
O_2 nadir (%)	1.05 (0.97, 1.14)	0.20	1.09 (0.96, 1.24)	0.19	1.05 (0.94, 1.16)	0.41
SaO_2 (%)	1.04 (0.80, 1.36)	0.76	1.21 (0.80, 1.82)	0.37	1.29 (0.81, 2.04)	0.29
N1 (%)	1.00 (0.94, 1.07)	0.90	1.06 (0.95, 1.18)	0.32	1.07 (0.96, 1.19)	0.26
N2 (%)	1.00 (0.95, 1.05)	0.99	1.00 (0.94, 1.06)	0.98	1.00 (0.94, 1.07)	0.92
N3 (%)	0.99 (0.94, 1.04)	0.60	0.96 (0.89, 1.03)	0.26	0.95 (0.87, 1.03)	0.22
REM (%)	1.03 (0.95, 1.12)	0.48	1.04 (0.93, 1.15)	0.53	1.03 (0.91, 1.16)	0.66
TST (h)	0.93 (0.57, 1.51)	0.76	0.74 (0.35, 1.56)	0.43	0.63 (0.29, 1.34)	0.23

Abbreviations: AHI, apnea-hypopnea index; TST90, percentage total sleep time with oxygen saturation <90%, ODI 3%, oxygen desaturation index 3%; O_2 nadir, oxygen saturation nadir; SaO_2, oxygen saturation; NREM, non-rapid eye movement; REM, rapid eye movement; CI, confidence interval; OR, odds ratio.
Estimates (MMSE): Odds ratios (95% CI) from univariable and multivariable binary logistic regression models are reported. MMSE dichotomised cognitive impairment ≤27/30.
Adjusted Model 1 (AHI /h, TST90 %, ODI 3%, O_2 nadir %, and SaO_2 %): adjusted for baseline age, highest educational attainment, socio-economic disadvantage, marital status, BMI, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes mellitus, or hypertension).
Adjusted Model 1 (N1 %, N2 %, N3 %, REM %, and TST h): adjusted for baseline age, AHI, arousal index, highest educational attainment, socio-economic disadvantage, marital status, BMI, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes mellitus, or hypertension).
Adjusted Model 2: additionally adjusted for baseline MMSE performance.
Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

4.4.6 Longitudinal associations between OSA and sleep macroarchitecture and reduction in TMT performance

The change in TMT-A and TMT-B performance from baseline to follow-up was examined. All participants recorded worse TMT-A (Figure 4.2) but not TMT-B (Figure 4.3) performance at follow-up compared to baseline. In unadjusted models, a higher % of N3 sleep was associated with greater odds of decline in TMT-A performance from baseline to follow-up, whereas a higher % of N1 sleep was protective. However, these associations did not persist in adjusted models. There were no unadjusted or adjusted associations between OSA and sleep macroarchitecture parameters and reduction in TMT-B performance from baseline to follow-up (Table 4.6).

Figure 4.3 Change in TMT-A performance from baseline to follow-up

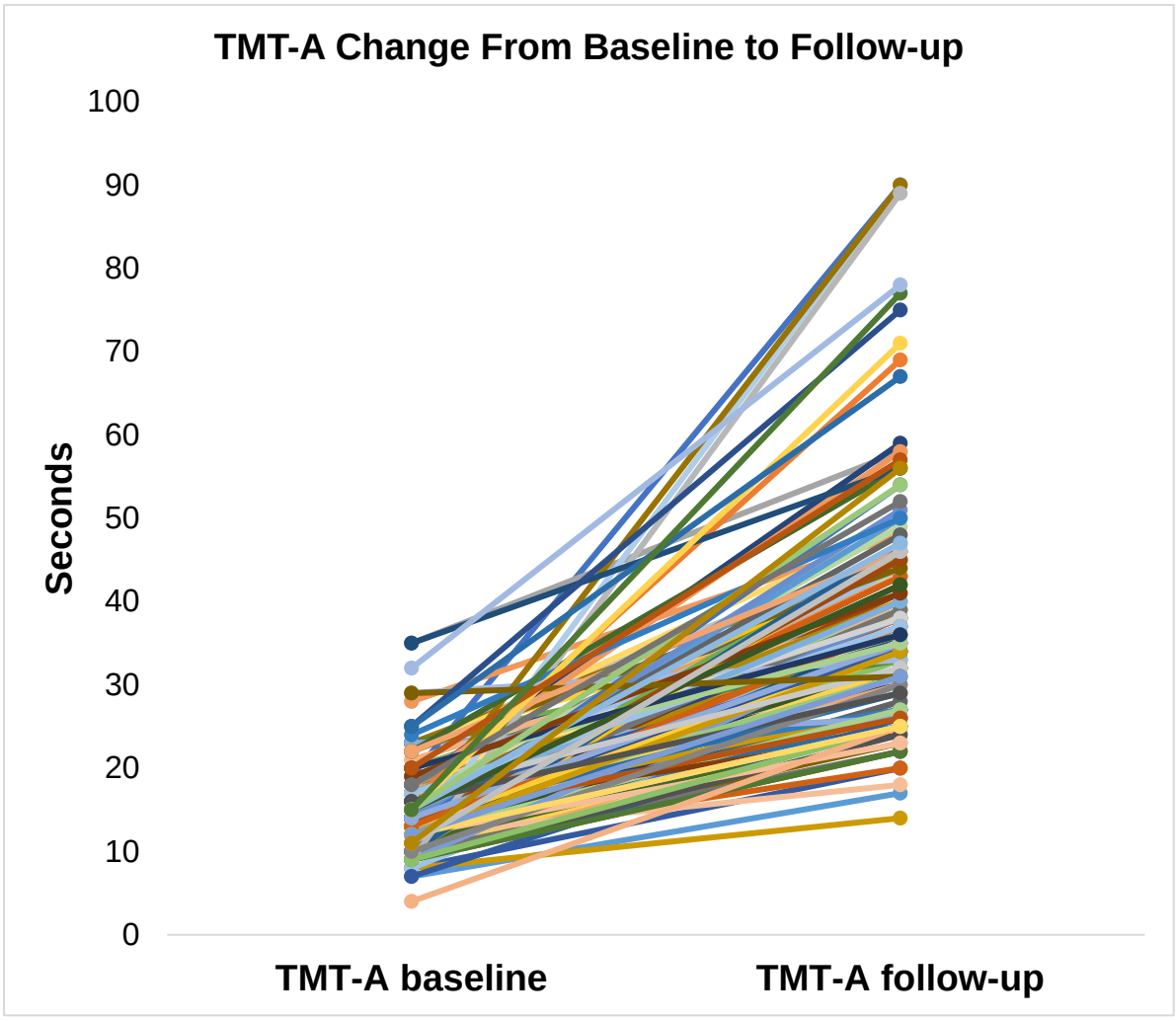


Figure 4.4 Change in TMT-B performance from baseline to follow-up

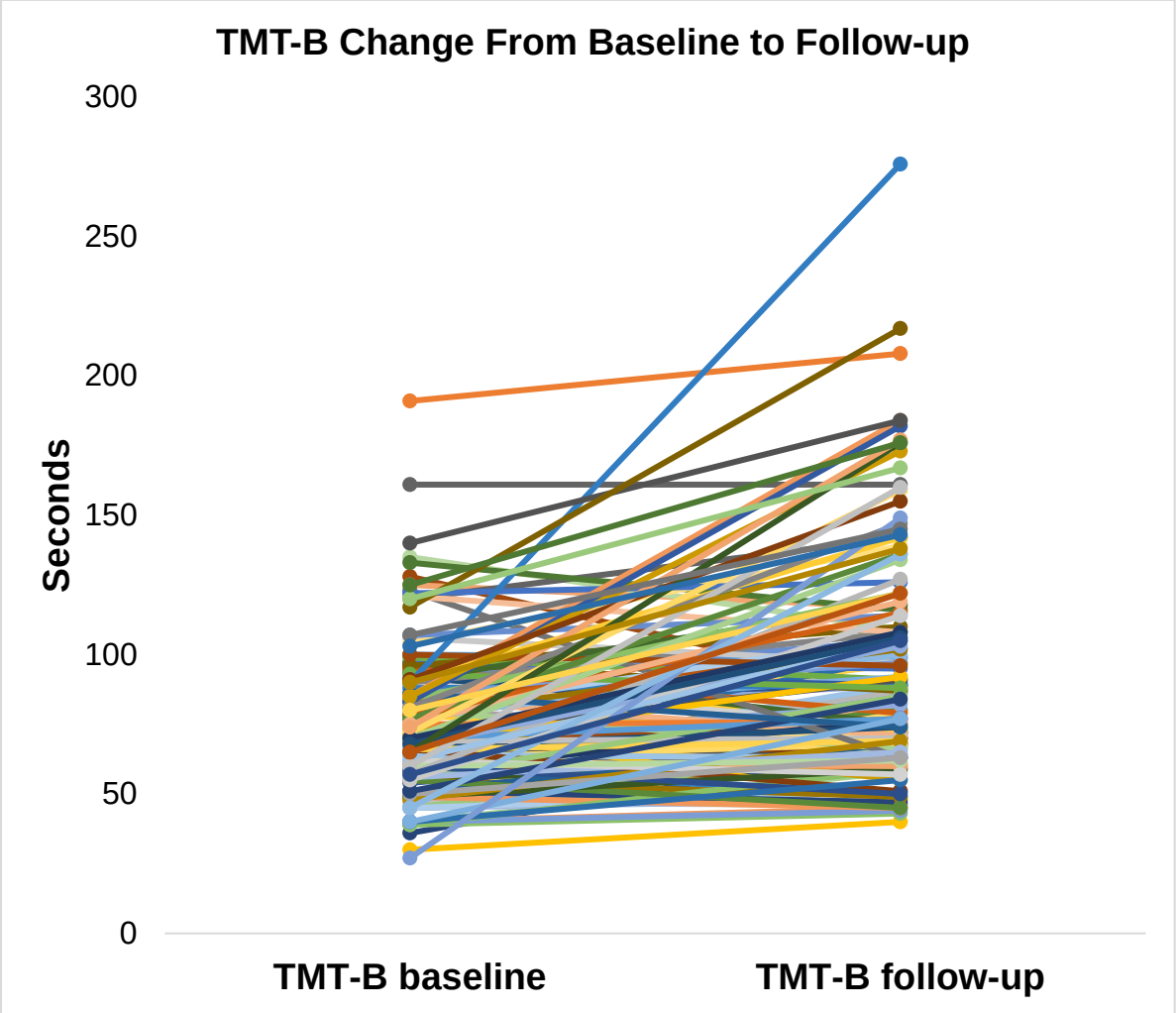


Table 4.6 Covariate unadjusted and adjusted associations between baseline OSA and sleep macroarchitecture parameters and change in TMT-A and TMT-B performance from baseline to follow-up

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
			TMT-A			
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
AHI (/h)	1.00 (0.98, 1.03)	0.96	0.99 (0.96, 1.03)	0.64	0.99 (0.95, 1.03)	0.63
TST90 (%)	1.04 (1.00, 1.07)	0.067	1.04 (0.99, 1.09)	0.098	1.04 (0.99, 1.09)	0.098
ODI 3% (%)	1.00 (0.99, 1.004)	0.80	0.998 (0.99, 1.005)	0.53	0.998 (0.991, 1.005)	0.51
O_2 nadir (%)	0.98 (0.95, 1.01)	0.19	0.98 (0.95, 1.01)	0.24	0.98 (0.95, 1.01)	0.24
SaO_2 (%)	0.89 (0.70, 1.13)	0.35	1.07 (0.76, 1.50)	0.70	1.07 (0.76, 1.50)	0.71
N1 (%)	0.93 (0.87, 0.99)	**0.048**	0.91 (0.82, 1.01)	0.069	0.91 (0.82, 1.01)	0.070
N2 (%)	0.98 (0.95, 1.03)	0.60	1.00 (0.95, 1.06)	0.87	1.01 (0.95, 1.06)	0.87
N3 (%)	1.05 (1.00, 1.10)	**0.048**	1.03 (0.97, 1.10)	0.32	1.03 (0.97, 1.10)	0.33
REM (%)	1.00 (0.93, 1.09)	0.89	1.00 (0.91, 1.10)	0.96	1.00 (0.91, 1.10)	0.95
TST (h)	0.93 (0.60, 1.46)	0.76	1.12 (0.58, 2.17)	0.74	1.11 (0.56, 2.17)	0.76
			TMT-B			
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
AHI (/h)	0.99 (0.96, 1.02)	0.40	0.98 (0.95, 1.02)	0.30	0.98 (0.95, 1.02)	0.30
TST90 (%)	0.99 (0.95, 1.04)	0.81	1.00 (0.95, 1.05)	0.99	1.00 (0.95, 1.05)	0.98
ODI 3% (%)	1.00 (0.99, 1.002)	0.33	0.996 (0.99, 1.003)	0.26	0.996 (0.99, 1.003)	0.26
O_2 nadir (%)	1.01 (0.97, 1.04)	0.70	1.01 (0.97, 1.05)	0.58	1.01 (0.97, 1.05)	0.64
SaO_2 (%)	0.91 (0.73, 1.13)	0.40	0.92 (0.70, 1.22)	0.57	0.92 (0.69, 1.21)	0.54
N1 (%)	0.99 (0.94, 1.06)	0.91	1.00 (0.93, 1.08)	0.98	1.00 (0.93, 1.08)	0.97
N2 (%)	0.98 (0.94, 1.02)	0.24	0.98 (0.94, 1.03)	0.38	0.98 (0.93, 1.03)	0.38
N3 (%)	1.02 (0.98, 1.06)	0.43	1.02 (0.97, 1.07)	0.48	1.02 (0.97, 1.07)	0.49
REM (%)	1.04 (0.96, 1.11)	0.34	1.02 (0.94, 1.11)	0.61	1.02 (0.94, 1.11)	0.63
TST (h)	1.08 (0.72, 1.63)	0.71	1.12 (0.69, 1.83)	0.65	1.11 (0.68, 1.82)	0.67

Abbreviations: TMT-A, trail-making test A; TMT-B, trail-making test B; AHI, apnea-hypopnea index; TST90, percentage total sleep time with oxygen saturation <90%; ODI 3%, oxygen desaturation index 3%; O_2 nadir, oxygen saturation nadir; SaO_2, oxygen saturation; N1, percentage of stage 1 sleep; N2, percentage of stage 2 sleep; N3, percentage of stage 3 sleep; REM, rapid eye movement sleep; TST, total sleep time; CI, confidence interval; OR, odds ratio.
Estimates (TMT-A and TMT-B): Odds ratios (95% CI) from univariable and multivariable binary logistic regression models are reported. Estimates represent the odds of a ≥0.5 *SD* decline in TMT-A and change in TMT-B scores from baseline to follow-up corresponding to a one-unit increase in the OSA or sleep macroarchitecture parameter at baseline.
Adjusted Model 1 (AHI/h, TST90 %, ODI 3%, O_2 nadir %, and SaO_2 %): adjusted for baseline age, education, socio-economic disadvantage, marital status, BMI, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes, or hypertension).
Adjusted Model 1 (N1 %, N2 %, N3 %, REM %, and TST h) adjusted for baseline arousal index, age, education, socio-economic disadvantage, marital status, BMI, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes, or hypertension).
Adjusted Model 2: additionally adjusted for baseline TMT performance.
Legend: p-values representing significant associations boldfaced.
Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

4.4.7 Effect of OSA treatment status on future cognitive function and cognitive change

When assessing absolute TMT performance at follow-up, OSA treatment status significantly affected TMT-A, $F_{2,143}$=3.19, p=0.044, but not TMT-B, $F_{2,142}$=2.51, p=0.085, performance. Bonferroni corrected post-hoc tests demonstrated that OSA-treated participants scored significantly better on TMT-A at follow-up compared to untreated participants (p=0.042). However, OSA treatment status did not significantly affect the change in TMT-A and TMT-B performance from baseline to follow-up (TMT-A, $F_{2,143}$=1.41, p=0.215; TMT-B, $F_{2,142}$=0.99, p=0.37).

4.5 Discussion

This community-based cohort study is one of the first to prospectively examine associations between OSA and sleep macroarchitecture and future cognitive function and decline among a sample of community-dwelling on average younger than 60 years at baseline. Overall, most OSA and sleep macroarchitecture parameters assessed at baseline (2010–2011) were not independently associated with cognitive function (TMT performance) 8–10 years later. However, a higher % of N1 sleep was associated with better visual attention and processing speed (TMT-A performance), whereas higher mean oxygen saturation was associated with worse TMT-A performance 8–10 years later. These findings extend previous clinical and community-based cohort studies in older participants predominantly with baseline cognitive impairment (mild cognitive impairment and Alzheimer's disease) and suggest that the OSA and sleep macroarchitecture associations with future cognitive function are limited with unclear clinical significance.

Several prospective clinical and community-based cohort studies previously examined longitudinal associations between OSA and/or sleep macroarchitecture parameters and future cognitive function decline (26-31). However, these studies predominantly recruited older participants with mild cognitive impairment and/or Alzheimer's disease. Importantly, OSA has been associated with earlier onset of mild cognitive impairment/Alzheimer's disease (27, 30) and reduced % of REM sleep with an increased risk of clinical dementia (29). Furthermore, severe OSA (apnea-hypopnea index ≥30/h) has been associated with attentional decline (worse TMT-A

performance) (26). Conversely, one study did not report any associations between baseline OSA and sleep macroarchitecture parameters and future cognitive function decline (28). Compared to previous prospective cohort studies, the novel contribution of the present cohort study is the inclusion of comparatively younger (mean age at baseline [2010–2011] >60 years) and cognitively unimpaired community-dwelling men and a comparatively longer follow-up period (8–10 years) to investigate whether OSA parameters may represent early markers of future impairment.

Contrasting with previous prospective cohort studies (26, 27, 29, 30) and the cross-sectional analysis in Chapter 3 of this thesis (338), conventional parameters of OSA disease severity (AHI) and intermittent nocturnal hypoxemia (TST90 and ODI 3%) assessed during the baseline PSG (2010–2011) were not independently associated with TMT performance 8–10 years later. The comparatively younger community-based sample could partly explain the absence of longitudinal associations between routine OSA parameters and future cognitive function. Age differences could account for discrepant findings, specifically as a consequence of cortical alterations observed with ageing and potentially exacerbated by the presence and severity of OSA that may negatively influence cognitive function (4).

Neuroimaging studies utilising magnetic resonance imaging (MRI) demonstrated cortical neuroanatomical alterations, including atrophy in frontal and parietal brain regions in community-dwelling men and women (348), gray matter density reduction in frontal, parietal, temporal, and hippocampal brain regions, and white matter density reduction in the bilateral hippocampus and frontotemporal brain regions in smaller samples of patients with OSA (349-352). Furthermore, in older adults with OSA, decreased thickness of the bilateral temporal pole and alterations in functional connectivity of the default mode network (353, 354), decreased thickness of the pre- and post-central gyri and superior central gyrus (355), and loss of white matter integrity and structural connectivity (356) have been identified, suggesting that cortical morphological alternations in older adults with OSA may be associated with increased intermittent hypoxemia and impaired cognitive function.

OSA-related cortical morphological alternations observed in previous studies may not have yet occurred in participants from the FAMAS cohort at the time of the follow-

up assessment, or OSA assessed at baseline might not have strongly influenced cortical activity, potentially explaining why most routine parameters of hypoxemia were not associated with cognitive function 8–10 years later. The present findings in a comparatively younger community-based cohort of men expand on findings in older adults and provide further evidence suggesting a lack of associations (unadjusted and adjusted) of most OSA parameters with future cognitive function. However, the present study did not utilise neuroimaging techniques to investigate the potential role of cortical morphological alterations on cognitive function. It will be necessary for future studies to utilise neuroimaging approaches to determine whether cortical morphological alterations influence the longitudinal associations between OSA parameters and cognitive function.

In the present study, the only significant adjusted longitudinal associations between OSA and sleep macroarchitecture associations and future cognitive function were a higher % of N1 sleep with better TMT-A performance, and greater mean oxygen saturation with worse TMT-A performance, respectively, at 8–10 years follow-up. These longitudinal associations contradict previous literature reporting that greater N1 sleep commonly stems from frequent arousals, and lower mean oxygen saturation may be associated with worse cognitive function (357-360). The counterintuitive longitudinal association between a higher % of N1 sleep and better TMT-A performance 8–10 years later similarly contradicts the independent cross-sectional association in older (≥65 years) community-dwelling reported in Chapter 3 of this thesis, which suggested that greater light or fragmented sleep is independently associated with worse TMT-A performance (338).

OSA treatment status may account for the contrasting, counterintuitive longitudinal findings. Some evidence suggests that greater N1 sleep and frequency of arousals at baseline are associated with improved sleepiness following CPAP treatment (361). The unexpected association with % of N1 sleep could also reflect more severe OSA that was subsequently treated and may have resulted in better cognition in adjusted analysis and less decline, at least in unadjusted analysis. Men treated with CPAP (≥4 hours/night), MAS, or surgery recorded significantly faster TMT-A completion times at follow-up compared to untreated participants. Given that men with mild OSA were unlikely to seek treatment, potentially leading to worse OSA over time, this may

explain why they were more likely to show a significant reduction in TMT performance from baseline to follow-up. However, the associations observed with % of N1 sleep and mean oxygen saturation were of small effect size and questionable clinical significance. Consequently, further prospective studies remain warranted to determine if % of N1 sleep and mean oxygen saturation are associated with future cognitive function and decline and how CPAP treatment may influence these associations.

Sensitivity cross-sectional analysis revealed that % of N1 sleep was not associated with TMT-A performance at baseline in men who participated in the follow-up cognitive examination. These findings suggest selection bias in men who chose to participate in the follow-up cognitive examination who may have been more resilient to poorer sleep or that OSA treatment may have influenced the associations between % of N1 sleep and mean oxygen saturation at baseline and TMT-A performance at follow-up. A relatively healthier population at follow-up (survivor effect) could also reflect why the present longitudinal association contradicts that observed in the cross-sectional analysis (338). Another factor that may influence the longitudinal associations is participant volunteer responder bias. Notably, a greater proportion of men who participated in the cognitive follow-up examination were partnered/married compared to non-participants. Previous cohort literature suggests marital status can strongly influence cognitive function (362-364), supporting the potential influence of this factor on the observed longitudinal associations. However, there were no significant differences in disease or chronic disease risk factors or subjective daytime sleepiness (Epworth Sleepiness Scale).

Interestingly, when examining associations between OSA parameters and future cognitive status assessed by the MMSE, lower oxygen saturation index 3% was associated with reduced odds of decline on the MMSE in adjusted analysis only. In the present study, it was not possible to examine associations between OSA and sleep macroarchitecture parameters at baseline and incident mild cognitive impairment due to limited statistical power. Only 14 of 157 men who participated in the follow-up cognitive examination showed evidence of incident mild cognitive impairment by scoring ≥28/30 on the MMSE at baseline but below the cut-off of ≤27/30 at follow-up. As such, further studies are needed to expand these findings

and determine if oxygen desaturation parameters are linked with future cognitive function decline.

The characteristics of uncaptured OSA and arousal events, including apneas versus hypopneas and their durations, flow limitation, arousal thresholds, and non-routine hypoxemia measures such as OSA-specific hypoxic burden, could have contributed to the contrasting and counterintuitive longitudinal associations. Hypoxic burden has been reported to be associated with cardiovascular disease-related mortality, all-cause mortality (335, 365, 366). Very recent findings suggest that frequent cortical arousals may, over time, reduce the level of hypoxia and promote less severe hypoxic events and arousal intensity (Ali Azarbarzin, “personal communication,” September 2, 2022). As such, these findings may, in part, explain the contradicting associations of % of N1 sleep and mean SaO_2 with better TMT-A performance at follow-up. However, in the present study, capturing OSA-specific hypoxic burden was not possible, and this non-routine hypoxemia measure should be carefully considered in future prospective studies.

Future studies should investigate independent longitudinal associations between finer-grained sleep EEG microarchitecture parameters derived from quantitative EEG (qEEG) power spectral analysis (44). These parameters may represent more sensitive early markers of cognitive impairment. Sleep microarchitecture parameters assessed during NREM and REM sleep have been independently associated with TMT performance in cross-sectional analyses among older (≥65 years) community-dwelling men (367). Therefore, longitudinal analyses in community-based cohort samples remain warranted to clarify the prognostic value of qEEG as an early brain-specific cognitive impairment marker to extend findings beyond conventional OSA disease severity and sleep macroarchitecture parameters.

This study has several strengths. It includes a comparatively younger understudied community-based sample representative of an adult male population. Data also included assessment of cognitive function by standardised and validated tests. Moreover, the extensive survey and biomedical data (303, 304, 320) 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 in men, with results in women remaining unknown. The

follow-up response rate over 8–10 years was low, possibly related to the cognitive tests being attached to a follow-up sleep study that was not well received. 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. Consequently, it remains uncertain whether objectively measured OSA and sleep macroarchitecture parameters at baseline are associated with future cognitive function in cognitive domains that were not assessed, which requires further longitudinal investigation.

In summary, among this sample of comparatively younger community-dwelling men, greater mean oxygen saturation at baseline was independently associated with worse TMT-A performance 8–10 years later, whereas a higher % of N1 sleep was independently associated with better TMT-A performance 8–10 years later. However, other routine PSG-derived OSA and sleep macroarchitecture parameters at baseline did not show independent prospective associations with future TMT-A performance. Given that the present study relied on traditional PSG parameters, future longitudinal studies should carefully consider characteristics of OSA and arousal events and non-routine measures of hypoxemia, such as OSA-specific hypoxic burden, which may show associations with cognitive function. Future studies in community-dwelling men and women should also examine performance across more comprehensive cognitive function domains and explore whether sleep microarchitecture parameters assessed through quantitative EEG power spectral analysis have prognostic value for identifying individuals at risk of future cognitive dysfunction.

4.6 Supplementary Tables

Supplementary Table 4.1 Standardised (z-score) TMT-A and TMT-B performance in relation to baseline participant demographic characteristics and OSA and sleep microarchitecture parameters

	TMT-A, baseline	TMT-A, follow-up	TMTA, change	TMT-B, baseline	TMT-B, follow-up	TMT-B, change
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Age (years)						
<50	-0.3 (0.6)	-0.5 (0.4)	-0.5 (0.5)	-0.3 (0.7)	-0.4 (0.7)	-0.3 (0.7)
50–59	-0.1 (0.9)	-0.2 (0.9)	-0.2 (0.9)	-0.1 (0.9)	-0.2 (0.9)	-0.1 (0.9)
60–69	0.08 (1.0)	0.2 (1.0)	0.1 (1.0)	0.2 (1.1)	0.09 (1.1)	-0.03 (1.1)
≥70	0.5 (1.3) *$	0.9 (1.2) *$+	0.8 (1.3) *$	0.2 (1.1)	0.7 (1.1) *$	0.7 (1.2) *$+
p	**0.012**	**<0.001**	**<0.001**	0.061	**<0.001**	**0.004**
Financial stress						
Spends >earns	-0.03 (1.0)	-0.06 (0.9)	-0.06 (0.9)	-0.03 (1.0)	-0.02 (1.0)	-0.005 (1.0)
Save a little/lot	0.2 (1.0)	0.4 (1.3)	0.3 (1.3)	0.2 (1.0)	0.1 (0.9)	0.03 (1.0)
p	0.37	0.15	0.17	0.30	0.59	0.88
Highest educational attainment						
≥Diploma, Certificate, Trade, Bachelor Degree or Higher	-0.04 (1.0)	-0.008 (0.9)	0.009 (0.9)	-0.07 (1.0)	-0.03 (1.0)	0.02 (1.0)
≤High school	0.1 (1.0)	0.02 (1.2)	-0.03 (1.3)	0.2 (1.1)	0.07 (0.9)	-0.05 (0.9)
p	0.34	0.87	0.87	0.12	0.58	0.74
SEIFA IRSD						
Quintile 1 (most socio-economic disadvantage)	-0.2 (0.9)	-0.02 (1.1)	0.04 (1.1)	-0.2 (0.7)	0.05 (1.0)	0.2 (1.1)
Quintile 2	0.4 (1.1)	0.5 (1.3)	0.4 (1.3)	-0.2 (0.9)	0.2 (1.1)	0.3 (1.2)
Quintile 3	-0.08 (1.0)	-0.1 (1.1)	-0.1 (1.1)	0.007 (1.1)	-0.3 (0.7)	-0.3 (0.6)
Quintile 4	0.1 (1.1)	-0.003 (0.8)	-0.04 (0.7)	0.1 (1.1)	0.2 (1.2)	0.1 (1.2)
Quintile 5 (least socio-economic disadvantage)	-0.09 (0.7)	-0.04 (0.7)	-0.01 (0.7)	0.2 (1.1)	-0.02 (0.8)	-0.2 (0.9)
p	0.39	0.27	0.49	0.59	0.25	0.076
Married/partner						
No	0.2 (1.1)	-0.2 (0.6)	-0.3 (0.5)	0.1 (1.3)	0.06 (1.2)	-0.05 (1.0)
Yes	-0.03 (1.0)	0.02 (1.0)	0.04 (1.0)	-0.02 (1.0)	-0.007 (1.0)	0.006 (1.0)
p	0.28	0.38	0.17	0.54	0.80	0.83
OSA severity (AHI)						
<10/h	-0.03 (1.0)	-0.2 (0.7)	-0.2 (0.6)	-0.1 (0.9)	-0.1 (1.0)	-0.08 (1.0)
10–19/h	0.005 (1.0)	0.3 (1.2)	0.3 (1.2)	0.1 (1.0)	0.3 (1.0)	0.2 (1.1)
20–29/h	0.2 (0.9)	0.5 (1.3)	0.4 (1.3)	0.05 (1.0)	-0.07 (0.7)	-0.05 (0.6)
≥30/h	-0.1 (1.2)	-0.3 (0.8) $+	-0.3 (0.7) $+	0.006 (1.4)	-0.2 (1.0)	-0.3 (0.4)
p	0.86	**0.004**	**0.004**	0.70	0.11	0.20
TST90 (%)						
TST90 <4%	-0.08 (0.9)	-0.002 (1.0)	0.03 (1.0)	-0.01 (1.0)	0.02 (1.0)	0.02 (1.0)
TST90 >4%	0.2 (1.1)	0.005 (0.9)	-0.08 (0.9)	0.03 (1.0)	-0.05 (0.9)	-0.06 (0.9)
p	0.093	0.97	0.54	0.80	0.69	0.64
ODI 3 (%)						
<15/h	-0.2 (0.9)	-0.3 (0.8)	-0.2 (0.8)	-0.03 (1.1)	-0.1 (0.8)	-0.2 (0.6)
≥15<30/h	0.03 (0.8)	-0.1 (0.6)	-0.2 (0.6)	-0.2 (0.8)	-0.1 (1.2)	0.03 (1.3)
≥30/h	0.04 (1.1)	0.1 (1.1)	0.1 (1.1)	0.05 (1.0)	0.1 (1.0)	0.03 (1.0)
p	0.54	0.19	0.26	0.62	0.65	0.71
TST (minutes)						
<360	0.2 (1.1)	0.01 (1.0)	-0.06 (1.0)	0.003 (1.1)	-0.05 (1.0)	-0.08 (0.9)

≥360	-0.1 (0.9)	-0.006 (1.0)	0.03 (1.0)	-0.002 (1.0)	0.03 (1.0)	0.05 (1.1)
p	0.10	0.92	0.559	0.98	0.61	0.47

Abbreviations: TMT-A, trail-making test A; TMT-B, trail-making test B; AHI, apnea-hypopnea index; TST90, percentage total sleep time with oxygen saturation <90%; ODI 3%, oxygen desaturation index 3% TST, total sleep time; SEIFA IRSD, Socio-Economic Indexes for Areas Index of Relative Socio-Economic Disadvantage; *SD*, standard deviation; IQR, interquartile range.
Legend: p-values representing statistically significant between-groups differences boldfaced.
Symbol legends (age): *One-way ANOVA post-hoc significantly different from <50 years; $One-way ANOVA post-hoc significantly different from 50–59 years; +One-way ANOVA post-hoc significantly different from 60–69 years.
Symbol legends (OSA): $One-way ANOVA post-hoc significantly different from AHI 10-19/h; +One-way ANOVA post-hoc significantly different from AHI 20-29/h.
Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

Supplementary Table 4.2 Standardised (z-score) TMT-A and TMT-B performance in relation to baseline participant chronic disease risk factors and disease conditions

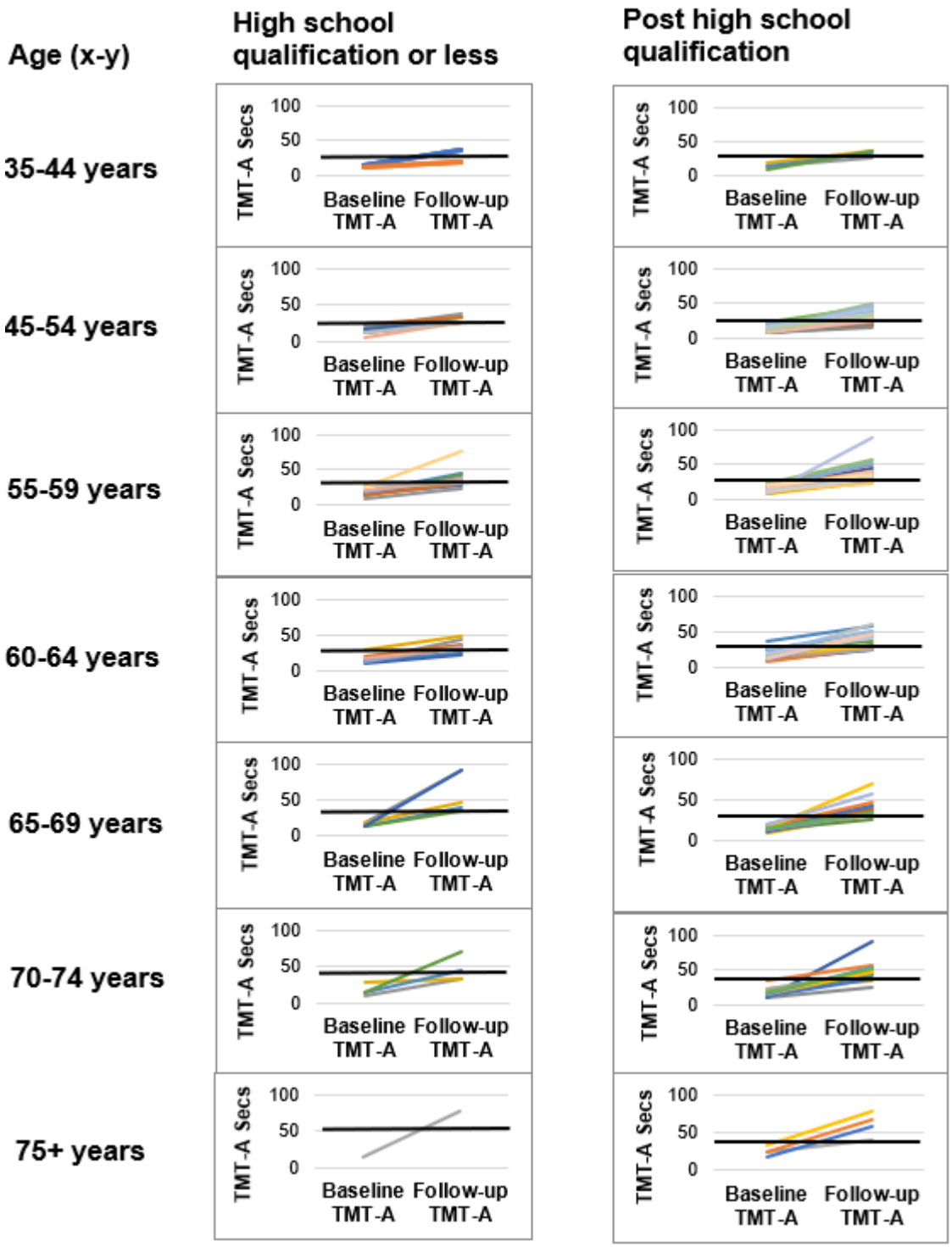
	TMT-A, baseline	TMT-A, follow-up	TMT-A, change	TMT-B, baseline	TMT-B, follow-up	TMT-B, change
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
BMI (kg/m^2)						
<25 (under/normal)	0.1 (1.2)	-0.09 (1.0)	-0.1 (1.1)	0.02 (0.9)	-0.1 (1.0)	-0.1 (1.0)
25 to <30 (overweight)	0.01 (1.1)	0.04 (0.9)	0.04 (0.9)	0.04 (1.1)	0.2 (1.1)	0.2 (1.1)
≥30 (obese)	-0.08 (0.8)	-0.004 (1.1)	0.03 (1.1)	-0.06 (0.9)	-0.2 (0.8)	-0.1 (0.8)
p	0.68	0.83	0.67	0.84	0.17	0.22
Smoking status						
Never/former	-0.04 (0.9)	0.03 (1.0)	0.04 (1.0)	0.002 (1.0)	-0.005 (1.0)	-0.006 (1.0)
Current	0.2 (1.3)	-0.2 (0.7)	-0.3 (0.6)	-0.001 (0.8)	0.03 (1.0)	0.03 (0.7)
p	0.27	0.42	0.19	0.96	0.87	0.86
Cardiovascular disease						
No	-0.005 (1.0)	-0.03 (1.0)	-0.03 (1.0)	-0.02 (1.0)	-0.009 (1.0)	0.003 (1.0)
Yes	0.1 (1.0)	0.5 (1.6)	0.5 (1.7)	0.3 (1.4)	0.2 (1.2)	-0.06 (0.7)
p	0.77	0.37	0.39	0.36	0.64	0.85
Diabetes mellitus						
No	-0.03 (1.0)	-0.04 (1.0)	-0.03 (1.0)	-0.07 (1.0)	-0.07 (1.0)	-0.02 (1.0)
Yes	0.1 (0.9)	0.2 (1.1)	0.1 (1.2)	0.3 (1.2)	0.3 (1.0)	0.1 (1.2)
p	0.48	0.32	0.42	0.059	0.068	0.52
Insomnia						
No	-0.05 (1.0)	-0.03 (1.0)	-0.02 (1.0)	-0.04 (1.0)	-0.04 (1.0)	-0.02 (1.0)
Yes	0.4 (1.0)	0.3 (1.0)	0.1 (0.8)	0.3 (0.7)	0.3 (1.0)	0.1 (1.2)
p	0.095	0.25	0.56	0.20	0.17	0.55
Hypertension						
No	0.004 (1.0)	-0.2 (0.9)	-0.2 (0.9)	-0.1 (0.9)	-0.01 (1.0)	0.07 (1.0)
Yes	-0.003 (1.0)	0.1 (1.0)	0.1 (1.0)	0.09 (1.1)	0.007 (1.0)	-0.05 (1.0)
p	0.97	0.10	0.074	0.20	0.91	0.45
Cardio-metabolic conditions						
No	-0.04 (1.0)	-0.2 (0.9)	-0.2 (0.9)	-0.1 (0.9)	-0.04 (1.0)	0.04 (1.0)
Yes	0.03 (1.0)	0.1 (1.0)	0.1 (1.0)	0.08 (1.1)	0.03 (1.0)	-0.02 (1.0)
p	0.66	0.056	0.059	0.20	0.66	0.71

Alcohol risk						
Non-low	-0.03 (1.0)	-0.01 (1.0)	0.002 (1.0)	-0.02 (1.0)	-0.02 (1.0)	-0.006 (1.0)
Medium-very high	0.3 (1.3)	0.07 (0.7)	-0.03 (0.6)	0.1 (1.0)	0.2 (1.2)	0.1 (1.2)
p	0.32	0.78	0.93	0.66	0.48	0.64
Physical activity level						
Sedentary behaviour	-0.2 (0.8)	-0.01 (1.0)	0.04 (1.0)	0.07 (1.0)	-0.1 (0.8)	-0.2 (0.9)
Low/moderate/vigorous	0.03 (1.0)	0.003 (1.0)	-0.01 (1.0)	-0.02 (1.0)	0.03 (1.0)	0.06 (1.0)
p	0.37	0.93	0.79	0.66	0.39	0.15
Psychoactive medication(s)						
No	-0.03 (1.0)	0.0008 (1.0)	0.01 (1.0)	-0.005 (1.0)	-0.003 (1.0)	-0.04 (1.0)
Yes	0.3 (1.2)	-0.009 (0.6)	-0.1 (0.5)	0.05 (1.0)	0.3 (1.1)	0.4 (1.4)
p	0.18	0.97	0.57	0.85	0.18	0.16
ESS ≥11						
No	0.03 (1.0)	-0.03 (1.0)	-0.05 (0.9)	-0.03 (1.0)	-0.005 (1.0)	0.008 (1.0)
Yes	-0.2 (0.8)	0.03 (0.9)	0.1 (1.1)	0.006 (0.7)	0.04 (1.0)	0.04 (1.0)
p	0.26	0.77	0.44	0.86	0.82	0.89

Abbreviations: TMT-A, trail-making test A; TMT-B, trail-making test B; ESS, Epworth Sleepiness Scale; BMI, body mass index; *SD*, standard deviation; IQR, interquartile range.
BMI: body mass index categorised according to international criteria (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 kg/m^2 [obese]).
Cardiovascular disease: self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke.
Diabetes mellitus: self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L [126 mg/dL], haemoglobin A1C ≥6.5%, or reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).
Insomnia: difficulty initiating or maintaining sleep occurring at least three nights/week (PSQI dimensions) and significant daytime fatigue defined as an SF-36 Vitality Scale score one standard deviation below the mean.
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.
Psychoactive medication(s): self-reported use of one or more of opiates, antipsychotics, antiepileptics, antidepressants, or benzodiazepines.
Legend: p-values representing statistically significant between-groups differences boldfaced.
Symbol legends: *One-way ANOVA post-hoc significantly different from <50 years; $One-way ANOVA post-hoc significantly different from 50–59 years; +One-way ANOVA post-hoc significantly different from 60–69 years.

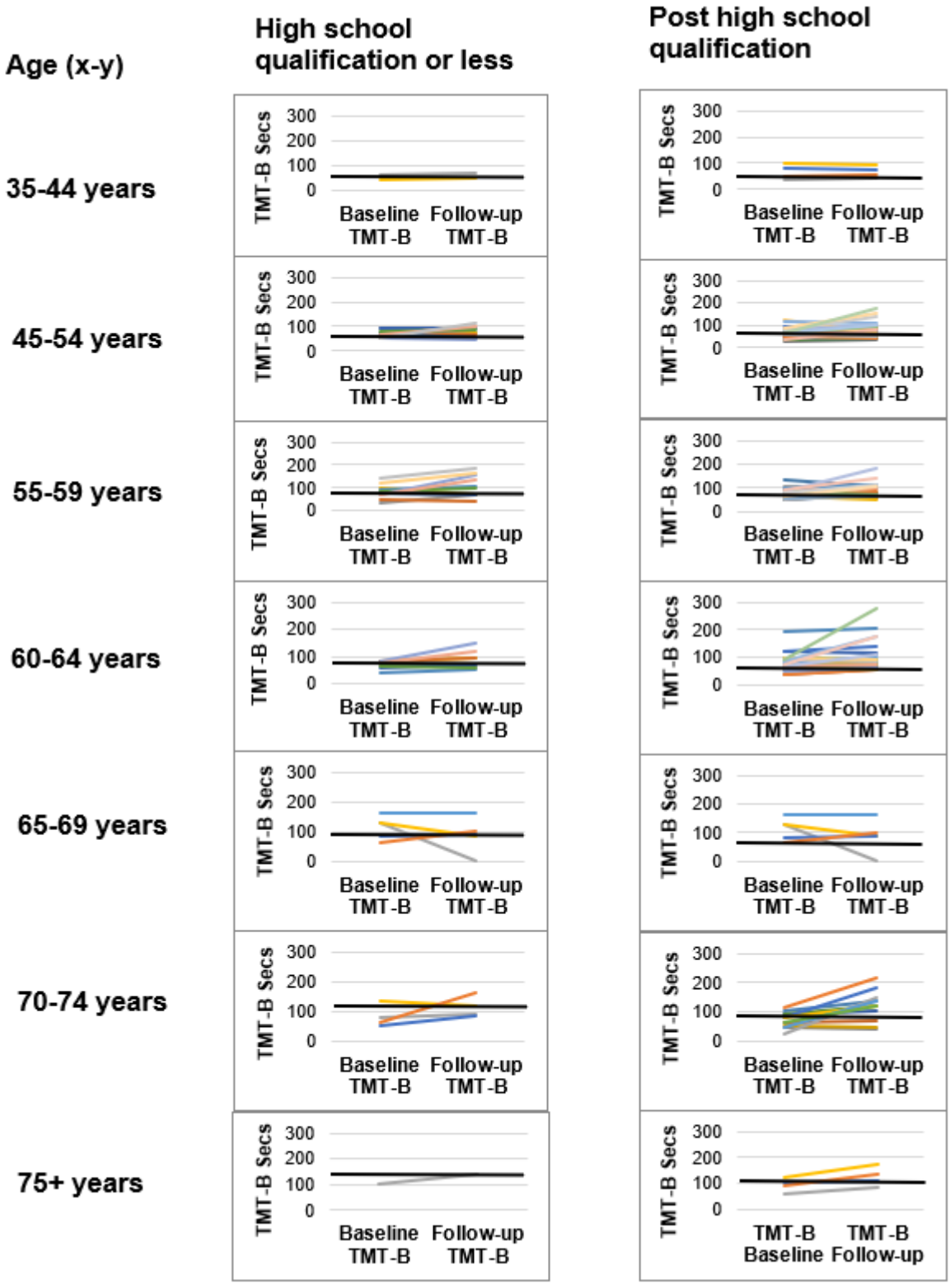
4.7 Supplementary Figures

Supplementary Figure 4.1 Baseline and follow-up TMT-A times relative to normative values of age and highest educational attainment



Black lines represent previously reported normative TMT-A scores relative to age and educational attainment. Categories: 35–44 years, high school qualification or less [n=2] and post high school qualification [n=4]; 45–54 years, high school qualification or less [n=9] and post high school qualification [n=36]; 55–59 years, high school qualification or less [n=10] and post high school qualification [n=22]; 60–64 years, high school qualification or less [n=8] and post high school qualification [n=26]; 65–69 years, high school qualification or less [n=5] and post high school qualification [n=13]; 70–74 years, high school qualification or less [n=4] and post high school qualification [n=12]; and 75+ years, high school qualification or less [n=1] and post high school qualification [n=4]).

Supplementary Figure 4.2 Baseline and follow-up TMT-B times relative to normative values of age and highest educational attainment



Black lines represent previously reported normative TMT-B scores relative to age and educational attainment. Categories: 35–44 years, high school qualification or less [n=2] and post high school qualification [n=4]; 45–54 years, high school qualification or less [n=9] and post high school qualification [n=36]; 55–59 years, high school qualification or less [n=10] and post high school qualification [n=22]; 60–64 years, high school qualification or less [n=8] and post high school qualification [n=26]; 65–69 years, high school qualification or less [n=5] and post high school qualification [n=13]; 70–74 years, high school qualification or less [n=4] and post high school qualification [n=12]; and 75+ years, high school qualification or less [n=1] and post high school qualification [n=4]).

CHAPTER 5. THE ASSOCIATION BETWEEN OBSTRUCTIVE SLEEP APNEA AND SLEEP SPINDLES IN MIDDLE-AGED AND OLDER MEN: A COMMUNITY-BASED COHORT STUDY

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and was primarily responsible for research design (70%), data collection and analysis (80%), and writing and editing (80%). My supervisors and the wider author group assisted with manuscript editing and revisions and all authors approved the final version.

5.1 Abstract

Study objectives: Sleep spindles show morphological changes in obstructive sleep apnea (OSA). However, previous small studies have limited generalisability, leaving associations between OSA severity measures and spindle metrics uncertain. This study examined cross-sectional associations between OSA severity measures and spindle metrics among a large population-based sample of men.

Methods: Community-dwelling men with no previous OSA diagnosis underwent home-based polysomnography. All-night EEG (F4-M1) recordings were processed for artefacts and spindle events identified using previously validated algorithms. Spindle metrics of interest included frequency (Hz), amplitude (μV^2), overall density (11–16 Hz), slow density (11–13 Hz), and fast density (13–16 Hz) (number/minute). Multivariable linear regression models controlling for demographic, biomedical, and behavioural confounders were used to examine cross-sectional associations between OSA severity measures and spindle metrics.

Results: In adjusted analyses, higher apnea-hypopnea index (AHI/h, as a continuous variable) and percentage total sleep time with oxygen saturation <90% (TST90) were associated with decreased slow spindle density (AHI, *B*= -0.003, p=0.032; TST90, *B*= -0.004, p=0.047) but increased frequency (AHI, *B*=0.002, p=0.009; TST90, *B*=0.002, p=0.043). Higher TST90 was also associated with greater spindle amplitude (N2 sleep, *B*=0.04, p=0.011; N3 sleep, *B*=0.11, p<0.001). Furthermore, higher arousal index was associated with greater spindle amplitude during N2 sleep (*B*=0.31, p<0.001) but decreased overall density (*B*= -1.27, p=0.030) and fast density (*B*= -4.36, p=0.028) during N3 sleep.

Conclusions: Among this large population-based sample of men, OSA severity measures were independently associated with spindle abnormalities. Further

population studies are needed to determine associations between spindle metrics and functional outcomes.

5.2 Introduction

Obstructive sleep apnea (OSA) is characterised by recurrent pharyngeal collapse leading to intermittent hypoxemia and sleep fragmentation (81, 82). Sleep macroarchitecture abnormalities observed by visual electroencephalogram (EEG) analysis, including decreased slow-wave sleep and rapid eye movement (REM) sleep, are reported in patients with OSA (292). This conventional approach based on manual EEG scoring superficially quantifies electrical brain activity and consequently may miss clinically informative finer-grained electrophysiological information (44). Emerging evidence suggests that sleep microarchitecture parameters assessed using quantitative EEG power spectral analysis could provide clinically useful information regarding functional and health-associated impacts of OSA-related sleep disruption (34, 44).

Sleep spindles are particularly prominent sleep microarchitecture parameters observed during non-REM (NREM) sleep consisting of waxing and waning neuronal activity that generate 11–16 Hz EEG oscillations (280). Spindles predominantly occur during N2 and less frequently during N3 sleep (269, 280) and are thought to represent thalamocortical network integrity and cortical reorganisation processes involved in learning and overnight memory consolidation (48, 271). Accordingly, spindle morphologies could provide cognitive function markers (280, 283).

Previous small studies consistently report decreased overall spindle density (11–16 Hz, number/minute), frontal slow spindle density (11–13 Hz, number/minute), centroparietal fast spindle density (13–16 Hz, number/minute), and overall spindle frequency in clinical samples of patients with OSA compared to age- or gender-matched controls (44, 46, 283, 368). Some evidence also suggests spindle abnormalities partly improve with OSA therapy, including increased spindle density in the central bilateral hemisphere and a greater spindle occurrence (11–16 Hz, count) across NREM sleep after treatment with continuous positive airway pressure (CPAP) (368, 369). Himanen et al. (46) recruited 12 patients (6 males and 6 females) with obstructive sleep apnea syndrome (OSAS, OSA associated with excessive

daytime sleepiness) and 12 age- and sex-matched healthy control subjects and identified that patients with OSA showed a pattern of significantly slower spindle frequency compared to the matched control group, which remained consistent throughout the night. Furthermore, several small studies showed associations of a greater number of obstructive breathing episodes with reduced spindle deceleration and decreased spindle density (47, 370, 371). The small sample size and recruitment of patients with OSA limits the generalisability of the findings to the broader population, leaving the significance of cross-sectional associations between OSA severity measures and spindle metrics uncertain.

No large, well-characterised community-based cohort studies have examined the effect of objectively measured OSA severity measures on spindle morphologies. Therefore, the aim of this study was to investigate independent cross-sectional associations between three OSA severity measures (AHI, TST90, and arousal index) and five spindle metrics (average frequency, amplitude, overall density, slow density, and fast density) among a large community-based sample of men. It was hypothesised that markers of more severe OSA would be independently associated with spindle metrics.

5.3 Methods

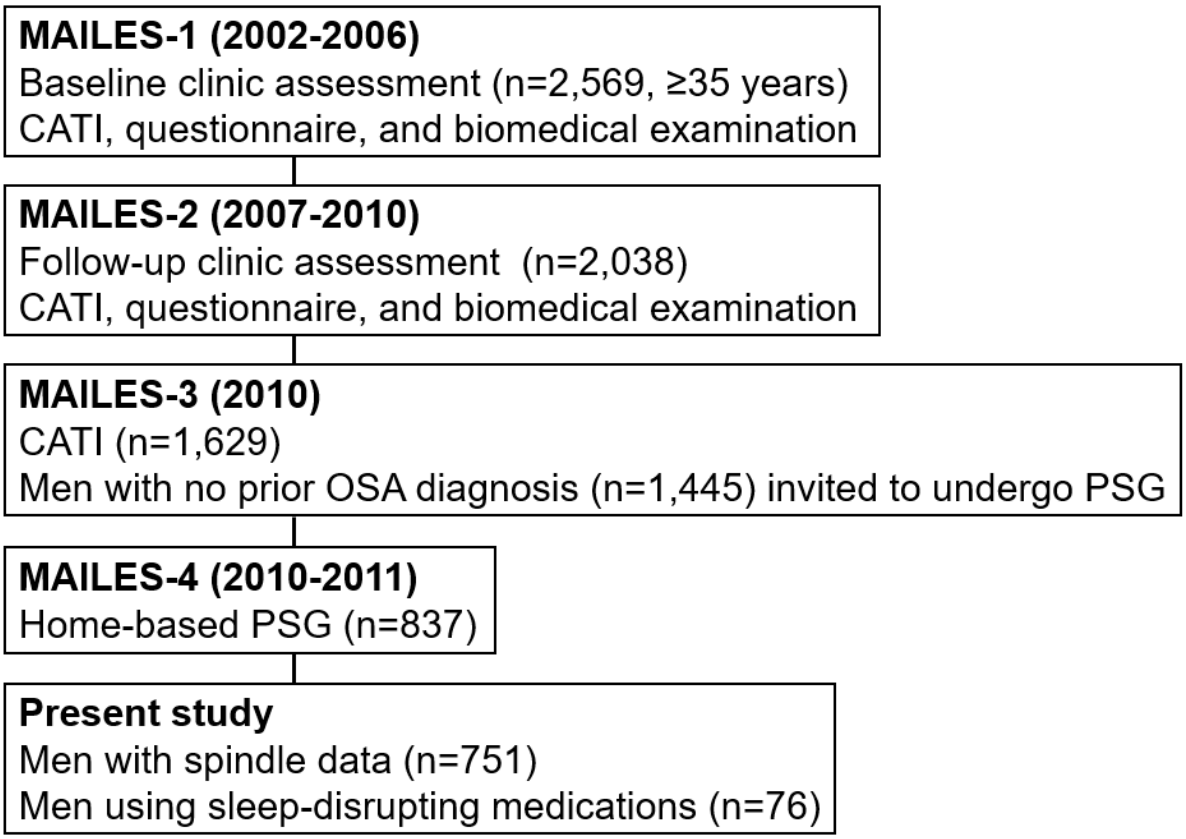
5.3.1 Study participants

The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study includes unselected urban community-dwelling men (n=2,569) ≥35 years at baseline (2002–2006) of predominantly Australian or European descent (96%) (303). The overarching aim of the MAILES study is to investigate the effect of sex steroids, inflammation, environmental, and biopsychosocial factors on cardio-metabolic disease risk in men.

During a computer-assisted telephone interview follow-up in 2010, 1,629 men were asked, “have you ever been diagnosed with OSA with a sleep study?” Men who responded “yes” (n=184) were considered to have previously diagnosed OSA and were not asked to undertake a further sleep study. Men who responded “no” (n=1,445) were invited to undergo eight-channel home-based polysomnography

(PSG) from which 75.2% (n=1,087) agreed to participate. Of these, 837 sleep studies were completed (Figure 5.1). The MAILES study was conducted in accordance with the Declaration of Helsinki and approved by the Human Research Ethics Committees of the North West Adelaide Health Service (approval number: 2010054). All participants provided written informed consent.

Figure 5.1 MAILES Study clinical and sleep study assessments



MAILES, Men Androgen Inflammation Lifestyle Environment and Stress. CATI, computer-assisted telephone interview. PSG, polysomnography.

5.3.2 Sleep study assessment

Participants underwent eight-channel home-based ambulatory PSG (Embletta X100, Embla Systems, Broomfield, Colorado, USA), which recorded electrical brain activity (EEG, F4-M1) and left electrooculography with 12-bit signal resolution, 200 Hz sampling rate, and band-pass filters (0.3–35 Hz) along with submental electromyography, nasal cannula pressure, thoracic and abdominal motion, finger pulse oximetry, and body position. Trained staff set-up and attached the sleep study

equipment, administered the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scale (ESS), and obtained anthropometric measures (height, weight, and body mass index [BMI, kg/m^2]).

A single experienced sleep technician manually scored all PSG measures according to 2007 American Academy of Sleep Medicine (AASM) *Alternative* scoring criteria, recommended by an expert panel of the Australasian Sleep Association for use in prospective epidemiological studies (321). OSA was identified by an apnea-hypopnea index (AHI) ≥10/h and further categorised as mild (10–19/h), moderate (20–29/h), or severe (≥30/h). Ruehland et al. (32) have shown that an AHI of 5/h used to define sleep-disordered breathing by the *Recommended* criteria is approximately equivalent to 10/h using the *Alternative* criteria and 15/h using the older 1999 *Chicago* criteria. Therefore, an AHI cut-off of 10/h was chosen to maintain comparability with previous work. Apnea was defined as a complete or near-complete airflow cessation (≥90%) measured using nasal cannula pressure excursions with breathing lasting ≥10 seconds. Hypopnea was defined as a ≥50% decrease in nasal cannula pressure excursions with an associated ≥3% oxygen desaturation or EEG arousal (32). Sleep hypoxemia was assessed from the percentage of total sleep time with oxygen saturation <90% (TST90). Acceptable sleep studies were those with ≥3.5 h of sleep and ≥5.5 h of total-recorded study time with technically acceptable respiratory and EEG signals for the majority of the recording.

5.3.3 Sleep spindle detection algorithm

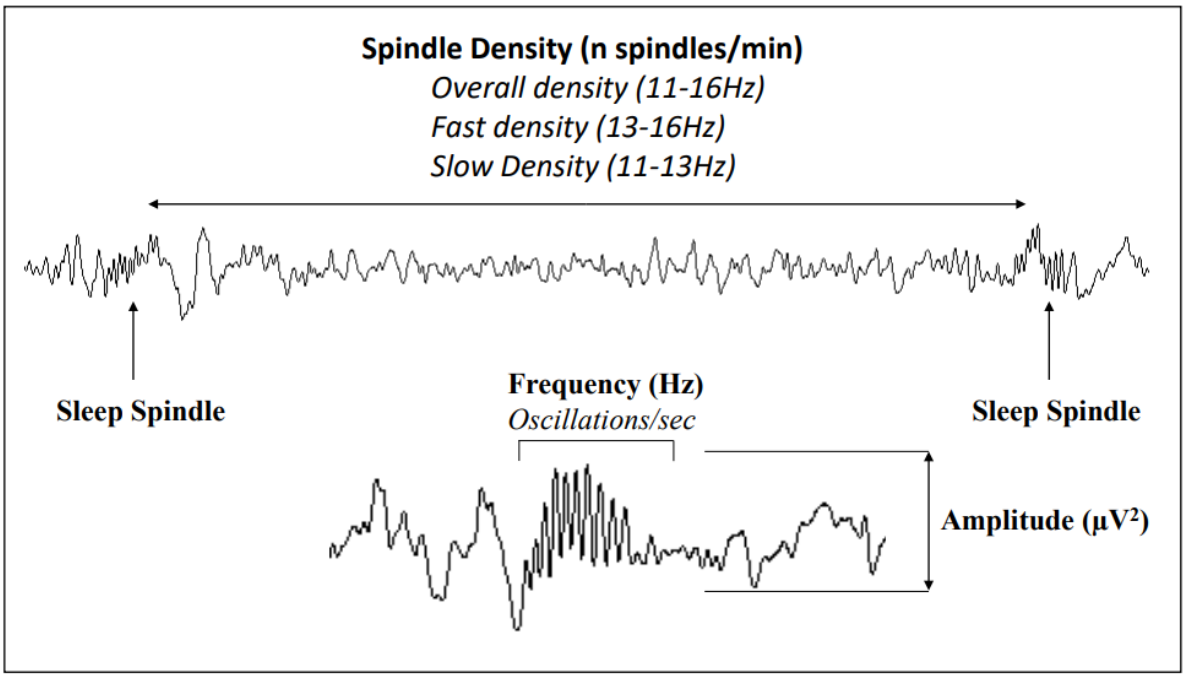
All PSGs were exported to standardised European Data Format, from which overnight F4-M1 EEG recordings underwent automated artefact detection using a previously validated algorithm (372). Spindle events were identified using an automated detection tool developed and written in Java, version 1.6 (Oracle, Santa Clara, California, USA) and previously validated in OSA samples (373). A 128-order band-passing Finite-Impulse-Response filter was applied to the raw EEG signal, yielding a time course of sigma activity (11–16 Hz, ≥0.5 and ≤3 seconds). An algorithm identified artefactual EEG data over consecutive non-overlapping 5-second epochs based on previously validated artefact detection threshold

parameters (372), and contaminated epochs were subsequently excluded from the analysis.

5.3.4 Sleep spindle metrics

Average spindle frequency (Hz), spindle amplitude (µV), overall spindle density (11–16 Hz), slow spindle density (11–13 Hz), and fast spindle density (13–16 Hz) (number of spindle events/artefact-free sleep minutes) were calculated for N2 and N3 sleep. Average spindle frequency was determined from the number of spindle cycles per second, whereas amplitude was calculated by measuring from the base to the maximum height of the spindle. Figure 5.2 illustrates sleep spindles depicting the various metrics of interest (frequency, amplitude, and density).

Figure 5.2 Examples of sleep spindles depicting the various spindle metrics of interest (frequency, amplitude, and densities)



Of the 837 men who underwent sleep studies, spindle data were of adequate quality for analysis in 751. Spindle data in 86 men were excluded due to absence of a SaO_2 trace (n=14), insufficient sleep (<4 h, n=35), absence of or poor nasal or thoracic/abdominal traces (n=3), poor traces (n=2), all traces failing (n=3), and outliers identified before signal processing and subsequently determined to be the result of bad EEG quality (n=28).

5.3.5 Covariate assessments

MAILES clinic assessments (303) included assessment of smoking and alcohol use by self-report and depressive symptoms identified with the Centre for Epidemiological Studies Depression Scale (score ≥16) or Beck Depression Inventory-1a (score ≥13). The 36-Item Short Form Survey Instrument (SF-36) Physical and Mental Component Summary scales were calculated to generate a mean of 50 with a standard deviation (*SD*) of 10. BMI was categorised according to international criteria (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 kg/m² [obese]) (308). Clinic assessment (2007–2010) included anthropometry (BMI and waist circumference), seated sphygmomanometer blood pressure, and a fasting blood sample. Composite cardiovascular disease (self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke) and diabetes mellitus (self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L [126 mg/dL], haemoglobin A1C [≥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 at least three nights/week (PSQI dimensions) and significant daytime fatigue, defined as an SF-36 Vitality Scale score one *SD* below the mean (310). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use (311). Sleep-disrupting medications recorded on the night of the sleep study included opiates, antipsychotics, antiepileptics, antidepressants, and benzodiazepines.

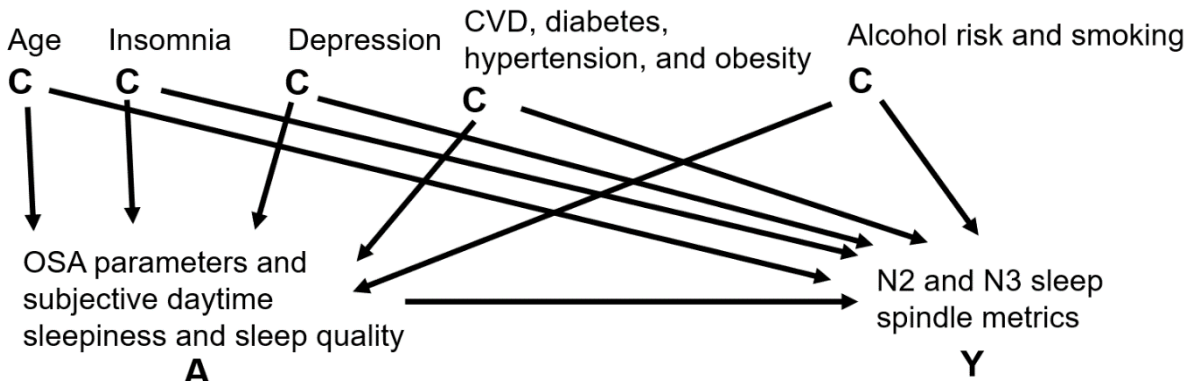
5.3.6 Statistical analysis methodology

Data were analysed using IBM SPSS version 25.0 (IBM Corporation, Armonk, New York, USA). Descriptive statistics are presented as mean (*SD*) for continuous variables and percentage (proportion) for categorical variables. Differences in population characteristics concerning clinical OSA categories (none, mild, moderate, and severe) were determined by Pearson’s chi-squared tests for categorical variables and one-way analysis of variance (ANOVA) for continuous variables, including Bonferroni correction for multiple comparisons.

Univariable and multivariable linear regression models were used to examine associations between OSA severity measures and N2 and N3 sleep spindle metrics. Unstandardised beta (*B*) coefficients (95% confidence interval [CI]) are reported. Two regression models were developed: an unadjusted model and an adjusted model, including age, BMI, diabetes, alcohol risk, smoking, hypertension, cardiovascular disease, insomnia, and depression. Linear regression analyses were performed to determine if OSA severity measures were independently associated with sleep spindle metrics. Equal variances were observed between OSA severity measures and spindle metrics, representing homoscedasticity. Furthermore, variance inflation factor values were near 1 for all covariates, representing an absence of multicollinearity. Linear regression analyses treated AHI as a continuous exposure variable and an exposure variable with clinical OSA categories (none, mild, moderate, and severe). TST90 was used to assess sleep hypoxemia as the oxygen desaturation index was highly colinear with AHI. The filter function in SPSS was used to ensure only participants with complete case cognition, PSG, and covariate data were included in the final analysis.

As a supplementary analysis, associations between subjective sleep quality (PSQI) and daytime sleepiness (ESS) and spindle metrics were examined, with PSQI and ESS treated as continuous exposure variables in linear regression analyses adjusted for the same covariates mentioned previously with the addition of AHI. Clinical cut-offs were also used to examine associations of poor sleep quality (PSQI ≥5) and excessive daytime sleepiness (ESS ≥11) with clinical OSA severity categories. For all analyses, a two-sided $p<0.05$ was considered statistically significant. Multiple comparison adjustments were not performed (346, 347).

Figure 5.3 Overview of relationships between variables



Legend: A=exposure/treatment/intervention/primary independent variable, C=confounder, Y=outcome variable.

5.4 Results

5.4.1 Participant characteristics

Analyses were conducted in 675 men after excluding 76 (10.1%) who reported using one or more sleep-disrupting medications. The prevalence of OSA (AHI ≥10/h) was 50.9%, and 11.7% had severe OSA (AHI ≥30/h). Participant characteristics overall and by clinical OSA categories are reported in Table 5.1. Men with severe OSA were older, more obese, had a higher incidence of diabetes, hypertension, cardiovascular disease, and depression, and more were current smokers compared to men without OSA (AHI <10/h).

Table 5.1 Participant characteristics overall and by clinical OSA categories

Participant characteristics	AHI <10/h (n=331)	AHI 10–19/h (n=174)	AHI 20–29/h (n=91)	AHI ≥30/h (n=79)	Overall sample (n=675)
Demographic and biomedical					
Mean (*SD*)					
Age (years)	57.6 (10.5)	60.6 (10.8)	60.7 (10.1)	62.5 (11.5) *****	59.4 (10.8)
BMI (kg/m^2)	27.6 (3.8)	28.3 (3.9)	29.0 (4.0)	30.6 (4.6) ***+**	28.3 (4.1)
% (n)					
Diabetes	12.4 (41)	20.3 (35)	12.4 (11)	27.6 (21) **#**	16.2 (16)
Hypertension	32.6 (108)	47.0 (79)	47.2 (42)	39.4 (28) **#**	39.2 (257)
Cardiovascular disease	5.7 (19)	7.5 (13)	11.0 (10)	11.4 (9) **#**	7.6 (51)
Current smokers	17.1 (56)	9.4 (16)	20.2 (18)	5.3 (4) **#**	14.2 (94)
Med-very high alcohol risk	3.3 (11)	7.5 (13)	5.6 (5)	2.5 (2)	4.6 (31)
Respiratory events					
% (n)					
TST90 ≥4%	11.6 (38)	20.1 (35)	38.5 (35)	51.9 (41) **#**	22.1 (149)
Mean (*SD*)					
Arousal index	15.0 (6.2)	17.6 (5.8)	22.2 (7.1)	27.6 (9.6) ***+$**	18.1 (7.9)
Sleep macroarchitecture					
Mean (*SD*)					
Total sleep time, minutes	373.8 (59.3)	374.1 (53.3)	380.5 (52.9)	370.9 (49.4)	374.4 (55.8)
NREM sleep time, minutes	316.2 (53.4)	317.3 (47.3)	323.9 (47.8)	319.4 (46.1)	317.9 (50.3)
Daytime dysfunction					
% (n)					
Insomnia	10.0 (33)	12.1 (21)	8.8 (8)	13.9 (11)	10.8 (73)
Depression	5.4 (17)	8.5 (14)	9.3 (8)	12.3 (9) **#**	7.5 (48)
ESS ≥11 (EDS)	11.8 (39)	14.8 (22)	12.9 (12)	12.0 (9)	12.1 (82)
PSQI ≥5 (poor sleep quality)	45.0 (149)	39.7 (69)	40.7 (37)	57.0 (45)	44.4 (300)
N2 sleep spindle metrics					
Mean (*SD*)					
Average frequency (Hz)	12.8 (0.3)	12.8 (0.3)	12.8 (0.3)	12.9 (0.3) *****	12.8 (0.3)
Amplitude (μV)	13.7 (3.3)	13.6 (4.5)	13.8 (3)	14.3 (4)	13.7 (3.7)
Overall density (11–16 Hz)	1.1 (0.7)	1.0 (0.7)	1.0 (0.6)	0.9 (0.6) *****	1.0 (0.7)
Fast density (13–16 Hz)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.4 (0.4)	0.4 (0.3)
Slow density (11–13 Hz)	0.7 (0.5)	0.6 (0.5)	0.6 (0.5)	0.5 (0.4) *****	0.7 (0.5)
N3 sleep spindle metrics					
Average frequency (Hz)	12 (2.6)	11.9 (2.8)	12.1 (2.3)	11.1 (4.3)	11.9 (2.9)
Amplitude (μV)	12.5 (6.2)	12.8 (7.5)	12.3 (4)	13.2 (8.5)	12.6 (6.6)
Overall density (11–16 Hz)	0.6 (0.6)	0.5 (0.5)	0.5 (0.5)	0.4 (0.5) *****	0.5 (0.6)
Fast density (13–16 Hz)	0.1 (0.1)	0.1 (0.1)	0.1 (0.1)	0.1 (0.2)	0.1 (0.2)
Slow density (11–13 Hz)	0.5 (0.6)	0.4 (0.4)	0.4 (0.4)	0.3 (0.3) *****	0.4 (0.5)

Abbreviations: AHI, apnea-hypopnea index; TST90, percentage total sleep time with oxygen saturation <90%; NREM, non-rapid eye movement sleep; N2, stage 2 sleep; N3, stage 3 sleep; ESS, Epworth Sleepiness Scale; EDS, excessive daytime sleepiness; PSQI, Pittsburgh Sleep Quality Index; BMI, body mass index; *SD*, standard deviation.
BMI: body mass index.
Diabetes: self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L (126 mg/Dl), haemoglobin A1C ≥6.5%, or reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).
Insomnia: at least one of two PSQI dimensions (difficulty initiating or maintaining sleep) and significant daytime fatigue defined as an SF-36 Vitality Scale score one *SD* below the mean.
Depression: depressive symptoms were identified with the Centre for Epidemiological Studies Depression scale (score ≥16) or Beck Depression Inventory-1a (score ≥13).
Hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use.
Cardiovascular disease: self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke.
Symbol legends: *One-way ANOVA p<0.05 compared with AHI <10/h; +One-way ANOVA p<0.05 compared with AHI 10–19/h; $One-way ANOVA p<0.05 compared with AHI 20–29/h; #Pearson's chi-squared test p<0.05 compared with AHI <10/h.

Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

5.4.2 Spindle metrics

Overall and slow spindle density during N2 and N3 sleep were lower in men with severe OSA compared to those without OSA. Furthermore, average spindle frequency during N2 sleep was higher in men with severe OSA compared to those without OSA (Table 5.1). Older age, diabetes, and hypertension were associated with lower spindle density during N2 sleep (Supplementary Table 5.1). Moreover, older age and diabetes were associated with lower average spindle frequency and overall spindle density during N3 sleep (Supplementary Table 5.2).

5.4.3 Associations between AHI and spindle metrics

Unadjusted and adjusted associations between AHI and spindle metrics are reported in Table 5.2. In unadjusted analyses, a higher AHI was associated with increased average spindle frequency but reduced overall and slow spindle density during N2 sleep. A higher AHI was also associated with decreased overall and slow spindle density and average spindle frequency during N3 sleep. In adjusted analyses, associations of a higher AHI with increased average spindle frequency and decreased slow spindle density during N2 sleep persisted. The same adjusted associations were seen in models using clinical OSA severity categories (Supplementary Table 5.3).

Table 5.2 Covariate unadjusted and adjusted associations between continuous AHI and spindle metrics

	Unadjusted Model		Adjusted Model	
	B (95% CI)	*p*	*B* (95% CI)	*p*
N2 sleep spindle metrics				
Average frequency (Hz)	0.002 (0.001, 0.004)	**0.003**	0.002 (0.001, 0.004)	**0.009**
Amplitude (μV)	0.01 (-0.006, 0.03)	0.18	0.02 (-0.003, 0.04)	0.088
Overall density (11–16 Hz)	-0.007 (-0.01, -0.004)	**<0.001**	-0.002 (-0.006, 0.002)	0.29
Fast density (13–16 Hz)	-0.001 (-0.003, 0.001)	0.37	0.001 (-0.001, 0.003)	0.21
Slow density (11–13 Hz)	-0.006 (-0.009, -0.004)	**<0.001**	-0.003 (-0.006, 0.000)	**0.032**
N3 sleep spindle metrics				
Average frequency (Hz)	-0.02 (-0.03, 0.000)	**0.046**	-0.005 (-0.02, 0.01)	0.56
Amplitude (μV)	0.006 (-0.03, 0.04)	0.73	0.01 (-0.03, 0.06)	0.50
Overall density (11–16 Hz)	-0.004 (-0.007, -0.001)	**0.010**	-0.001 (-0.005, 0.002)	0.47
Fast density (13–16 Hz)	0.001 (0.000, 0.001)	0.17	0.001 (0.000, 0.002)	0.052
Slow density (11–13 Hz)	-0.005 (-0.007, -0.002)	**0.001**	-0.002 (-0.005, 0.001)	0.15

Abbreviations: N2, stage 2 sleep; N3, stage 3 sleep; CI, confidence interval.
Coefficients: unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates: represent the change in spindle metrics corresponding to a one-unit increase in AHI/h.
Statistical adjustment: multivariable linear regression models were adjusted for age, BMI, diabetes mellitus, alcohol risk, smoking, hypertension, cardiovascular disease, insomnia, and depression.
Legend: p-values representing significant associations boldfaced.

5.4.4 Associations between TST90 and spindle metrics

Unadjusted and adjusted associations between TST90 and spindle metrics are reported in Table 5.3. In unadjusted analyses, a higher TST90 was associated with decreased overall and slow spindle density during N2 and N3 sleep. A higher TST90 was also associated with greater spindle amplitude but decreased slow spindle density during N3 sleep. In adjusted analyses, associations of a higher TST90 with decreased slow spindle density and increased average spindle frequency during N2 sleep and greater spindle amplitude during N3 sleep persisted, plus a new association of a higher TST90 with greater spindle amplitude during N2 sleep emerged.

Table 5.3 Covariate unadjusted and adjusted associations between TST90 and spindle metrics

	Unadjusted Model		Adjusted Model	
	B (95% CI)	*p*	*B* (95% CI)	*p*
N2 sleep spindle metrics				
Average frequency (Hz)	0.002 (0.000, 0.004)	0.076	0.002 (0.000, 0.004)	**0.043**
Amplitude (μV)	0.03 (-0.001, 0.05)	0.058	0.04 (0.008, 0.06)	**0.011**
Overall density (11–16 Hz)	-0.009 (-0.01, -0.004)	**<0.001**	-0.003 (-0.008, 0.001)	0.17
Fast density (13–16 Hz)	-0.002 (-0.004, 0.000)	0.11	-0.001 (-0.002, 0.003)	0.74
Slow density (11–13 Hz)	-0.007 (-0.01, -0.003)	**<0.001**	-0.004 (-0.007, 0.000)	**0.047**
N3 sleep spindle metrics				
Average frequency (Hz)	-0.01 (-0.03, 0.01)	0.33	0.01 (-0.01, 0.03)	0.34
Overall density (11–16 Hz)	-0.005 (-0.009, -0.001)	**0.010**	-0.003 (-0.007, 0.001)	0.18
Amplitude (μV)	0.07 (0.02, 0.12)	**0.004**	0.11 (0.06, 0.16)	**<0.001**
Fast density (13–16 Hz)	-0.001 (-0.002, 0.000)	0.61	-0.001 (-0.001, 0.001)	0.99
Slow density (11–13 Hz)	-0.005 (-0.008, -0.001)	**0.007**	-0.003 (-0.006, 0.001)	0.13

Abbreviations: N2, stage 2 sleep; N3, stage 3 sleep; CI, confidence interval.
Coefficients: unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates: estimates represent the change in spindle metrics corresponding to a one-unit increase in TST90.
Statistical adjustment: multivariable linear regression models were adjusted for age, BMI, diabetes mellitus, alcohol risk, smoking, hypertension, cardiovascular disease, insomnia, and depression.
Legend: p-values representing significant associations boldfaced.

5.4.5 Associations between arousal index and spindle metrics

Unadjusted and adjusted associations between arousal index and spindle metrics are reported in Supplementary Table 5.4. In unadjusted analyses, a higher arousal index was associated with decreased overall and slow spindle density during N2 and N3 sleep and decreased fast spindle density during N3 sleep. A higher arousal index was also associated with greater spindle amplitude during N2 sleep and lower average spindle frequency during N3 sleep. In adjusted analyses, associations of a higher arousal index with decreased overall and fast spindle density during N3 sleep and greater spindle amplitude during N2 sleep persisted.

5.4.6 Associations between subjective sleep quality and daytime sleepiness and spindle metrics

Unadjusted and adjusted associations between PSQI and ESS scores and spindle metrics are reported in Table 5.4. In unadjusted analyses, subjective sleep quality (PSQI) and sleepiness (ESS) were not associated with spindle metrics during N2 or N3 sleep. However, in adjusted analyses, an association of a higher PSQI with decreased average spindle frequency during N3 sleep emerged. There were no other adjusted associations between PSQI and ESS scores and spindle metrics.

Table 5.4 Covariate unadjusted and adjusted associations between PSQI and ESS scores and spindle metrics

	Unadjusted Model		Adjusted Model	
		PSQI		
	B (95% CI)	*p*	*B* (95% CI)	*p*
N2 sleep spindle metrics				
Average frequency (Hz)	0.002 (-0.004, 0.008)	0.53	0.003 (-0.004, 0.01)	0.42
Amplitude (μV)	0.05 (-0.03, 0.13)	0.24	-0.006 (-0.09, 0.07)	0.88
Overall density (11–16 Hz)	0.008 (-0.007, 0.02)	0.29	0.01 (-0.006, 0.03)	0.21
Fast density (13–16 Hz)	0.002 (-0.005, 0.01)	0.52	0.003 (-0.005, 0.01)	0.47
Slow density (11–13 Hz)	0.006 (-0.006, 0.02)	0.31	0.008 (-0.005, 0.02)	0.24
N3 sleep spindle metrics				
Average frequency (Hz)	-0.04 (-0.11, 0.03)	0.23	-0.08 (-0.15, -0.005)	**0.037**
Amplitude (μV)	0.006 (-0.15, 0.16)	0.94	0.03 (-0.12, 0.18)	0.68
Overall density (11–16 Hz)	0.003 (-0.01, 0.02)	0.66	0.002 (-0.01, 0.02)	0.74
Fast density (13–16 Hz)	-0.001 (-0.005, 0.002)	0.40	-0.001 (-0.005, 0.002)	0.47
Slow density (11–13 Hz)	0.004 (-0.007, 0.02)	0.46	0.004 (-0.009, 0.02)	0.55
		ESS		
	B (95% CI)	*p*	*B* (95% CI)	*p*
N2 sleep spindle metrics				
Average frequency (Hz)	-0.001 (-0.007, -0.005)	0.75	-0.001 (-0.007, 0.005)	0.66
Amplitude (μV)	0.04 (-0.03, 0.12)	0.26	-0.006 (-0.09, 0.07)	0.88
Overall density (11–16 Hz)	0.008 (-0.006, 0.02)	0.28	0.001 (-0.01, 0.02)	0.84
Fast density (13–16 Hz)	0.003 (-0.004, 0.009)	0.39	0.001 (-0.006, 0.007)	0.81
Slow density (11–13 Hz)	0.005 (-0.006, 0.02)	0.36	0.001 (-0.01, 0.01)	0.91
N3 sleep spindle metrics				
Average frequency (Hz)	0.05 (-0.01, 0.11)	0.11	0.04 (-0.03, 0.10)	0.25
Amplitude (μV^2)	0.10 (-0.04, 0.23)	0.16	0.03 (-0.12, 0.18)	0.68
Overall density (11–16 Hz)	0.007 (-0.005, 0.02)	0.25	0.005 (-0.007, 0.02)	0.44
Fast density (13–16 Hz)	0.002 (-0.001, 0.006)	0.12	0.002 (-0.001, 0.005)	0.23
Slow density (11–13 Hz)	0.004 (-0.006, 0.01)	0.42	0.003 (-0.008, 0.01)	0.63

Abbreviations: N2, stage 2 sleep; N3, stage 3 sleep; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale; CI, confidence interval.
Coefficients: unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates: estimates represent the change in spindle metrics corresponding to a one-unit increase in arousal index.
Statistical adjustment: multivariable linear regression models were adjusted for age, AHI, BMI, diabetes mellitus, alcohol risk, smoking, hypertension, cardiovascular disease, insomnia, and depression.
Legend: p-values representing significant associations boldfaced.

5.5 Discussion

This study is the first to examine cross-sectional associations between OSA severity measures (AHI and TST90) and sleep fragmentation (arousal index) and spindle metrics among a large community-based sample of men while accounting for potential confounders. Measures of OSA severity and sleep fragmentation were independently associated with spindle abnormalities during N2 and N3 sleep. As assessed by the PSQI, poorer subjective sleep quality appeared to be independently associated with lower spindle frequency but only during N3 sleep.

The findings of decreased overall and slow spindle density during N2 and N3 sleep in men with severe OSA (AHI ≥30/h) compared to men without OSA (AHI <10/h) and a linear association of a higher AHI with decreased slow spindle density during N2 sleep are partly in line with a previous small study. Mohammadi et al. (370) examined overall spindle density during N2 and N3 sleep in 31 patients with OSA and 23 controls. Patients with moderate-severe OSA showed lower overall spindle density compared to controls and patients with mild OSA. However, differences were only observed for spindle density during N3 sleep and without separating slow and fast spindles. Thus, the finding in the present study of decreased slow spindle density during N2, not N3 sleep, in men with severe OSA compared to controls contrasts with Mohammadi et al. (370).

When comparing OSA severity categories, men with AHI ≥30/h showed decreased spindle density during N2 and N3 sleep compared to men with AHI <10/h. This finding is partly in line with a previous small study by Li et al. (371), who reported decreased spindle density during N3 sleep in participants with AHI ≥30/h compared to those with AHI <30/h. In another small study, Carvalho et al. (47) examined spindle frequency modulation in 21 patients with OSA and 7 controls. Compared to controls and patients with mild OSA, patients with moderate OSA showed a reduced percentage of slow spindles with frequency deceleration in frontal and parietal brain regions. However, no differences were found for the group with severe OSA (47). Although the present study did not assess spindle frequency deceleration, the findings partly agree and show decreased slow spindle density during N2 sleep in men with greater AHI severity. The advantage of the present study is that the large sample allows for control of potential confounders, thus providing more robust

supporting evidence that a higher AHI is associated with decreased frontal slow spindle density.

Along with AHI, it is important to consider if sleep hypoxemia is more specifically associated with spindle metrics. The associations between higher AHI and TST90 and greater spindle frequency during N2 sleep differ from a previous small study. Himanen et al. (46) compared spindle frequency between patients with OSA (n=12) and controls (n=12) and found lower spindle frequency in patients with OSA, which the authors speculated might reflect altered neural mechanisms through disturbed sleep (46). Interestingly, while the present study found an increase in overall spindle frequency with greater sleep hypoxemia, a consistent decrease in slow spindle density with increasing AHI was also observed. The increase in overall spindle frequency may reflect less slow frequency spindles and a greater proportion of higher frequency spindles with increasing AHI. These findings may also reflect a shift from slow to fast spindles with greater sleep hypoxemia, which has not been identified in smaller studies with less power and an inability to control for confounders. Another potential explanation for the contrasting results is that the spindle metrics identified were limited to the frontal derivation, which is well placed to measure slow spindles. The central derivations by Himanen et al. (46) and Mohammadi et al. (370) may have resulted in different associations as spindle morphology varies across scalp locations, with a higher percentage of slow spindles in frontal regions and faster spindles in central and parietal brain regions (374).

The associations of a higher arousal index with decreased overall and fast spindle density during N3 sleep were not apparent with AHI. Given that spindles have been reported to play a key role in sleep maintenance (269), these associations may reflect a large number of arousals limiting the ability of the thalamocortical network to generate spindles. However, there is limited evidence from previous small studies to support these findings. Thus, further cohort studies remain warranted to clarify if increased arousals from sleep are consistently associated with decreased overall and fast spindle density.

A higher TST90 was associated with greater spindle amplitude during N2 and N3 sleep, whereas a higher arousal index was only associated with greater spindle amplitude during N2 sleep. Previous data on spindle amplitude in people with and

without OSA are limited. Taillard et al. (281) examined spindle metrics in older men and women (mean age ~70 years) with (n=29) versus without (n=29) cognitive impairment, and maximal spindle amplitude was lower in the cognitive impairment group. However, both groups showed mild-moderate OSA with no difference in AHI or hypoxemia and without a control group, making it difficult to compare studies. Nevertheless, associations between spindle amplitude and cognitive impairment may indicate spindle involvement in neuronal processes underlying cognitive decline and warrant further exploration. The associations of higher arousal index and TST90 with greater spindle amplitude may also reflect thalamocortical network involvement (375). Thalamocortical networks relay excitatory and inhibitory neural traffic to the cortex (376), and consequently, excitatory connections within the thalamocortical network could act as a defensive mechanism to compensate for hypoxemia.

While subjective daytime sleepiness (ESS) was not associated with spindle metrics, poorer subjective sleep quality (PSQI) was associated with lower average spindle frequency during N3 sleep in the adjusted analysis only. Spindle frequencies have been found to increase with age (377), although adjusting for age did not change the associations in the present study. The association between poorer subjective sleep quality and lower average spindle frequency during N3 sleep was not significant in unadjusted or partly adjusted analysis and only became significant after adjusting for symptoms of insomnia or depression. Although inconsistent, there is evidence that insomnia and affective disorders impact spindle activity (378, 379). Thus, this finding may reflect the complex association between sleep quality, insomnia, and mental health outcomes, but this requires further study.

Several small case-controlled studies provide preliminary evidence that lower spindle frequency and density may be associated with cognitive decline (41, 281, 380). The independent associations between OSA severity measures and spindle metrics in the present study support that spindle metrics may be valuable markers of cognitive decline. Therefore, longitudinal studies are warranted to determine whether spindle morphology is independently associated with cognitive decline in middle-aged to older adults.

The key strengths of this study include the large community-based sample, sleep stage-specific spindle data, and the ability to control for confounders that can impact

sleep spindles and cortical activity. However, the cross-sectional design does not provide the means to infer causality. Also, the sleep sub-study was performed exclusively in men; thus, results in women remain unknown. Furthermore, spindle data were collected using only the frontal derivation, and important topographical differences in spindle metrics may have been missed. Moreover, a single night of PSG was conducted; however, multiple nights of sleep testing are impractical in the context of an epidemiological study. Another limitation is the inability to adjust for sleep-associated movement disorders such as REM sleep behaviour disorder, restless legs syndrome, and periodic limb movements of sleep, which may modify specific sleep microarchitecture characteristics such as infraslow periodicities in fall-band EEG or band-limited sigma power. Nevertheless, the quantitative EEG analysis software focused on EEG frequencies between 0.5–34 Hz, which likely minimised the impact of infraslow periodicities. Lastly, although significant, the observed independent associations between OSA severity measures and spindle metrics were relatively weak, and the coefficients were small. Therefore, their clinical significance is uncertain, and further study is required to link sleep spindles to important functional outcomes.

In summary, among this large community-based sample of men, measures of OSA severity (AHI and TST90) and sleep fragmentation (arousal index) were independently associated with spindle abnormalities, extending previous small studies, and providing more robust evidence that sleep-disordered breathing affects sleep spindle morphology. Large community-based and case-controlled studies are warranted to examine cross-sectional and prospective associations between spindle metrics and health-related functional outcomes and cognitive decline. If this link is established, further evidence from randomised controlled trials (368, 369) is required to determine if OSA treatment can reverse spindle abnormalities.

5.6 Supplementary Tables

Supplementary Table 5.1 Spindle metrics during N2 sleep in relation to demographic and other risk factors

	Average frequency (11–16 Hz)	Amplitude (μV)	Overall density (11–16 Hz)	Fast density (13–16 Hz)	Slow density (11–13 Hz)
	Mean (*SD*)	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**
Age (years)					
<50	12.8 (0.3)	14.8 (3.1)	1.4 (0.7)	0.5 (0.3)	0.8 (0.6)
50–69	12.8 (0.3)	13.8 (3.1)	1.1 (0.7)	0.4 (0.3)	0.7 (0.5)
≥70	12.8 (0.3)	12.6 (5.1)	0.3 (0.4)	0.2 (0.2)	0.4 (0.3)
p	0.41	**<0.001**	**<0.001**	**<0.001**	**<0.001**
BMI (kg/m^2)					
<25	12.8 (0.3)	13.6 (2.3)	1.2 (0.7)	0.5 (0.4)	0.8 (0.6)
25 to <30	12.8 (0.3)	13.9 (5.0)	1.1 (0.7)	0.4 (0.3)	0.7 (0.6)
≥30	12.9 (0.3)	14.4 (3.5)	1.0 (0.6)	0.4 (0.4)	0.6 (0.4)
p	0.15	0.39	**0.021**	0.28	**0.003**
Diabetes					
No	12.8 (0.3)	13.8 (3.8)	1.0 (0.7)	0.4 (0.3)	0.7 (0.5)
Yes	12.8 (0.3)	13.4 (3.2)	0.8 (0.6)	0.2 (0.2)	0.5 (0.4)
p	0.28	0.39	**<0.001**	**<0.001**	**0.002**
Alcohol risk					
Non–low	12.8 (0.3)	13.8 (3.7)	1.0 (0.7)	0.4 (0.3)	0.7 (0.5)
Medium–very high	12.9 (0.2)	13.4 (2.1)	1.3 (0.8)	0.5 (0.4)	0.7 (0.5)
p	0.17	0.64	0.082	**0.016**	0.41
Smoking status					
Never/former	12.8 (0.3)	13.6 (3.8)	1.0 (0.7)	0.4 (0.3)	0.7 (0.5)
Current	12.8 (0.3)	13.2 (3.3)	1.2 (0.7)	0.4 (0.3)	0.8 (0.5)
p	0.083	0.17	0.056	0.28	0.061
Hypertension					
No	12.8 (0.3)	14.2 (4.1)	1.1 (0.7)	0.4 (0.3)	0.7 (0.5)
Yes	12.8 (0.3)	13.0 (2.9)	0.9 (0.6)	0.3 (0.3)	0.6 (0.4)
p	0.60	**<0.001**	**<0.001**	**0.004**	**<0.001**
Cardiovascular disease					
No	12.8 (0.3)	13.7 (3.6)	1.1 (0.7)	0.4 (0.3)	0.7 (0.5)
Yes	12.8 (0.3)	14.0 (4.1)	0.8 (0.6)	0.3 (0.2)	0.5 (0.5)
p	0.54	0.61	**0.004**	0.44	0.12
Insomnia					
No	12.8 (0.3)	13.7 (3.7)	1.1 (0.7)	0.4 (0.3)	0.7 (0.5)
Yes	12.9 (0.2)	13.8 (3)	1.0 (0.7)	0.4 (0.3)	0.6 (0.4)
p	0.10	0.85	0.49	0.39	0.14
Depression					
No	12.8 (0.3)	13.7 (3.8)	1.1 (0.7)	0.4 (0.3)	0.7 (0.5)
Yes	12.8 (0.3)	14.5 (2.9)	1.1 (0.6)	0.4 (0.3)	0.7 (0.5)
p	0.75	0.15	0.99	0.98	0.97
EDS (ESS ≥11)					
No	12.8 (0.3)	13.7 (3.7)	1.0 (0.7)	0.4 (0.3)	0.7 (0.5)
Yes	12.8 (0.3)	13.7 (3.1)	1.0 (0.7)	0.4 (0.3)	0.6 (0.5)
p	0.60	0.94	0.89	0.69	0.67
Poor sleep quality (PSQI ≥5)					
No	12.8 (0.3)	13.5 (3.9)	1.0 (0.6)	0.4 (0.3)	0.6 (0.5)
Yes	12.8 (0.3)	14 (3.3)	1.1 (0.7)	0.4 (0.3)	0.7 (0.6)
p	0.15	0.12	0.090	0.12	0.19

Abbreviations: *SD*, standard deviation; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index.

BMI: body mass index categorised according to international criteria (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 kg/m^2 [obese]).
Diabetes: self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L (126 mg/Dl), haemoglobin A1C ≥6.5%, or reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).
Insomnia: at least one of two PSQI dimensions (difficulty initiating or maintaining sleep) and significant daytime fatigue defined as an SF-36 Vitality Scale score one *SD* below the mean.
Depression: depressive symptoms were identified with the Centre for Epidemiological Studies Depression scale (score ≥16) or Beck Depression Inventory-1a (score ≥13).
Hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use.
Cardiovascular disease: self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke.
Legend: p-values representing statistically significant between-group differences boldfaced.

Supplementary Table 5.2 Spindle metrics during N3 sleep in relation to demographic and other risk factors

	Average frequency (11–16 Hz)	Amplitude (μV)	Overall density (11–16 Hz)	Fast density (13–16 Hz)	Slow density (11–13 Hz)
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Age (years)					
<50	12.4 (1.5)	13.9 (5.4)	0.7 (0.6)	0.1 (0.2)	0.5 (0.5)
50–69	12.0 (2.6)	12.7 (5.8)	0.6 (0.6)	0.1 (0.2)	0.5 (0.5)
≥70	10.9 (4.3)	11.1 (9.3)	0.3 (0.5)	0.1 (0.1)	0.3 (0.4)
p	**<0.001**	**0.002**	**<0.001**	**0.002**	**<0.001**
BMI (kg/m^2)					
<25	11.9 (2.7)	12.1 (5.2)	0.6 (0.6)	0.1 (0.1)	0.5 (0.6)
25 to <30	12.0 (2.6)	13.0 (7.8)	0.6 (0.6)	0.1 (0.2)	0.5 (0.5)
≥30	11.7 (3.2)	12.3 (5.3)	0.5 (0.5)	0.1 (0.2)	0.3 (0.4)
p	0.54	0.33	**0.027**	0.76	**0.011**
Diabetes					
No	12.0 (2.6)	12.7 (6.0)	0.6 (0.6)	0.1 (0.2)	0.5 (0.5)
Yes	11.2 (3.8)	12.6 (9.1)	0.4 (0.4)	0.1 (0.1)	0.3 (0.3)
p	**0.049**	0.92	**<0.001**	**<0.001**	**<0.001**
Alcohol risk					
Non–low	11.8 (2.9)	12.6 (6.7)	0.5 (0.6)	0.1 (0.2)	0.4 (0.5)
Medium–very high	12.3 (2.3)	12.9 (4.7)	0.6 (0.6)	0.2 (0.2)	0.4 (0.5)
p	0.42	0.81	0.72	0.13	0.94
Smoking status					
Never/former	11.8 (3.0)	12.5 (6.9)	0.5 (0.5)	0.1 (0.2)	0.4 (0.5)
Current	12.4 (1.4)	13.5 (4.4)	0.7 (0.7)	0.1 (0.2)	0.6 (0.6)
p	**0.003**	0.17	**0.010**	0.41	**0.008**
Hypertension					
No	11.9 (2.7)	12.9 (6.7)	0.6 (0.6)	0.1 (0.2)	0.5 (0.5)
Yes	11.8 (3.1)	12.1 (6.3)	0.5 (0.5)	0.1 (0.2)	0.4 (0.5)
p	0.59	0.11	**0.015**	0.78	**0.007**
Cardiovascular disease					
No	11.9 (2.8)	12.8 (6.7)	0.6 (0.6)	0.1 (0.2)	0.4 (0.5)
Yes	11.1 (4.1)	11.0 (5.7)	0.4 (0.5)	0.1 (0.1)	0.3 (0.4)
p	0.15	0.063	0.11	0.44	0.12
Insomnia					
No	11.8 (3.0)	12.5 (6.6)	0.6 (0.6)	0.1 (0.2)	0.4 (0.5)
Yes	12.3 (2.1)	13.5 (6.7)	0.5 (0.5)	0.1 (0.2)	0.3 (0.4)
p	0.19	0.23	0.54	0.55	0.38
Depression					
No	11.9 (2.8)	12.6 (6.6)	0.5 (0.5)	0.1 (0.2)	0.4 (0.5)
Yes	12.2 (1.8)	14.8 (7.3)	0.7 (0.8)	0.1 (0.2)	0.6 (0.8)
p	0.45	**0.029**	0.26	0.99	0.24
EDS (ESS ≥11)					
No	11.8 (3)	12.5 (6.6)	0.5 (0.6)	0.1 (0.1)	0.4 (0.5)
Yes	12.3 (2.1)	13.5 (7.0)	0.5 (0.6)	0.1 (0.2)	0.4 (0.5)
p	0.071	0.22	0.99	0.22	0.65
Poor sleep quality (PSQI ≥5)					
No	12.0 (2.7)	12.7 (7)	0.5 (0.5)	0.1 (0.2)	0.4 (0.5)
Yes	11.7 (3.2)	12.5 (6.1)	0.6 (0.6)	0.1 (0.1)	0.5 (0.5)
p	0.30	0.67	0.37	0.94	0.31

Abbreviations: *SD*, standard deviation; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; PSQI, Pittsburgh Sleep Quality Index.
BMI: body mass index categorised according to international criteria (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 kg/m^2 [obese]).
Diabetes: self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L (126 mg/Dl), haemoglobin A1C ≥6.5%, or reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).

Insomnia: at least one of two PSQI dimensions (difficulty initiating or maintaining sleep) and significant daytime fatigue defined as an SF-36 Vitality Scale score one *SD* below the mean.
Depression: depressive symptoms were identified with the Centre for Epidemiological Studies Depression scale (score ≥16) or Beck Depression Inventory-1a (score ≥13).
Hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use.
Cardiovascular disease: self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke.
Legend: p-values representing statistically significant between-group differences boldfaced.

Supplementary Table 5.3 Covariate unadjusted and adjusted associations between clinical OSA severity categories and spindle metrics

	Unadjusted Model		Adjusted Model	
	B (95% CI)	*p*	*B* (95% CI)	*p*
N2 sleep spindle metrics				
Average frequency (Hz)	0.02 (0.004, 0.04)	**0.020**	0.02 (0.001, 0.05)	**0.038**
Amplitude (μV)	0.16 (-0.11, 0.43)	0.23	0.27 (-0.02, 0.56)	0.071
Overall density (11–16 Hz)	-0.10 (-0.15, -0.05)	**<0.001**	-0.03 (-0.08, 0.02)	0.26
Fast density (13–16 Hz)	-0.01 (-0.04, 0.01)	0.28	0.01 (-0.01, 0.04)	0.27
Slow density (11–13 Hz)	-0.08 (-0.12, -0.05)	**<0.001**	-0.04 (-0.08, -0.004)	**0.032**
N3 sleep spindle metrics				
Average frequency (Hz)	-0.19 (-0.40, 0.03)	0.083	-0.04 (-0.26, 0.19)	0.76
Amplitude (μV)	0.15 (-0.33, 0.63)	0.55	0.33 (-0.20, 0.87)	0.22
Overall density (11–16 Hz)	-0.06 (-0.10, -0.02)	**0.003**	-0.03 (-0.07, 0.02)	0.24
Fast density (13–16 Hz)	0.006 (-0.005, 0.02)	0.28	0.01 (-0.001, 0.03)	0.068
Slow density (11–13 Hz)	-0.07 (-0.10, -0.03)	**<0.001**	-0.04 (-0.08, 0.001)	0.055

Abbreviations: N2, stage 2 sleep; N3, stage 3 sleep; CI, confidence interval.
Coefficients: unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates: represent the change in spindle metrics corresponding to a one-category increase in clinical OSA severity categories.
Statistical adjustment: multivariable linear regression models were adjusted for age, BMI, diabetes, alcohol risk, smoking, hypertension, cardiovascular disease, insomnia, and depression.
Legend: p-values representing significant associations boldfaced.

Supplementary Table 5.4 Covariate unadjusted and adjusted associations between arousal index and spindle metrics

	Unadjusted Model		Adjusted Model	
	B (95% CI)	*p*	*B* (95% CI)	*p*
N2 sleep spindle metrics				
Average frequency (Hz)	-1.29 (-3.47, 0.88)	0.24	-1.35 (-3.60, 0.90)	0.24
Amplitude (μV)	0.23 (0.07, 0.39)	**0.005**	0.31 (0.14, 0.48)	**<0.001**
Overall density (11–16 Hz)	-1.03 (-1.91, -0.15)	**0.023**	-0.34 (-1.34, 0.66)	0.51
Fast density (13–16 Hz)	-1.30 (-3.19, 0.59)	0.18	-0.07 (-2.14, 2.01)	0.95
Slow density (11–13 Hz)	-1.32 (-2.49, -0.14)	**0.028**	-0.54 (-1.82, 0.75)	0.41
N3 sleep spindle metrics				
Average frequency (Hz)	-0.26 (-0.46, -0.05)	**0.015**	-0.19 (-0.41, 0.04)	0.10
Amplitude (μV)	-0.01 (-0.10, 0.08)	0.76	0.001 (-0.09, 0.10)	0.99
Overall density (11–16 Hz)	-1.63 (-2.70, -0.57)	**0.003**	-1.27 (-2.42, -0.13)	**0.030**
Fast density (13–16 Hz)	-4.75 (-8.47, -1.03)	**0.012**	-4.36 (-8.25, -0.47)	**0.028**
Slow density (11–13 Hz)	-1.56 (-2.75, -0.37)	**0.011**	-1.12 (-2.40, 0.17)	0.089

Abbreviations: N2, stage 2 sleep; N3, stage 3 sleep; CI, confidence interval.
Coefficients: unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates: estimates represent the change in spindle metrics corresponding to a one-unit increase in arousal index.
Statistical adjustment: multivariable linear regression models were adjusted for age, BMI, diabetes, alcohol risk, smoking, hypertension, cardiovascular disease, insomnia, and depression.
Legend: p-values representing significant associations boldfaced.

CHAPTER 6. THE ASSOCIATION BETWEEN SLEEP SPINDLES AND COGNITIVE FUNCTION IN MIDDLE-AGED AND OLDER MEN FROM A COMMUNITY-BASED COHORT STUDY

6.1 Abstract

Study objectives: Previous studies assessing associations between sleep spindles and cognitive function attempted to account for obstructive sleep apnea (OSA) with little consideration for potential moderation. Therefore, to elucidate associations between sleep spindles, cognition, and OSA, this study of community-dwelling men examined cross-sectional associations between spindle metrics and cognitive outcomes before and after adjustment for OSA and potential OSA moderating effects.

Methods: Florey Adelaide Male Ageing Study participants (n=477) reporting no previous OSA diagnosis underwent home-based polysomnography (2010–2011). Cognitive testing (2007–2010) included the inspection time task, trail-making tests A (TMT-A) and B (TMT-B), and Fuld object memory evaluation. Frontal spindle metrics (F4-M1) derived from sleep electroencephalography included occurrence (count), frequency (Hz), amplitude (μV), density of overall spindle events (11–16 Hz), and slow (11–13 Hz), and fast (13–16 Hz) spindle densities (number/minute of N2 and N3 sleep).

Results: Lower N2 spindle occurrence was associated with longer inspection times (*B*= -0.43, 95% CI [-0.85, -0.005] p=0.047), whereas higher N3 fast spindle density (*B*=20.7, 95% CI [0.44, 40.9], p=0.044) and overall frequency (*B*=1.48, 95% CI [0.12, 2.83], p=0.033) were associated with worse TMT-B performance. Effect moderator analysis showed that in men with severe OSA (apnea-hypopnea index ≥30/h), slower N2 spindle frequency was associated with worse TMT-A performance (Wald χ^2 =12.5, p=0.006).

Conclusions: Specific sleep spindle metrics were independently associated with cognitive function, and OSA severity moderated these associations. These observations support the utility of sleep spindles as useful cognitive function markers in OSA, which warrants further longitudinal investigation.

6.2 Introduction

Obstructive sleep apnea (OSA) is a highly prevalent sleep-related breathing disorder characterised by recurrent pharyngeal collapse leading to intermittent nocturnal hypoxemia (oxygen desaturation) and sleep fragmentation (82). Clinically, OSA is quantified utilising manual scoring of sleep electroencephalography (EEG) macroarchitecture and respiratory and physiological disturbances. Conventional assessment relies on visual inspection of whole-night EEG recordings. However, this process is unable to capture subtle shorter-time scale frequency and amplitude changes continuously occurring within the EEG that may be clinically informative. Quantitative EEG analysis approaches convert EEG signals from the time to the frequency domain to systematically examine finer-grained sleep EEG microarchitecture parameters. Emerging evidence supports that sleep microarchitecture parameters in patients with OSA differ from age- and gender-matched controls and could represent valuable brain-specific cognitive function markers (44). Sleep spindles are particularly prominent sleep microarchitecture parameters thought to play an important role in cortical reorganisation processes involved in learning capability and overnight declarative memory consolidation (269). Spindles are waxing and waning neuronal oscillations (11–16 Hz, ≥0.5 and ≤3 seconds) generated by signalling interplay between thalamic and thalamocortical nuclei that predominantly occur during N2 sleep (269).

Of three small studies that have examined associations between sleep spindle metrics and cognitive function outcomes in non-clinical samples (49-51), two of these studies recruited small samples of healthy young male and female participants with findings demonstrating that higher spindle occurrence (11–16 Hz, total events), density (11–16 Hz, number/minute), frequency (Hz), and amplitude (μV) during N2 sleep were associated with better fluid intelligence, reasoning, and memory performance (49, 50). In another study that recruited a small sample (n=58) of healthy middle-aged and older adults (age range, 50–91), higher spindle density

during N2 sleep was associated with better attention, vigilance, and verbal fluency (51). In addition to small studies, in a case-controlled study consisting of participants with isolated subjective cognitive complaints (SCC) or patients with mild cognitive impairment (MCI) (n=29, mean age 71 years) and cognitively normal controls (n=29, mean age 68 years) from the MEMENTO cohort, spindle maximal amplitude was significantly lower across non-rapid eye movement (NREM) sleep periods in patients with isolated SCC or MCI compared to cognitively normal controls (281).

Data regarding sleep spindles in OSA are sparse and require further investigation, particularly in community-based cohort studies. Small studies report that patients with OSA show a higher percentage of slow spindles (11–13 Hz) in frontal brain regions and fewer fast spindles (13–16 Hz) in parietal brain regions compared to age- and gender-matched controls (46, 277). Chapter 5 of this thesis utilised data from a community-based cohort study to extend preliminary findings from case-controlled studies. Chapter 5 reported that greater apnea-hypopnea index (AHI) and intermittent hypoxemia were associated with lower frontal N2 sleep slow spindle density but faster frequency (Hz) (340) in 675 community-dwelling middle-aged and older men. Furthermore, for the first time, Chapter 5 identified an association between greater hypoxemia and stage 3 (N3) sleep spindle amplitude (340), suggesting that N3 sleep spindles, although fewer, may also be affected by OSA and warrant investigation along with N2 sleep spindles.

Frontal brain regions play an important role in learning, memory, and executive function (13). Consequently, reported alterations in frontal spindle activity associated with OSA could be involved in cognitive dysfunction. However, only two small clinical studies have examined associations between sleep spindle metrics and cognitive function outcomes in patients with OSA (283, 381). Lower overall frontal spindle density during baseline sleep was associated with slower reaction times in male patients with OSA (n=8) following extended wakefulness (283). Furthermore, higher frontocentral fast spindle density was associated with better implicit statistical learning in male and female patients with OSA (n=47) (284). A study of late middle-aged and older adults (n=3,819) from the community-based Multi-Ethnic Study of Atherosclerosis (MESA) and Osteoporotic Fractures in Men Study (MrOS) cohorts reported that higher spindle occurrence and fast density (13–16 Hz, number/minute)

were associated with better executive function independent of OSA (45). Furthermore, a cross-sectional study (n=63) reported that higher overall spindle density was associated with better executive function independent of age, OSA, obesity, and periodic limb movement index (282).

The community-based cohort literature investigating associations between sleep spindle metrics and cognitive function outcomes and considering the potential impacts of OSA remains limited, highlighting the importance of conducting additional studies to extend the emerging evidence. Community-based cohort studies of this nature would provide the means to determine if the association between sleep spindle metrics and cognitive function outcomes differs by OSA severity. For example, it is possible that these associations, if present, may be strongest in people with severe OSA but potentially weaker in people with moderate or mild OSA. If these findings are observed, additional studies would be warranted to determine if CPAP treatment can reverse sleep spindle abnormalities, including reduced occurrence and decreased densities, average frequency, and amplitude, in patients with OSA.

The primary aim of this study was to investigate independent cross-sectional associations between spindle sleep metrics and cognitive function outcomes. The secondary aim was to determine if OSA severity moderated associations between sleep spindle metrics and cognitive function outcomes to implicate spindle involvement in cognitive impairment in OSA. It was hypothesised that sleep spindle metrics would be independently associated with cognitive function outcomes, and OSA severity would moderate these associations.

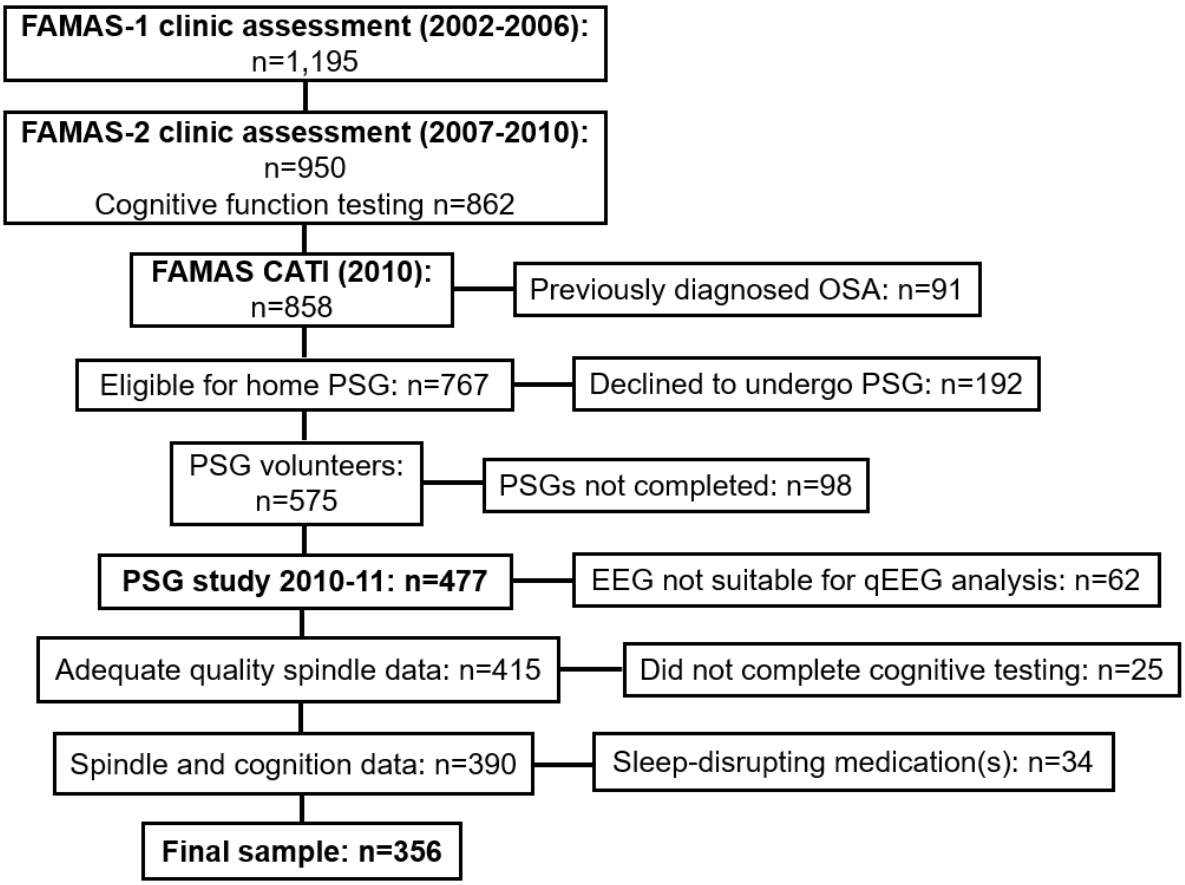
6.3 Methods

6.3.1 Study participants

The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study includes 2,569 urban community-dwelling men harmonised from two independent prospective community-based cohorts: all Florey Adelaide Male Ageing Study (FAMAS) and male North West Adelaide Health Study (NWAHS) participants (303). The present study includes FAMAS participants (n=1,195) aged 35–80 years at baseline (2002) residing in north-west Adelaide, South Australia (320).

A computer-assisted telephone interview follow-up in 2010 (n=858) identified FAMAS participants reporting no previous OSA diagnosis (n=767) who were invited to undergo home-based eight-channel polysomnography (PSG) (2010–2011) as part of a sub-study of the MAILES Study (303). Of these, 192 declined to undergo PSG. Of eligible participants who agreed to participate (n=575), 98 sleep studies were not completed due to time and budget constraints (Figure 6.1). FAMAS was conducted in accordance with the Declaration of Helsinki and approved by the Human Research Ethics Committees of the Royal Adelaide Hospital (approval number: 020305). All participants provided written informed consent.

Figure 6.1 FAMAS clinic and sleep study assessments and cognitive function testing



MAILES, Men Androgen Inflammation Lifestyle Environment and Stress. CATI, computer-assisted telephone interview. PSG, polysomnography. Qeeg, quantitative electroencephalography.

6.3.2 Sleep study assessment

Participants underwent home-based eight-channel ambulatory PSG (Embletta X100, Embla Systems, Broomfield, Colorado, USA), which measured frontal electrical brain activity (EEG, F4-M1) and left electrooculography 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 obtained anthropometric measurements (height, weight, and body mass index [BMI, kg/m^2]).

A single experienced sleep technician manually scored all PSG measures according to 2007 American Academy of Sleep Medicine (AASM) *Alternative* scoring criteria, recommended by an expert panel of the Australasian Sleep Association for use in prospective epidemiological studies (321). OSA was identified by an AHI ≥10/h and further categorised as mild (10–19/h), moderate (20–29/h), or severe (≥30/h). Ruehland et al. (32) have shown that an AHI of ≥5/h used to define sleep-disordered breathing by the AASM *Recommended* scoring criteria is approximately equivalent to ≥10/h using the AASM *Alternative* and ≥15/h using the older 1999 *Chicago* scoring criteria. Therefore, an AHI cut-off of ≥10/h was chosen to maintain comparability with previous work. Apnea was defined as complete or near-complete airflow cessation (≥90% amplitude reduction) assessed using nasal cannula pressure excursions lasting ≥10 seconds. Hypopnea was defined as a ≥50% decrease in nasal cannula pressure lasting ≥10 seconds with an associated ≥3% oxygen desaturation or EEG arousal (32). Nocturnal hypoxemia was assessed from the percentage of total sleep time with oxygen saturation <90%. Acceptable sleep studies were classified as those with ≥3.5 h of sleep and ≥5.5 h of total-recorded study time with technically acceptable respiratory and EEG signal quality.

6.3.3 EEG data processing

All PSGs were exported to standardised European Data Format, from which overnight F4-M1 EEG recordings underwent automated artefact detection using a validated algorithm (372). An algorithm identified artefactual EEG data over consecutive non-overlapping 5-second epochs based on previously validated

artefact detection amplitude threshold parameters (372). Contaminated epochs were excluded from the analysis.

6.3.4 Sleep spindle detection algorithm

Spindle events were visually identified using an automated detection tool developed and written in Java, version 1.6 (Oracle, Santa Clara, California, USA), and previously validated in OSA samples (382). A 128-order band-passing Finite-Impulse-Response filter was applied to the raw EEG signal, yielding a time course of sigma activity (11–16 Hz, ≥0.5 and ≤3 seconds) (383). Reference standard spindle events were marked from onset to offset and exported with start time and duration details. The onset and offset of spindle events were determined by the first and second amplitude threshold crossings. Spindle events were recorded where the edges of the amplitude threshold crossings showed a threshold of 20% and tolerance of 50% of spindle amplitude. Spindles meeting criteria of duration 0.5–3 seconds and an inter-event interval >1 second were counted as events.

6.3.5 Spindle metrics

Spindle occurrence (11–16 Hz, total overall spindle events), average frequency (Hz) of overall spindle events, amplitude (μV) of overall spindle events, and overall (11–16 Hz), slow (11 ≤ fz ≤ 13 Hz; fz: frequency), and fast (13 < fz ≤ 16 Hz) density (spindle events/per minute of sleep) were the spindle metrics of interest calculated during N2 and N3 sleep.

6.3.6 Cognitive assessments

Participants completed the following four standardised, validated, and well-established cognitive tests during the 2007–2010 FAMAS follow-up (338), including the inspection time task, trail-making test A (TMT-A) and B (TMT-B), and the Fuld object memory evaluation (FOME) test. Refer to CHAPTER 2 for a detailed description of the cognitive tests. Given that the MMSE is a measure of global or geriatric cognitive impairment it has not been included in the analyses for the present study.

6.3.7 Covariate assessments

Self-completed questionnaires assessed demographic factors (age, financial stress, highest educational attainment, and marital status), chronic disease risk factors (smoking status, alcohol risk, and physical activity), and health-related quality of life (the 36-item short-form survey instrument [SF-36]). Relative social disadvantage, based upon participants' residential postcode, was determined with the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-Economic Disadvantage (IRSD) (309). Clinic assessments (2007–2010) included anthropometry, seated sphygmomanometer blood pressure, and a fasting blood sample (320). Composite cardiovascular disease (self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke) and diabetes mellitus (self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L [126 mg/Dl], haemoglobin A1C ≥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 at least three nights/week (Pittsburgh Sleep Quality Index [PSQI] dimensions) and significant daytime fatigue defined as an SF-36 Vitality Scale score one standard deviation (*SD*) below the mean (310). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use (311). BMI was categorised according to international criteria (308).

6.3.8 Statistical analysis methodology

Data were analysed using IBM SPSS version 25.0 (IBM Corporation, Armonk, New York, USA). Descriptive statistics for normally distributed sleep spindle metrics (densities, frequency, and amplitude), continuous covariates, and cognitive test scores are reported as mean (*SD*). Spindle occurrence is reported as median (IQR) due to non-normality. Categorical covariates are reported as percentages (frequencies).

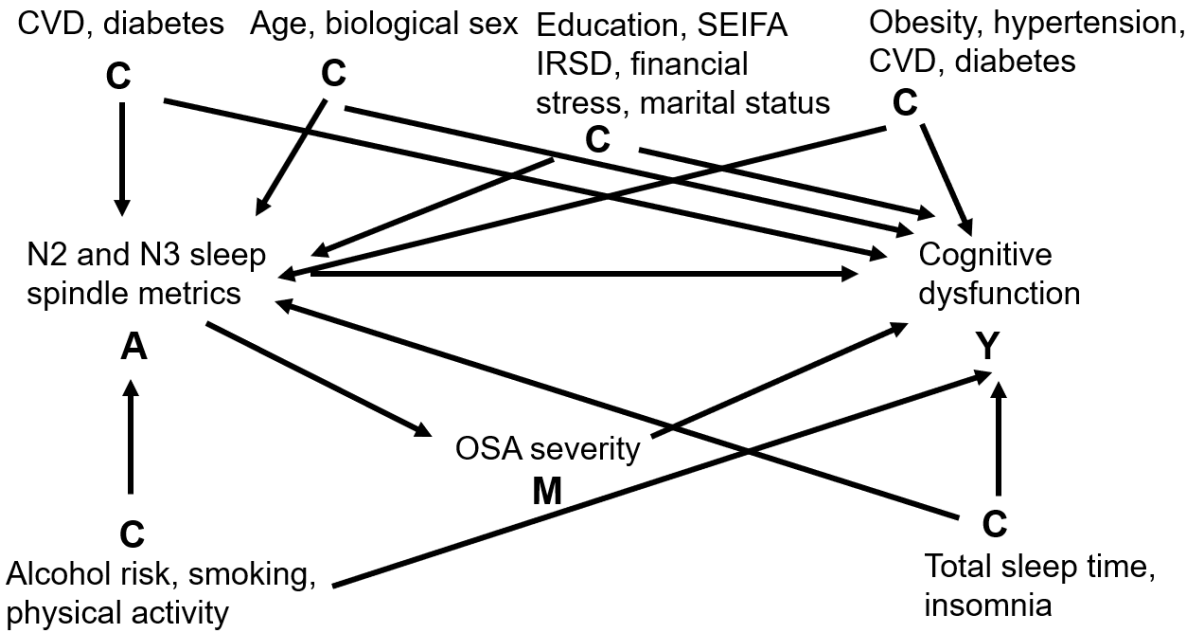
One-way analysis of variances and independent samples t-tests examined differences in spindle densities, frequency, and amplitude across OSA severity categories. Mann-Whitney U-tests examined differences in spindle occurrence

across OSA severity categories. Pearson's chi-squared tests examined differences in categorical variables. Characteristics of men with severe OSA were compared to men with mild or without OSA to provide greater insight into the effect of OSA severity on demographic and other risk factors and spindle metrics.

Univariable and multivariable linear regression models determined cross-sectional associations between sleep spindle metrics and cognitive function outcomes. Unstandardised beta (*B*) coefficients (95% confidence interval [CI]) and the range of Cohen's f^2 effect sizes are reported. Two covariate-adjusted regression models were constructed. Model 1 was adjusted for age and AHI. Model 2 was additionally adjusted for demographic (financial stress, highest educational attainment, socio-economic disadvantage, and marital status) and other (total sleep time [TST], BMI, alcohol risk, smoking, cardiovascular disease, diabetes mellitus, insomnia, and hypertension) covariates. Covariate adjustment was performed to determine if sleep spindle metrics were independently associated with cognitive function outcomes. The principal assumptions of linear regression modelling were satisfied, including linearity, normality, and homoscedasticity. Multicollinearity was assessed by examining the variance inflation factor. The filter function in SPSS was used to ensure only participants with complete case cognition, PSG, and covariate data were included in the final analysis.

Interaction terms between sleep spindles and OSA severity (AHI <10/h, 10–19/h, 20–29/h, and ≥30/h) were used to test the effect of OSA severity on the sleep spindle and cognition associations. These analyses were performed to determine if OSA played an important moderating role in associations between spindles and cognition. Wald χ^2 statistics, degrees of freedom, and p-values are reported for interaction, conditional, and main effects. No OSA (AHI <10/h) was used as the reference category for multiplicative interactions by OSA severity. Spindle metrics were centered (converted to standardised z-scores) for improved model interpretability. For all analyses, a two-sided $p<0.05$ was considered statistically significant. Based on previously reported practical considerations and given the exploratory nature of this analysis, multiple comparison adjustments were not performed (347).

Figure 6.2 Overview of relationships between variables



Legend: A=exposure/treatment/intervention/primary independent variable, C=confounder, M=mediator, Y=outcome variable.

6.4 Results

Of the 477 men who underwent PSG, 390 had adequate quality spindle and cognition data. Analyses were conducted on 356 men, excluding 34 (8.8%) who reported using one or more psychoactive medication(s), including opiates, antipsychotics, antiepileptics, antidepressants, or benzodiazepines (Figure 6.1).

6.4.1 Participant characteristics

The mean (*SD*) age of participants at the time of PSG assessment was 59.3 (10.8) years, with OSA (AHI ≥10/h) in 52% (n=185) and severe OSA (AHI ≥30/h) in 13% (n=47). Men with at least mild OSA were older, more obese, and had a higher incidence of diabetes and hypertension compared to men without OSA (AHI <10/h) (n=171). Moreover, men with severe OSA showed longer inspection times and worse TMT performance compared to men without OSA (Table 6.1). Higher age, lower education, and diabetes were associated with worse cognitive function (Supplementary Table 6.1).

6.4.2 Spindle metrics by OSA severity

Men with at least mild OSA (AHI ≥10/h) showed lower N2 and N3 sleep spindle densities and occurrence compared to men without OSA (Table 6.1). Also, men with severe OSA (AHI ≥30/h) showed lower N2 and N3 sleep slow spindle density and overall spindle occurrence and lower N2 sleep fast spindle density compared to men without OSA (AHI <10/h).

Table 6.1 Participant characteristics (sleep spindle metrics, demographic and other risk factor covariates, and cognitive test scores) in the overall sample and by clinical OSA severity categories

Overall sample (n=356)		**AHI <10/h (n=171) (no OSA)**	**AHI ≥10/h (n=185) (at least mild OSA)**	**AHI ≥30/h (n=47) (Severe OSA)**
Demographic risk factors				
Age (years)	**% (n)**	**% (n)**	**% (n)**	**% (n)**
<50	22.8 (81)	26.9 (46)	18.9 (35) $	14.9 (7) $$
50–69	59.0 (210)	56.1 (96)	64.3 (119) $	51.1 (24)
≥70	18.2 (65)	17.0 (29)	16.8 (31)	34.0 (16) $$
Financial stress	**% (n)**	**% (n)**	**% (n)**	**% (n)**
Spends >earns	10.7 (38)	15.4 (26)	18.3 (34)	17.0 (8)
Saves a little/lot	89.3 (318)	84.6 (144)	81.7 (151)	83.0 (39)
Highest educational attainment	**% (n)**	**% (n)**	**% (n)**	**% (n)**
≥Diploma, Certificate, Trade, Bachelor's degree or higher	76.7 (273)	71.0 (121)	68.3 (126)	70.2 (33)
SEIFA IRSD	**% (n)**	**% (n)**	**% (n)**	**% (n)**
Quintile 1 (highest socio-economic disadvantage)	23.9 (85)	21.1 (36)	25.0 (46)	17.0 (8)
Quintile 2	11.2 (40)	10.3 (17)	11.3 (21)	12.8 (6)
Quintile 3	24.7 (88)	31.4 (53)	24.4 (45)	27.7 (13)
Quintile 4	26.4 (94)	24.2 (41)	27.6 (51)	31.9 (15)
Quintile 5 (lowest socio-economic disadvantage)	13.8 (49)	13.0 (22)	11.6 (21)	10.6 (5)
Married/partner	90.2 (321)	80.7 (138)	79.9 (136)	83.0 (39)
N2 sleep spindle metrics	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Occurrence (11–16 Hz, count)	177.0 (98.0, 307.0)	208.0 (122.0, 322.8)	151.0 (80.0, 287.0) #	106.0 (55.0, 224.0) ##
	Mean (*SD*)	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**
Overall density (11–16 Hz, number/minute)	1.1 (0.7)	1.2 (0.7)	0.9 (0.6) *	0.7 (0.6) **
Fast density (13–16 Hz, number/minute)	0.4 (0.3)	0.4 (0.3)	0.4 (0.3)	0.3 (0.4) **
Slow density (11–13 Hz, number/minute)	0.7 (0.5)	0.7 (0.5)	0.6 (0.5) *	0.4 (0.4) **
Average frequency (Hz)	12.8 (0.3)	12.8 (0.3)	12.8 (0.2)	12.9 (0.3)
Amplitude (μV)	13.9 (4)	13.9 (3.4)	13.9 (4.5)	13.9 (3.6)
N3 sleep spindle metrics	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
Occurrence (11–16 Hz, count)	22.0 (7.0, 53.0)	24.5 (8.3, 63.5)	17.0 (6.0, 43.0)	11.0 (3.0, 32.5) **
	Mean (*SD*)	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**
Overall density (11–16 Hz, number/minute	0.6 (0.6)	0.7 (0.7)	0.5 (0.5) *	0.3 (0.4) **
Fast density (13–16 Hz, number/minute)	0.1 (0.2)	0.1 (0.1)	0.1 (0.2)	0.1 (0.2)
Slow density (11–13 Hz, number/minute)	0.4 (0.5)	0.5 (0.6)	0.4 (0.4) *	0.3 (0.3) **
Average frequency (Hz)	12.1 (2.5)	12.1 (2.5)	12.1 (2.5)	11.1 (4.3)
Amplitude (μV)	13.1 (6.8)	12.9 (6.3)	13.3 (7.3)	13.2 (8.8)
PSG measures	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**
Wake after sleep onset (mins)	79.6 (48.0)	76.3 (43.1)	82.6 (52)	97.0 (55.4) **
	% (n)			
Total sleep time (<360 minutes)	36.0 (128)	35.7 (61)	36.8 (68)	40.4 (19) $$
Total sleep time with oxygen saturation <90% (≥4%)	25.8 (92)	15.8 (27)	35.1 (65)	55.3 (26) $$
Cognitive tests	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**
Inspection time (milliseconds)	64.9 (31.0)	64.0 (29.3)	65.8 (32.5)	75.4 (40.8) **

TMT-A (seconds)	15.8 (6.5)	15.5 (5.6)	16.2 (7.3)	18.9 (11.7) **
TMT-B (seconds)	77.6 (34.1)	75.7 (33.2)	79.3 (34.9)	91.4 (52.3) **
FOME (number/10)	6.4 (1.7)	6.5 (1.7)	6.3 (1.8)	6.0 (1.8)
Other risk factors	**% (n)**	**% (n)**	**% (n)**	**% (n)**
BMI (kg/m^2)				
<25 (underweight/normal)	19.1 (68)	24.0 (41)	15.7 (29) $	14.9 (7) $$
25 to <30 (overweight)	48.9 (174)	53.8 (92)	44.3 (82) $	29.8 (14) $$
≥30 (obese)	32.0 (114)	22.2 (38)	40.0 (74) $	55.3 (26) $$
Low/moderate/vigorous physical activity level	80.1 (285)	81.3 (189)	77.8 (144)	76.6 (36)
Current smokers	18.0 (64)	17.1 (29)	11.3 (20) $	6.4 (3) $$
Cardiovascular disease	7.3 (26)	5.7 (9)	9.3 (17)	12.8 (6)
Diabetes mellitus	18.8 (67)	12.4 (21)	19.9 (36) $	27.7 (13) $$
Insomnia	13.5 (48)	17.1 (171)	11.6 (21)	19.1 (9)
Hypertension	49.7 (177)	33.0 (56)	45.4 (84) $	55.3 (26) $$
Cardio-metabolic conditions	60.4 (215)	49.7 (85)	70.8 (131) $	74.5 (35) $$
Medium–very high alcohol risk	5.9 (21)	3.3 (5)	5.8 (10)	7.5 (4)

Abbreviations: OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; BMI, body mass index; SEIFA IRSD, Socio-Economic Indexes for Areas Index of Socio-Economic Disadvantage; PSG, polysomnography; TMT-A, trail-making test A; TMT-B, trail-making test B; FOME, Fuld object memory evaluation; *SD*, standard deviation; IQR, interquartile range.
BMI: body mass index categorised according to international criteria (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 [obese]).
Cardiovascular disease: self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke.
Diabetes mellitus: self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), haemoglobin A1C ≥6.5%, or reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).
Insomnia: at least one of two PSQI dimensions (difficulty initiating or maintaining sleep) and significant daytime fatigue defined as an SF-36 Vitality Scale score one *SD* below the mean.
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 cardiovascular disease, diabetes mellitus, or hypertension.
Symbol legends: *****independent samples t-test p<0.05 compared with AHI <10/h; **$**Pearson's chi-squared test p<0.05 compared with AHI <10/h; ******independent samples t-test p<0.05 compared with AHI <10/h; **$$**Pearson's chi-squared test p<0.05 compared with AHI <10/h; **#**Mann-Whitney U-test p<0.05 compared with AHI <10/h; **##**Mann-Whitney U-test p<0.05 compared with AHI <10/h.
Notes: all PSG measures were scored according to AASM 2007 *alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to 5/h used to define sleep-disordered breathing by the AASM 2007 *recommended* scoring criteria.

6.4.3 Associations between N2 sleep spindle metrics and cognitive function outcomes

In unadjusted models, N2 sleep spindle metrics were associated with longer inspection times and worse TMT and FOME performance (Table 6.2). The association of lower N2 sleep spindle occurrence with slower inspection times did not persist in a model adjusted for age and OSA (Model 1). However, this association persisted in the fully adjusted model (Model 2) with a small effect size.

Table 6.2 Covariate unadjusted and adjusted associations between N2 sleep spindle metrics and cognitive function outcomes

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Inspection time						
Occurrence	-0.81 (-1.19, -0.42)	**<0.001**	-0.34 (-0.74, 0.07)	0.10	-0.43 (-0.85, -0.005)	**0.047**
Average frequency	0.02 (-11.9, 12.0)	0.99	2.21 (-9.12, 13.5)	0.70	1.80 (-9.93, 13.5)	0.76
Amplitude	-0.76 (-1.55, 0.03)	0.060	-0.10 (-0.87, 0.68)	0.80	-0.25 (-1.04, 0.54)	0.53
Overall density	-9.88 (-14.4, -5.37)	**<0.001**	-4.17 (-8.99, 0.66)	0.091	-3.44 (-8.36, 1.48)	0.17
Fast density	-17.4 (-27.3, -7.43)	**0.001**	-5.96 (-16.2, 4.23)	0.25	-5.45 (-15.9, 5.02)	0.31
Slow density	-11.3 (-17.4, -5.16)	**<0.001**	-4.77 (-11.1, 1.51)	0.14	-3.78 (-10.2, 2.62)	0.25
Cohen's f^2 range	0.00 – 0.05		0.14 – 0.15		0.25 – 0.27	
TMT-A						
Occurrence	-0.11 (-0.19, -0.03)	**0.009**	0.06 (-0.03, 0.14)	0.19	0.06 (-0.01, 0.12)	0.16
Average frequency	-1.95 (-4.51, 0.61)	0.13	-1.40 (-3.68, 0.88)	0.23	-1.02 (-3.35, 1.32)	0.39
Amplitude	-0.10 (-0.27, 0.07)	0.24	0.10 (-0.06, 0.25)	0.22	0.04 (-0.11, 0.20)	0.59
Overall density	-1.40 (-2.38, -0.42)	**0.005**	0.64 (-0.33, 1.62)	0.20	0.58 (-0.39, 1.68)	0.23
Fast density	-2.97 (-5.12, -0.83)	**0.007**	0.66 (-1.40, 2.72)	0.53	1.72 (-0.37, 3.80)	0.11
Slow density	-1.40 (-2.73, -0.07)	**0.039**	0.83 (-0.44, 2.10)	0.20	1.08 (-0.19, 2.36)	0.096
Cohen's f^2 range	0.004 – 0.02		0.28 – 0.30		0.43 – 0.45	
TMT-B						
Occurrence	-0.55 (-0.99, -0.10)	**0.016**	-0.54 (-0.98, -0.10)	**0.017**	0.33 (-0.13, 0.78)	0.16
Average frequency	-1.84 (-15.5, 11.8)	0.79	1.35 (-10.8, 13.5)	0.83	2.20 (-10.3, 14.6)	0.73
Amplitude	-0.74 (-1.64, 0.16)	0.11	0.29 (-0.54, 1.12)	0.49	0.19 (-0.64, 1.03)	0.65
Overall density	-7.93 (-13.1, -2.71)	**0.003**	2.16 (-3.04, 7.35)	0.41	3.57 (-1.64, 8.79)	0.18
Fast density	-15.6 (-27.0, -4.23)	**0.007**	2.77 (-8.18, 13.7)	0.62	7.05 (-4.04, 18.1)	0.21
Slow density	-8.39 (-15.4, -1.34)	**0.020**	2.60 (-4.16, 9.36)	0.45	3.41 (-3.38, 10.2)	0.33
Cohen's f^2 range	0.00 – 0.03		0.28 – 0.30		0.43 – 0.45	
FOME						
Occurrence	0.003 (0.004, 0.05)	**0.021**	-0.004 (-0.03, 0.02)	0.76	-0.007 (-0.03, 0.02)	0.60
Average frequency	0.54 (-0.14, 1.21)	0.12	0.40 (-0.23, 1.04)	0.21	0.36 (-0.31, 1.02)	0.29
Amplitude	0.008 (-0.04, 0.05)	0.72	-0.03 (-0.08, 0.01)	0.15	-0.03 (-0.07, 0.02)	0.22
Overall density	0.35 (0.09, 0.61)	**0.009**	-0.009 (-0.28, 0.26)	0.95	-0.05 (-0.33, 0.23)	0.72
Fast density	1.00 (0.44, 1.57)	**<0.001**	0.39 (-0.19, 0.96)	0.19	0.27 (-0.33, 0.86)	0.38
Slow density	0.25 (-0.11, 0.60)	0.17	-0.16 (-0.52, 0.19)	0.37	-0.19 (-0.55, 0.18)	0.31
Cohen's f^2 range	0.00 – 0.03		0.15 – 0.16		0.25 – 0.27	

Abbreviations: TMT-A, trail-making test A; TMT-B, trail-making test B; FOME, Fuld object memory evaluation; CI, confidence interval.
Coefficients: unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates: estimates represent the change in cognitive test scores corresponding to a one-unit increase in the spindle metric of interest.
Spindle metrics: occurrence (11–16 Hz, total events), average frequency (Hz), amplitude (μV), overall spindle density (11–16 Hz, number/minute), fast spindle density (13–16 Hz, number/minute), and slow spindle density (11–13 Hz, number/minute),
Adjusted Model 1: adjusted for age and AHI.
Adjusted Model 2: adjusted for age, AHI, total sleep time, financial stress, highest educational attainment, socio-economic disadvantage, marital status, alcohol risk, BMI, current smoking status, physical activity level, cardiovascular disease, diabetes mellitus, insomnia, and hypertension.
Legend: p-values representing significant associations boldfaced.
Notes: multicollinearity tests displayed acceptable variance inflation factor values for all covariates; AHI was scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

6.4.4 Associations between N3 sleep spindle metrics and cognitive function outcomes

In unadjusted models, lower N3 sleep spindle density, average spindle frequency, and spindle amplitude were associated with longer inspection times (Table 6.3). Furthermore, lower N3 sleep spindle occurrence and overall and slow spindle densities were associated with worse TMT performance. These associations did not persist in adjusted models. Although not observed in unadjusted models or models adjusted for age and OSA, associations of higher N3 sleep average spindle frequency and fast spindle density with worse TMT-B performance emerged in the fully adjusted model (Model 2) with medium effect sizes.

Table 6.3 Covariate unadjusted and adjusted associations between N3 sleep spindle metrics and cognitive function outcomes

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Inspection time						
Occurrence	-0.96 (-3.92, 1.99)	0.52	1.63 (-1.29, 4.56)	0.27	1.55 (-1.44, 4.54)	0.31
Average frequency	-1.59 (-2.91, -0.26)	**0.019**	-1.02 (-2.29, 0.26)	0.12	-0.92 (-2.21, 0.36)	0.16
Amplitude	-0.64 (-1.09, -0.18)	**0.007**	-0.36 (-0.80, 0.09)	0.12	-0.42 (-0.86, 0.02)	0.061
Overall density	-5.73 (-11.4, -0.10)	**0.046**	-0.36 (-5.97, 5.25)	0.90	-0.14 (-5.80, 5.51)	0.96
Fast density	-10.3 (-30.1, 9.62)	0.31	3.15 (-16.0, 22.3)	0.75	2.93 (-16.6, 22.4)	0.77
Slow density	-6.29 (-12.7, 0.09)	0.053	-0.80 (-7.11, 5.51)	0.80	-0.50 (-6.87, 5.88)	0.88
Cohen's f^2 range	0.001 – 0.02		0.14 – 0.15		0.25 – 0.27	
TMT-A						
Occurrence	-0.87 (-1.49, -0.24)	**0.007**	-0.12 (-0.71, 0.47)	0.70	0.007 (-0.59, 0.60)	0.98
Average frequency	-0.15 (-0.43, 0.14)	0.31	0.03 (-0.23, 0.29)	0.81	0.14 (-0.12, 0.39)	0.30
Amplitude	-0.05 (-0.15, 0.05)	0.36	0.04 (-0.05, 0.13)	0.38	0.03 (-0.06, 0.12)	0.50
Overall density	-1.85 (-3.05, -0.65)	**0.003**	-0.26 (-1.39, 0.87)	0.65	-0.08 (-1.21, 1.05)	0.88
Fast density	-3.55 (-7.80, 0.71)	0.10	0.27 (-3.59, 4.12)	0.89	1.73 (-2.15, 5.62)	0.38
Slow density	-2.00 (-3.36, -0.64)	**0.004**	-0.36 (-1.63, 0.92)	0.58	-0.29 (-1.56, 0.98)	0.65
Cohen's f^2 range	0.002 – 0.03		0.28 – 0.30		0.43 – 0.45	
TMT-B						
Occurrence	-3.71 (-7.05, -0.37)	**0.030**	0.17 (-2.98, 3.32)	0.92	0.44 (-2.73, 3.62)	0.78
Average frequency	0.02 (-1.50, 1.53)	0.98	0.92 (-0.45, 2.28)	0.19	1.48 (0.12, 2.83)	**0.033**
Amplitude	-0.29 (-0.83, 0.25)	0.30	0.20 (-0.29, 0.69)	0.42	0.22 (-0.26, 0.70)	0.37
Overall density	-6.99 (-13.4, -0.60)	**0.032**	1.26 (-4.75, 7.28)	0.68	2.18 (-3.81, 8.17)	0.47
Fast density	-6.75 (-29.4, 15.9)	0.56	13.1 (-7.36, 33.6)	0.21	20.7 (0.55, 40.9)	**0.044**
Slow density	-8.27 (-15.5, -1.03)	**0.025**	0.17 (-6.60, 6.94)	0.96	0.80 (-5.96, 7.56)	0.82
Cohen's f^2 range	0.00 – 0.03		0.28 – 0.30		0.43 – 0.45	
FOME						
Occurrence	0.16 (-0.004, 0.33)	0.055	0.03 (-0.14, 0.19)	0.73	0.04 (-0.13, 0.21)	0.68
Average frequency	0.07 (-0.002, 0.15)	0.056	0.04 (-0.03, 0.12)	0.23	0.04 (-0.03, 0.11)	0.26
Amplitude	0.01 (-0.02, 0.04)	0.37	-0.006 (-0.03, 0.02)	0.65	-0.004 (-0.03, 0.02)	0.77
Overall density	0.29 (-0.03, 0.60)	0.079	-0.01 (-0.33, 0.31)	0.95	-0.006 (-0.33, 0.31)	0.97
Fast density	1.06 (-0.06, 2.18)	0.064	0.35 (-0.73, 1.42)	0.53	0.13 (-0.97, 1.24)	0.81
Slow density	0.26 (-0.11, 0.62)	0.16	-0.05 (-0.41, 0.31)	0.78	-0.02 (-0.38, 0.34)	0.90
Cohen's f^2 range	0.002 – 0.01		0.13 – 0.15		0.25 – 0.27	

Abbreviations: TMT-A, trail-making test A; TMT-B, trail-making test B; FOME, Fuld object memory evaluation; CI, confidence interval.
Coefficients: unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates: estimates represent the change in cognitive test scores corresponding to a one-unit increase in the spindle metric of interest.
Spindle metrics: occurrence (11–16 Hz, total events), average frequency (Hz), amplitude (μV), overall spindle density (11–16 Hz, number/minute), fast spindle density (13–16 Hz, number/minute), and slow spindle density (11–13 Hz, number/minute).
Adjusted Model 1: adjusted for age and AHI.
Adjusted Model 2: adjusted for age, AHI, total sleep time, financial stress, highest educational attainment, socio-economic disadvantage, marital status, alcohol risk, BMI, current smoking status, physical activity level, cardiovascular disease, diabetes mellitus, insomnia, and hypertension.
Legend: p-values representing significant associations boldfaced.
Notes: multicollinearity tests displayed acceptable variance inflation factor values for all covariates; AHI was scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

6.4.5 Interaction analysis by OSA severity

Significant OSA severity-by-spindle metric interactions with cognitive function were observed (Tables 6.4 and 6.5). With an increase in N2 sleep average spindle frequency, there was a decrease in TMT-A completion times (better performance) in men with severe OSA (Figure 6.2, Table 6.6). Furthermore, with an increase in N2 sleep spindle amplitude, there was an increase in TMT-B completion times (worse performance) in men with mild OSA (Figure 6.3, Table 6.6). Moreover, with an increase in N3 sleep spindle occurrence, there was an improvement in FOME performance (higher scores) in men with mild OSA but a decline (lower scores) in men with moderate OSA (Figure 6.4, Table 6.7).

Table 6.4 Interaction effects of OSA severity-by-N2 sleep spindle metrics with cognitive function outcomes

	Inspection time			TMT-A			TMT-B			FOME		
	Wald χ^2	df	*p*	Wald χ^2	df	*p*	Wald χ^2	df	*p*	Wald χ^2	df	*p*
Occurrence												
OSA	1.64	3	0.65	7.25	3	0.064	4.21	3	0.24	1.57	3	0.67
Occurrence	10.5	1	0.001	3.41	1	0.065	1.75	1	0.19	1.15	1	0.28
OSA*occurrence	1.33	3	0.72	1.14	3	0.77	0.58	3	0.90	2.55	3	0.47
Overall density												
OSA	1.25	3	0.74	6.83	3	0.078	4.29	3	0.23	1.51	3	0.68
Overall density	12.1	1	<0.001	3.00	1	0.083	2.68	1	0.10	1.54	1	0.21
OSA*overall density	1.76	3	0.63	1.19	3	0.76	0.99	3	0.81	3.23	3	0.36
Fast density												
OSA	3.12	3	0.37	7.21	3	0.066	3.71	3	0.29	1.42	3	0.70
Fast density	8.51	1	0.004	4.68	1	0.031	4.17	1	0.041	4.09	1	0.043
OSA*fast density	1.08	3	0.78	4.15	3	0.25	0.97	3	0.81	4.80	3	0.19
Slow density												
OSA	1.62	3	0.66	12.1	3	0.007	8.10	3	0.044	1.95	3	0.58
Slow density	6.77	1	0.009	0.05	1	0.83	0.08	1	0.78	0.18	1	0.67
OSA*slow density	1.00	3	0.80	4.53	3	0.21	5.69	3	0.13	2.25	3	0.52
Average frequency												
OSA	5.73	3	0.13	15.5	3	0.001	7.44	3	0.059	2.63	3	0.45
Frequency	0.49	1	0.49	5.81	1	0.016	0.44	1	0.51	0.89	1	0.35
OSA*frequency	1.97	3	0.58	12.5	3	**0.006**	6.35	3	0.096	5.43	3	0.14
Amplitude												
OSA	5.24	3	0.16	10.6	3	0.014	5.53	3	0.14	1.84	3	0.61
Amplitude	4.25	1	0.039	2.73	1	0.099	4.60	1	0.032	0.99	1	0.32
OSA*amplitude	2.99	3	0.39	3.91	3	0.27	8.16	3	**0.043**	5.58	3	0.13

Abbreviations: df, degrees of freedom; TMT-A, trail-making test A; TMT-B, trail-making test B; FOME, Fuld object memory evaluation.
Spindle metrics: occurrence (11–16 Hz, total events), overall density (11–16 Hz, number/minute), fast density (13–16 Hz, number/minute), slow density (11–13 Hz, number/minute), average frequency (Hz), and amplitude (μV).
Legend: p-values representing significant interaction terms boldfaced.

Table 6.5 Interaction effects of OSA severity-by-N3 sleep spindle metrics with cognitive function outcomes

	Inspection time			TMT-A			TMT-B			FOME		
	Wald χ^2	df	*p*	Wald χ^2	df	*p*	Wald χ^2	df	*p*	Wald χ^2	df	*p*
Occurrence												
OSA	2.35	3	0.50	5.12	3	0.16	2.87	3	0.41	1.18	3	0.76
Occurrence	2.50	1	0.11	6.62	1	0.010	2.33	1	0.13	0.72	1	0.40
OSA*occurrence	5.22	3	0.16	4.89	3	0.18	1.63	3	0.65	9.61	3	**0.022**
Overall density												
OSA	1.73	3	0.63	5.15	3	0.16	2.96	3	0.40	0.85	3	0.84
Overall density	4.49	1	0.034	6.80	1	0.009	2.93	1	0.087	1.66	1	0.20
OSA*overall density	3.56	3	0.31	2.79	3	0.43	0.37	3	0.95	4.78	3	0.19
Fast density												
OSA	4.59	3	0.20	9.67	3	0.022	5.06	3	0.17	1.66	3	0.65
Fast density	0.66	1	0.42	0.92	1	0.34	0.05	1	0.82	0.33	1	0.57
OSA*fast density	2.53	3	0.47	1.80	3	0.62	1.60	3	0.66	3.37	3	0.34
Slow density												
OSA	1.19	3	0.76	4.31	3	0.23	2.86	3	0.41	0.44	3	0.93
Slow density	4.79	1	0.029	6.86	1	0.009	2.62	1	0.11	2.56	1	0.11
OSA*slow density	3.39	3	0.34	3.03	3	0.39	0.17	3	0.98	5.78	3	0.12
Average frequency												
OSA	3.59	3	0.31	9.54	3	0.023	7.26	3	0.064	1.31	3	0.73
Frequency	0.05	1	0.82	0.39	1	0.53	1.37	1	0.24	0.48	1	0.49
OSA*frequency	2.11	3	0.55	0.32	3	0.96	2.41	3	0.49	3.52	3	0.32
Amplitude												
OSA	5.80	3	0.12	10.5	3	0.015	5.19	3	0.16	1.81	3	0.61
Amplitude	1.66	1	0.20	0.71	1	0.40	0.88	1	0.35	1.21	1	0.27
OSA*amplitude	5.40	3	0.15	2.21	3	0.53	1.43	3	0.70	5.85	3	0.12

Abbreviations: df, degrees of freedom; TMT-A, trail-making test A; TMT-B, trail-making test B; FOME, Fuld object memory evaluation.
Spindle metrics: occurrence (11–16 Hz, total events), overall density (11–16 Hz, number/minute), fast density (13–16 Hz, number/minute), slow density (11–13 Hz, number/minute), average frequency (Hz), and amplitude (μV).
Legend: p-values representing significant interaction terms boldfaced.

Table 6.6 Multiplicative interactions terms of OSA severity-by-N2 sleep spindle metrics with cognitive function outcomes

	Inspection time		TMT-A		TMT-B		FOME	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Occurrence								
AHI 10–19/h	-1.78 (-9.37, 5.81)	0.65	-0.88 (-2.52, 0.77)	0.30	1.66 (-7.11, 10.4)	0.71	0.18 (-0.25, 0.62)	0.41
AHI 20–29/h	2.81 (-7.35, 13.0)	0.59	-0.02 (-2.22, 2.17)	0.98	0.32 (-11.4, 12.1)	0.96	-0.29 (-0.87, 0.30)	0.50
AHI ≥30/h	-4.53 (-15.2, 6.13)	0.41	-0.17 (-2.48, 2.13)	0.88	4.50 (-7.81, 16.8)	0.47	-0.21 (-0.83, 0.40)	0.50
Overall density								
AHI 10–19/h	-0.98 (-8.30, 6.34)	0.79	-0.68 (-2.26, 0.91)	0.40	0.77 (-7.67, 9.21)	0.86	0.17 (-0.25, 0.59)	0.42
AHI 20–29//h	3.60 (-6.01, 13.2)	0.46	0.48 (-1.60, 2.57)	0.65	1.23 (-9.85, 12.3)	0.83	-0.30 (-0.85, 0.25)	0.28
AHI ≥30/h	-5.24 (-16.3, 5.83)	0.35	-0.07 (-2.46, 2.33)	0.96	6.44 (-6.32, 19.2)	0.32	-0.27 (-0.91, 0.36)	0.40
Fast density								
AHI 10–19/h	-1.39 (-8.99, 6.22)	0.72	-0.53 (-2.16, 1.09)	0.52	1.79 (-6.92, 10.5)	0.69	0.03 (-0.40, 0.46)	0.90
AHI 20–29//h	2.04 (-8.27, 12.3)	0.70	0.90 (-1.30, 3.10)	0.42	4.16 (-7.63, 16.0)	0.49	-0.51 (-1.09, 0.07)	0.084
AHI ≥30/h	-3.77 (-12.8, 5.22)	0.41	-1.56 (-3.48, 0.36)	0.11	-2.14 (-12.4, 8.17)	0.68	-0.35 (-0.86, 0.16)	0.17
Slow density								
AHI 10–19/h	-1.69 (-9.36, 5.99)	0.67	-0.79 (-2.43, 0.86)	0.35	-0.98 (-9.73, 7.77)	0.83	0.25 (-0.19, 0.69)	0.27
AHI 20–29//h	3.10 (-6.67, 12.9)	0.53	0.08 (-2.02, 2.18)	0.94	-1.30 (-12.4, 9.84)	0.82	-0.11 (-0.67, 0.45)	0.70
AHI ≥30/h	-3.32 (-16.2, 9.60)	0.61	2.43 (-0.34, 5.20)	0.085	17.0 (2.29, 31.7)	0.082	-0.24 (-0.99, 0.50)	0.52
Frequency								
AHI 10–19/h	-1.96 (-10.2, 6.28)	0.64	0.42 (-1.30, 2.15)	0.63	5.41 (-3.89, 14.7)	0.25	-0.46 (-0.92, 0.005)	0.052

AHI 20–29//h	-0.18 (-9.89, 9.53)	0.97	0.68 (-1.35, 2.71)	0.51	5.99 (-4.97, 16.9)	0.28	-0.43 (-0.98, 0.12)	0.12
AHI ≥30/h	-7.25 (-17.6, 3.15)	0.17	-3.46 (-5.64, -1.29)	**0.002**	-9.88 (-21.7, 2.00)	0.10	0.02 (-0.57, 0.61)	0.95
Amplitude								
AHI 10–19/h	3.95 (-2.55, 10.4)	0.23	1.25 (-0.14, 2.64)	0.077	9.89 (2.53, 17.3)	**0.008**	-0.41 (-0.78, -0.04)	0.13
AHI 20–29//h	3.52 (-6.51, 13.5)	0.49	0.47 (-1.67, 2.60)	0.67	3.84 (-7.50, 15.2)	0.51	-0.15 (-0.72, 0.42)	0.60
AHI ≥30/h	-3.73 (-14.4, 6.95)	0.49	-0.19 (-2.47, 2.08)	0.87	-0.35 (-12.5, 11.8)	0.96	0.001 (-0.61, 0.61)	0.99

Abbreviations: AHI, apnea-hypopnea index; FOME, Fuld object memory evaluation.
Spindle metrics: occurrence (11–16 Hz, total events), overall density (11–16 Hz, number/minute), fast density (13–16 Hz, number/minute), slow density (11–13 Hz, number/minute), mean frequency (Hz), and mean maximum amplitude (μV).
Legend: p-values representing significant multiplicative interaction terms boldfaced.

Table 6.7 Multiplicative interactions terms of OSA severity-by-N3 sleep spindle metrics with cognitive function outcomes

	Inspection time		TMT-A		TMT-B		FOME	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Occurrence								
AHI 10–19/h	-4.88 (-12.7, 2.98)	0.22	-0.67 (-2.33, 0.99)	0.43	0.60 (-8.33, 9.53)	0.90	0.53 (0.09, 0.97)	**0.019**
AHI 20–29/h	-0.68 (-12.0, 10.6)	0.91	0.54 (-1.86, 2.93)	0.66	2.98 (-9.89, 15.8)	0.65	-0.53 (-1.17, 0.10)	**0.020**
AHI ≥30/h	-13.3 (-25.9, -0.72)	0.092	-2.76 (-5.42, -0.09)	0.18	-8.26 (-22.7, 6.14)	0.26	0.09 (-0.62, 0.80)	0.81
Overall density								
AHI 10–19/h	-3.37 (-10.9, 4.14)	0.38	-0.75 (-2.35, 0.84)	0.35	0.45 (-8.12, 9.01)	0.92	0.39 (-0.04, 0.81)	0.075
AHI 20–29/h	0.98 (-9.48, 11.4)	0.86	0.28 (-1.93, 2.50)	0.80	-0.44 (-12.4, 11.5)	0.94	-0.23 (-0.82, 0.37)	0.45
AHI ≥30/h	-10.5 (-22.5, 1.49)	0.086	-1.83 (-4.38, 0.71)	0.16	-3.95 (-17.7, 9.75)	0.57	0.25 (-0.44, 0.93)	0.48
Fast density								
AHI 10–19/h	-4.13 (-11.6, 3.38)	0.28	-0.47 (-2.07, 1.13)	0.57	1.00 (-7.56, 9.56)	0.82	0.13 (-0.29, 0.56)	0.37
AHI 20–29/h	1.14 (-11.5, 13.7)	0.86	0.89 (-1.79, 3.57)	0.52	4.15 (-10.2, 18.5)	0.57	-0.46 (-1.17, 0.25)	0.21
AHI ≥30/h	-5.78 (-14.4, 2.82)	0.19	-0.88 (-2.71, 0.95)	0.35	-4.57 (-14.4, 5.23)	0.36	-0.22 (-0.71, 0.26)	0.37
Slow density								
AHI 10–19/h	-3.37 (-11.4, 4.64)	0.41	-0.98 (-2.68, 0.72)	0.26	-0.77 (-9.89, 8.36)	0.87	0.46 (0.002, 0.91)	0.28
AHI 20–29/h	0.79 (-9.48, 11.0)	0.88	0.08 (-2.10, 2.26)	0.94	-1.53 (-13.2, 10.2)	0.80	-0.14 (-0.72, 0.44)	0.64
AHI ≥30/h	-12.4 (-26.8, 2.03)	0.092	-2.19 (-5.25, 0.87)	0.16	-2.81 (-19.3, 13.6)	0.74	0.53 (-0.29, 1.34)	0.21
Frequency								
AHI 10–19/h	-4.43 (-15.7, 6.86)	0.44	0.28 (-2.14, 2.70)	0.82	-5.15 (-18.0, 7.72)	0.43	0.52 (-0.12, 1.16)	0.11

AHI 20–29/h	20.5 (-32.2, 73.1)	0.45	-2.84 (-14.1, 8.45)	0.62	35.9 (-24.1, 95.8)	0.24	0.08 (-2.90, 3.06)	0.96
AHI ≥30/h	-4.76 (-13.2, 3.68)	0.27	0.15 (-1.67, 1.96)	0.88	1.33 (-8.31, 11.0)	0.79	-0.07 (-0.55, 0.41)	0.78
Amplitude								
AHI 10–19/h	2.14 (-4.71, 8.99)	0.54	1.06 (-0.42, 2.54)	0.16	4.45 (-3.45, 12.3)	0.27	-0.41 (-0.81, -0.02)	0.16
AHI 20–29/h	8.59 (-7.52, 24.7)	0.30	0.07 (-3.41, 3.55)	0.97	-0.49 (-19.1, 18.1)	0.96	0.02 (-0.91, 0.94)	0.97
AHI ≥30/h	-6.20 (-14.3, 1.92)	0.13	0.15 (-1.60, 1.91)	0.86	0.33 (-9.97, 10.6)	0.95	0.09 (-0.43, 0.60)	0.74

Abbreviations: AHI, apnea-hypopnea index; FOME, Fuld object memory evaluation.
Spindle metrics: occurrence (11–16 Hz, total events), overall density (11–16 Hz, number/minute), fast density (13–16 Hz, number/minute), slow density (11–13 Hz, number/minute), mean frequency (Hz), and mean maximum amplitude (μV).
Legend: p-values representing significant multiplicative interaction terms boldfaced.

Figure 6.3 Significant interaction of OSA severity-by-N2 sleep overall spindle frequency with TMT-A performance

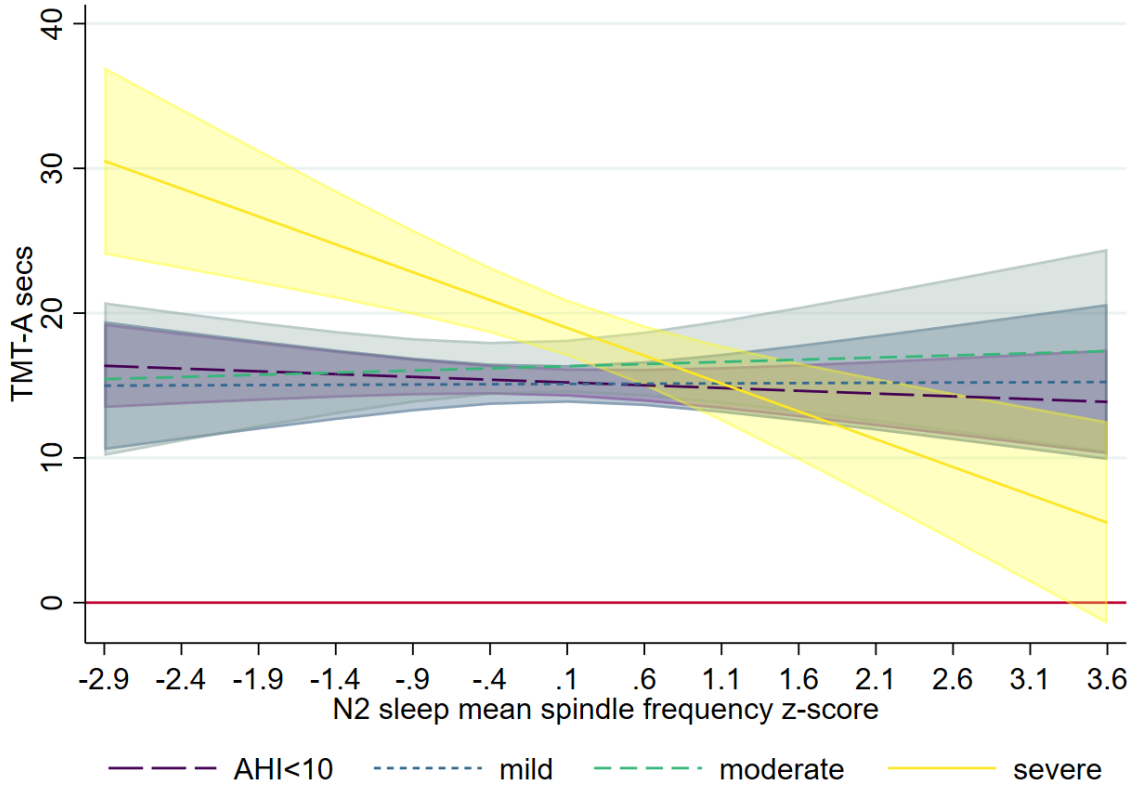


Figure 6.4 Significant interaction of OSA severity-by-N2 sleep overall spindle amplitude with TMT-B performance

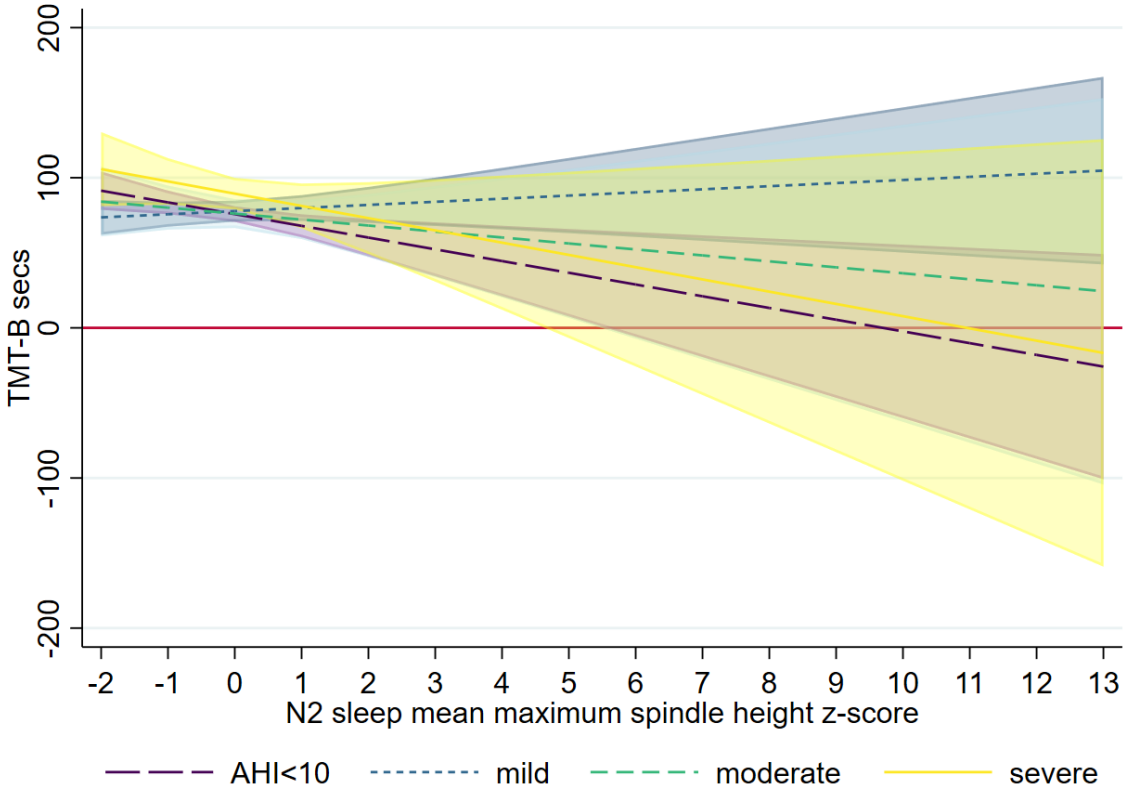
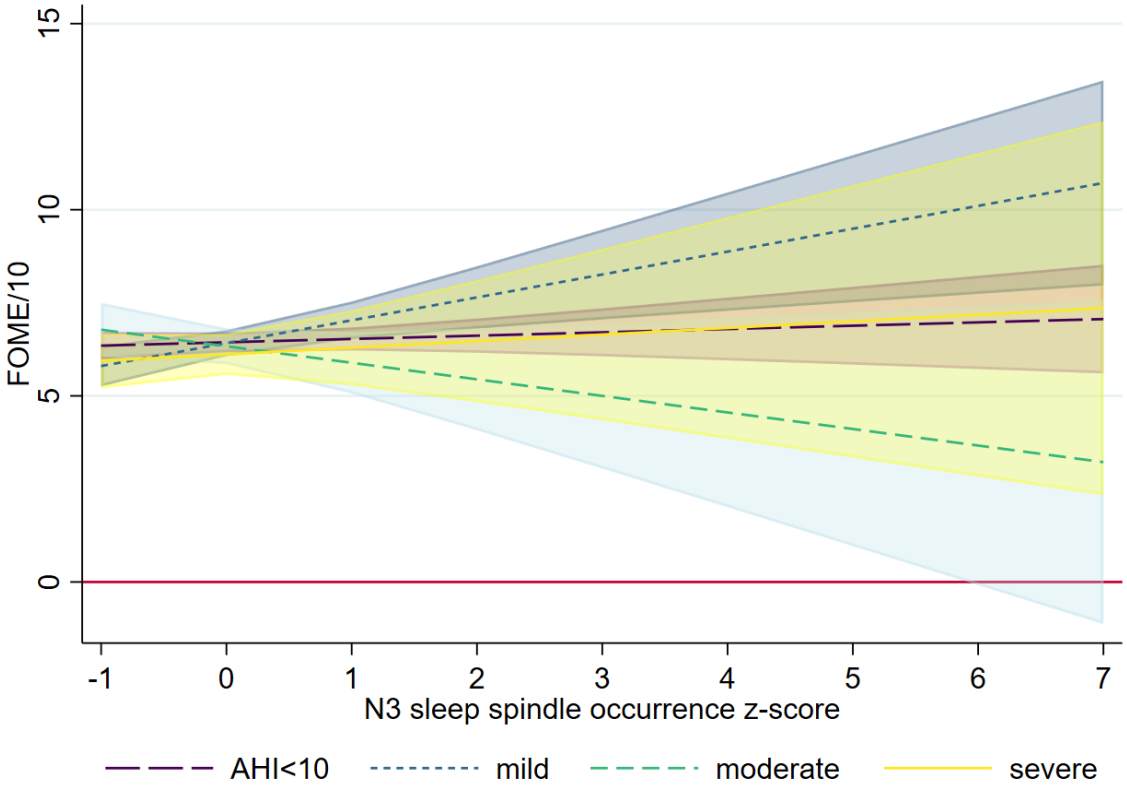


Figure 6.5 Significant interaction of OSA severity-by-N3 sleep overall spindle occurrence with FOME performance



6.5 Discussion

In this sample of community-dwelling middle-aged and older men, significant cross-sectional associations were identified between several sleep spindle metrics and cognitive function outcomes, and OSA severity significantly moderated these associations. These results extend smaller experimental studies and support the involvement of sleep spindles in cognitive impairment in OSA.

Evidence supporting spindle deficits in OSA comes from small studies reporting lower spindle occurrence, density, and frequency in patients with OSA compared to age- and gender-matched controls (46, 277). The results of the present study partly support previous small studies as men with at least mild through to severe OSA showed lower N2 and N3 sleep spindle densities compared to men without OSA. The finding of deficits in spindle metrics with increasing OSA severity extends smaller studies and highlights the importance of further investigation to determine if spindle deficits in OSA are reversible with treatment.

The unadjusted associations between N2 sleep spindle metrics and memory performance (FOME test) support small studies (49, 50, 281). Hennies et al. (50) presented healthy young men and women (n=23) with a set of facts from which higher N2 sleep spindle density was associated with better fact recall. Gais et al. (49) also found that higher N2 sleep fast and slow spindle densities were associated with better learning and memory in healthy young men and women (n=49). In the present study, the associations between N2 sleep spindle occurrence and densities and FOME performance were diluted after controlling for age and OSA. Consequently, age and OSA likely confound unadjusted associations of spindle occurrence and densities with memory performance in the FAMAS cohort and small studies.

The associations between higher N3 sleep fast spindle density and average frequency and worse TMT-B performance were unexpected, as faster spindles during N2 sleep are typically associated with better cognitive function (269). This finding supports that the association between fast spindle density and executive function differs during N2 versus N3 sleep. Although significant, these associations had small-medium effect sizes. Therefore, clinical significance remains uncertain and should be interpreted with caution.

Given that fast spindles are often maximal in the centroparietal brain region (269), studies measuring high-resolution EEG are warranted to clarify the potential role of regional fast spindles in executive function. The significant associations between higher N3 sleep fast spindle density and frequency and worse executive function, when these spindle metrics are typically associated with better performance during N2 sleep, highlights the importance of exploring sleep spindles during N2 and N3 sleep separately as these may represent different neurobiological phenomena in relation to cognitive function.

The adjusted association between higher N2 spindle occurrence and longer inspection times is challenging to compare to previous studies. The association between sleep spindles during N2 and N3 sleep and visual processing speed has not been investigated previously. Consequently, this association warrants further investigation in community-based cohort studies.

The present study expands on literature that has examined sleep spindle metrics in relation to non-memory cognitive function outcomes. Guadagni et al. (282) examined associations between N2 and N3 sleep spindle densities and executive function amongst healthy middle-aged and older men and women (n=63) independent of age, AHI, BMI, and periodic limb movement index. Higher N2 fast and slow spindle densities were associated with better executive function. In another study, Lafortune et al. (51) found that higher N2 overall spindle density was associated with better attention, vigilance, and verbal fluency amongst healthy middle-aged and older men and women (n=58). However, these studies utilised discrepant cognitive function outcomes, analysis approaches, and sample sizes. The present study used raw cognitive test scores and z-scores for spindle metrics, whereas Guadagni et al. (282) utilised principal component analysis to distil multiple cognitive outcomes into three factors. Furthermore, given the relatively small sample, Lafortune et al. (51) (n=58) were more limited in their ability to control for potential confounding variables compared to the comparatively larger FAMAS cohort.

Emerging evidence for differences in sleep spindle metrics between people with and without OSA (46, 277) and associations with cognitive function (283, 381) emphasises the importance of utilising data from community-based samples to

determine if OSA plays an important moderating role in these associations. Djonlagic et al. (45) examined cross-sectional associations between sleep spindle metrics and cognitive function outcomes in late middle-aged and older men and women (n=3,819) from the community-based MESA and MrOS cohorts. While the authors reported an association of higher N2 fast spindle density with better executive function (TMT-B performance), N3 sleep spindle metrics were not associated with executive function, contrasting with the present study. However, Djonlagic et al. (45) did not investigate the potential moderation effects of OSA, which was the original contribution of the present study.

The significant interaction effect where decreased N2 sleep spindle frequency was associated with worse TMT-A performance in men with severe OSA is suggestive of potentially disrupted thalamocortical network integrity. Previous literature reports significantly altered brain network organisation, topology, and functional connectivity in patients with OSA across whole-brain, frontal, parietal, and centroparietal regions where spindle events typically occur (384). In the FAMAS cohort, men with severe OSA could have had altered functional connectivity, which may partly explain the association between decreased sleep spindle frequency and worse TMT-A performance. However, functional connectivity was not assessed in the FAMAS cohort. Therefore, further research remains warranted to determine if cortical connectivity influences the associations between spindles and cognition in patients with severe OSA. Also, preliminary evidence suggests an improvement in spindle frequency with continuous positive airway pressure (CPAP) (368, 383). Therefore, further studies remain warranted to determine whether spindle frequency can be improved with CPAP and how this relates to cognitive function.

The significant interaction effect where decreased N2 sleep spindle amplitude was associated with worse TMT-B performance, but only in men with mild OSA, is difficult to compare with smaller studies. Only one study previously examined associations between spindle amplitude and cognitive impairment and reported lower maximum spindle amplitude in patients with subjective cognitive complaints and mild cognitive impairment compared to controls with normal cognitive function (281). No studies have investigated spindle amplitude during N2 or N3 sleep in patients with OSA and how these variables potentially interact to influence cognitive function. The significant

interaction effect in the present study may reflect a decrease in activation of the thalamocortical network in patients with mild OSA, which could have potentially resulted in lower spindle amplitude during N2 sleep. The lack of an OSA severity and N3 sleep spindle amplitude interaction effect on TMT-A performance suggests that spindles during N2 and N3 sleep in patients with OSA may differentially affect cognitive function. Further research is needed to clarify the interactions between OSA severity and spindle amplitude separately for N2 and N3 sleep with cognitive function.

Sleep spindle events may play an important role in memory formation and be associated with synaptic plasticity. Cox et al. (271) found that N3 sleep spindles were responsible for potentiating memories. In the present study, interaction analysis revealed that the mild and moderate OSA severity categories showed differential associations between FOME performance and N3 spindle occurrence. In men with mild OSA, FOME performance improved with increasing N3 sleep spindle occurrence, whereas FOME performance decreased in men with moderate OSA. The significant interaction effect in men with moderate OSA could be partly related to cortical changes associated with OSA. Conversely, in patients with mild OSA, the effect of cortical changes on sleep spindles may not have been as prominent. Interestingly, in two groups of 20 patients with newly diagnosed OSA, Hoth et al. (385) reported that higher levels of hypoxemia resulted in better memory performance, which conflicts with the present study. Furthermore, previous findings suggest that hypoxic preconditioning or continued exposure to mild levels of OSA and hypoxia may induce a compensatory response and increase resistance to subsequent hypoxia (386), which may, in part, explain the significant interaction effect in men with mild OSA. Further large cohort studies are needed to provide evidence on the moderating role of OSA and associated physiological consequences on the association between sleep spindle events and memory function.

The main strength of the present study is the well-characterised sample of community-dwelling men with objectively measured sleep spindles and the use of multiple standardised and validated cognitive tests (68, 306, 387). The community-based sample provided the advantage of conducting interaction analyses to determine if OSA severity significantly moderated associations between sleep

spindle metrics and cognitive function outcomes. Another important strength is the availability of extensive survey and biomedical data (303, 320), allowing for control of key confounders and OSA, which could influence sleep spindles, cortical activity, and cognitive function.

The main limitation of the present study is a cross-sectional design, preventing conclusions regarding causal inference. Also, the cognitive tests administered are typically less extensive than those employed in the extant literature necessary to provide comprehensive cognitive assessments across multiple domains (388). Given that the PSG assessments were performed on average 26.6 months (*SD* = 11.8 range: 3–51) after cognitive testing and cognition typically declines with age (338), the associations between sleep spindle metrics and cognitive function outcomes are likely underestimated. Sleep spindle metrics were identified using only a single frontal EEG derivation (F4–M1), and topographical differences may have been missed. Lastly, the sleep sub-study was conducted exclusively in men, with results in women remaining unknown.

In summary, among this relatively large sample of community-dwelling middle-aged and older men with an objective assessment of OSA, specific N2 and N3 sleep spindle metrics were independently associated with cognitive function. Moreover, OSA severity was an important moderator of associations between sleep spindle metrics and cognitive function outcomes. Randomised controlled trials remain warranted to determine if CPAP treatment can reverse spindle abnormalities. Longitudinal studies are also warranted to determine if spindle metrics in mid-life predict cognitive decline in older age and are modified by OSA treatment.

6.6 Supplementary Tables

Supplementary Table 6.1 Cognitive function outcomes across risk factor covariate categories

	Inspection time (milliseconds)	TMT-A (seconds)	TMT-B (seconds)	FOME (number/10)
Age (years)	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**
<50	55.8 (15.9)	13.1 (3.9)	62.8 (20.9)	7.1 (1.5)
50–69	62.1 (23.7)	15.1 (4.9)	75.7 (25.9)	6.4 (1.7)
≥70	84.7 (50.7)	21.3 (9.8)	101.8 (52.4)	5.4 (1.6)
p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Financial stress				
Spends >earns	62.3 (19.9)	17.5 (6.6)	84.0 (29.4)	6.2 (1.6)
Saves a little/lot	65.4 (32.7)	15.5 (6.5)	76.4 (34.9)	6.4 (1.7)
p	0.52	**0.033**	0.12	0.43
Highest educational attainment				
≥Certificate, diploma, trade, bachelor's degree or higher	61.7 (19.9)	15.4 (5.4)	73.7 (26.8)	6.4 (1.7)
≤High school	73.2 (48.3)	17.1 (8.2)	87.9 (47.1)	6.2 (1.6)
p	**0.020**	**0.018**	**0.004**	0.15
SEIFA IRSD				
Quintile 1 (highest socio-economic disadvantage)	66.2 (36.7)	15.9 (8.6)	78.4 (39.7)	6.1 (1.7)
Quintile 2	65.5 (36.6)	15.8 (5.6)	80.1 (47.8)	6.5 (1.6)
Quintile 3	63.6 (34.2)	15.6 (5.5)	76.3 (27.9)	6.7 (1.8)
Quintile 4	64.8 (24.8)	15.5 (5.5)	73.8 (29.9)	6.1 (1.7)
Quintile 5 (lowest socio-economic disadvantage)	65.5 (14.9)	16.9 (7.1)	84.8 (31.5)	6.3 (1.6)
p	0.98	0.81	0.45	0.16
Married/partner				
No	63.3 (23.1)	18.3 (10.9)	85.6 (48.4)	6.2 (1.9)
Yes	65.2 (32.2)	15.4 (5.3)	76.2 (30.8)	6.4 (1.7)
p	0.66	0.051	0.055	0.55
BMI (kg/m^2)				
<25 (underweight/normal)	60.5 (18.0)	16.0 (6.4)	76.6 (27.9)	6.1 (1.9)
25 to <30 (overweight)	62.9 (19.6)	15.7 (5.5)	78.1 (30.9)	6.4 (1.5)
≥30 (obese)	70.5 (46.4)	16.0 (7.9)	77.5 (41.5)	6.5 (1.8)
p	**0.041**	0.89	0.95	0.31
Physical activity level				
Sedentary behaviour	60.9 (29.8)	14.5 (5.1)	74.9 (28.2)	6.6 (1.8)
Low/moderate/vigorous	65.5 (30.7)	16.1 (6.9)	78.4 (36.3)	6.3 (1.7)
p	0.24	0.066	0.42	0.26
Smoking status				
Never/former	66.4 (33.2)	15.0 (12.0, 18.0)	78.1 (35.6)	6.3 (1.7)
Current	57.5 (14.4)	15.0 (12.0, 18.8)	75.0 (25.7)	6.5 (1.7)
p	**0.001**	0.69	0.49	0.40
Cardiovascular disease				
No	64.1 (30.5)	15.5 (5.5)	76.1 (30.9)	6.4 (1.7)
Yes	76.0 (35.6)	20.9 (13.5)	97.4 (61.0)	6.2 (1.7)
p	0.063	0.057	0.10	0.14
Diabetes mellitus				
No	62.9 (26.3)	15.3 (5.5)	73.9 (27.8)	6.4 (1.7)
Yes	74.4 (46.0)	18.4 (9.8)	95.0 (51.7)	6.2 (1.7)
p	**0.039**	**0.010**	**<0.001**	0.25
Insomnia				
No	64.4 (30.2)	15.7 (6.6)	76.9 (34.2)	6.3 (1.7)
Yes	68.7 (36.2)	16.8 (6.3)	82.7 (33.4)	6.6 (1.6)
p	0.42	0.28	0.30	0.25
Hypertension				

No	63.1 (34.0)	15.6 (5.4)	75.7 (31.3)	6.4 (1.7)
Yes	67.0 (27.1)	16.1 (7.6)	79.8 (37.1)	6.3 (1.7)
p	0.15	0.34	0.19	0.65
Cardio-metabolic conditions				
No	59.9 (29.5)	14.7 (5.1)	71.0 (26.5)	6.3 (1.7)
Yes	68.3 (31.6)	16.6 (7.2)	82.0 (37.8)	6.3 (1.7)
p	**0.009**	**0.007**	**0.001**	0.93
Alcohol risk				
Non–low	62.3 (31.7)	15.9 (6.6)	78.0 (34.7)	6.3 (1.7)
Medium–very high	58.5 (13.6)	14.9 (6.0)	70.4 (21.1)	7.4 (1.5)
p	0.49	0.20	0.51	**0.008**
Total sleep time				
<360 minutes	62.9 (25.3)	17.0 (8.0)	80.5 (42.4)	6.3 (1.7)
≥360 minutes	66.1 (33.9)	15.2 (5.4)	75.9 (28.1)	6.3 (1.7)
p	0.34	**0.007**	0.20	0.93

Abbreviations: BMI, body mass index; 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; FOME, Fuld object memory evaluation; *SD*, standard deviation.
BMI: body mass index categorised according to international criteria (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 [obese]).
Cardiovascular disease: self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke.
Diabetes mellitus: self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L [126 mg/dL], haemoglobin A1C ≥6.5%, or reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).
Insomnia: at least one of two PSQI dimensions (difficulty initiating or maintaining sleep) and significant daytime fatigue defined as an SF-36 Vitality Scale score one *SD* below the mean.
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 cardiovascular disease, diabetes mellitus, or hypertension.
Legend: p-values representing statistically significant differences boldfaced.
Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria, in which an AHI of 10/h is approximately equivalent to 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

CHAPTER 7. THE ASSOCIATION BETWEEN SLEEP MICROARCHITECTURE AND COGNITIVE FUNCTION IN MIDDLE-AGED AND OLDER MEN: A COMMUNITY-BASED COHORT STUDY

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7.1 Abstract

Study objectives: Sleep microarchitecture parameters determined by quantitative power spectral analysis (PSA) of electroencephalograms (EEGs) have been proposed as potential brain-specific markers of cognitive dysfunction. However, data from community samples remains limited. This study examined cross-sectional associations between sleep microarchitecture and cognitive dysfunction in community-dwelling men.

Methods: Florey Adelaide Male Ageing Study participants (n=477) underwent home-based polysomnography (PSG) (2010–2011). All-night EEG recordings were processed using PSA following artefact exclusion. Cognitive testing (2007–2010) included the inspection time task, trail-making tests A (TMT-A) and B (TMT-B), and Fuld object memory evaluation. Complete case cognition, PSG, and covariate data were available in 366 men. Multivariable linear regression models controlling for demographic, biomedical, and behavioural confounders determined cross-sectional associations between sleep microarchitecture and cognitive dysfunction overall and by age-stratified subgroups.

Results: In the overall sample, worse TMT-A performance was associated with higher NREM theta and REM theta and alpha but lower delta power (all $p<0.05$). In men ≥65 years, worse TMT-A performance was associated with lower NREM delta but higher NREM and REM theta and alpha power (all $p<0.05$). Furthermore, in men ≥65 years, worse TMT-B performance was associated with lower REM delta but higher theta and alpha power (all $p<0.05$).

Conclusions: Sleep microarchitecture parameters may represent important brain-specific markers of cognitive dysfunction, particularly in older community-dwelling men. Therefore, this study extends the emerging community-based cohort literature on a potentially important link between sleep microarchitecture and cognitive dysfunction. Utility of sleep microarchitecture for predicting prospective cognitive dysfunction and decline warrants further investigation.

7.2 Introduction

Cognitive dysfunction affects a considerable proportion of the general population and is particularly prevalent among older adults (3, 301). Insufficient sleep and sleep disorders are similarly associated with cognitive dysfunction (389). Emerging evidence, predominantly from small samples, suggests sleep microarchitecture may be associated with daytime cognitive dysfunction (44). However, evidence from community samples controlling for potential confounders remains scarce, leaving the nature of this association unclear.

Sleep microarchitecture parameters determined by quantitative power spectral analysis (PSA) of electroencephalograms (EEGs) may represent important brain-specific cognitive dysfunction markers (44). However, as reviewed by D'Rozario et al. (301), the emerging evidence is inconsistent. Three small case-controlled studies previously examined sleep microarchitecture in patients with mild cognitive impairment (MCI) compared to age-matched controls (40-42). Westerberg et al. (42) identified that patients with amnestic MCI (aMCI) (n=18) showed lower rapid eye movement (REM) sleep theta activity and low-frequency non-REM (NREM) sleep delta and theta activity compared to controls (n=10). Brayet et al. (40) identified that patients with aMCI (n=22) showed greater REM sleep EEG slowing (ratio of slow to fast EEG frequencies) compared to controls (n=33). Gorgoni et al. (41) identified that patients with aMCI showed lower NREM sleep fast spindle density (number/minute of ~13–16 Hz EEG bursts, ≥0.5 and ≤3 seconds) compared to controls (both n=15). In a community-based case-controlled study, the Study of Osteoporotic Fractures (n=85 MCI cases and n=85 age-matched controls), Djonlagic et al. (43) reported that community-dwelling women ≥65 years who had developed MCI five years after a baseline sleep study exhibited higher NREM sleep alpha and theta activity and REM sleep alpha and sigma activity compared to controls. In a similarly sized study, Waser

et al. (390) reported that men with cognitive decline from early to late adulthood showed greater NREM sleep EEG slowing compared to men without cognitive decline. Although previous case-controlled studies have investigated differences in sleep microarchitecture parameters between patients with MCI or cognitive decline and controls, these have not thoroughly examined associations between sleep microarchitecture and cognitive dysfunction.

Ageing is associated with an increase in sleep disorders such as obstructive sleep apnea (OSA), characterised by repeated complete (apnea) or partial (hypopnea) pharyngeal collapse (391). These nocturnal events lead to intermittent hypoxemia and hypercapnia, augmented breathing, sleep fragmentation, and blood pressure surges associated with frequent arousals (392). Sleep microarchitecture has also been impaired in patients with OSA relative to matched controls (44, 285, 287, 291). Reported abnormalities include lower NREM sleep delta activity (291, 293, 393), higher fast-frequency NREM sleep beta activity (293, 393), decreased spindle frequency and occurrence (280), reduced K-complex density (number/minute of <1 Hz EEG bursts) (394), and greater REM sleep EEG slowing (285, 287). Although OSA was associated with increased EEG power all frequency bands and greater EEG slowing during REM sleep in the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study cohort, OSA was not associated with qEEG power bands in overall sleep (34). Therefore, in contrast to Chapter 6 of this thesis, the present chapter instead treats OSA as a continuous covariate and age as a stratified moderator.

A community-based cohort study (n=664) reported that increased intermittent hypoxemia was independently associated with greater REM sleep EEG slowing and higher NREM sleep fast-frequency beta activity (34). Another community-based cohort study (n=3,819) that recruited late middle-aged and older participants from two independent community-based cohorts, the Multi-Ethnic Study of Atherosclerosis (MESA) and Osteoporotic Fractures in Men Study (MrOS), found that lower NREM sleep delta activity was associated with worse executive function (TMT-B performance) while accounting for OSA and other potential confounders (45). However, no additional community-based cohort studies have investigated potential links between sleep microarchitecture and cognitive dysfunction while accounting for

OSA and other potential confounders. Furthermore, no community-based cohort studies have determined whether sleep microarchitecture parameters are differentially associated with cognitive dysfunction amongst early to middle-aged versus older community-dwelling participants. Djonlagic et al. (45) recruited community-dwelling men and women ≥54 years, whereas the MAILES Study cohort includes participants aged 41–87 years at the time of polysomnography. The wider age range of participants in the MAILES Study provides the opportunity to perform age-stratified analyses to determine differences in the associations between sleep microarchitecture and cognitive function among early-to-middle-aged versus older community-dwelling men, which is an analysis that is yet to be performed in the extant literature.

The primary aim of the present study was to extend the emerging community-based cohort literature by investigating independent cross-sectional associations between sleep microarchitecture and cognitive dysfunction in community-dwelling men. A secondary aim was to examine cross-sectional associations between sleep microarchitecture and cognitive dysfunction in early to middle-aged (<65 years) and older (≥65 years) men to determine whether sleep microarchitecture is differentially associated with cognitive dysfunction amongst early to middle-aged versus older community-dwelling men. It was hypothesised that lower NREM sleep delta power, higher power in faster-frequency EEG bands during NREM sleep, and greater EEG slowing during REM sleep would be independently associated with worse cognitive function.

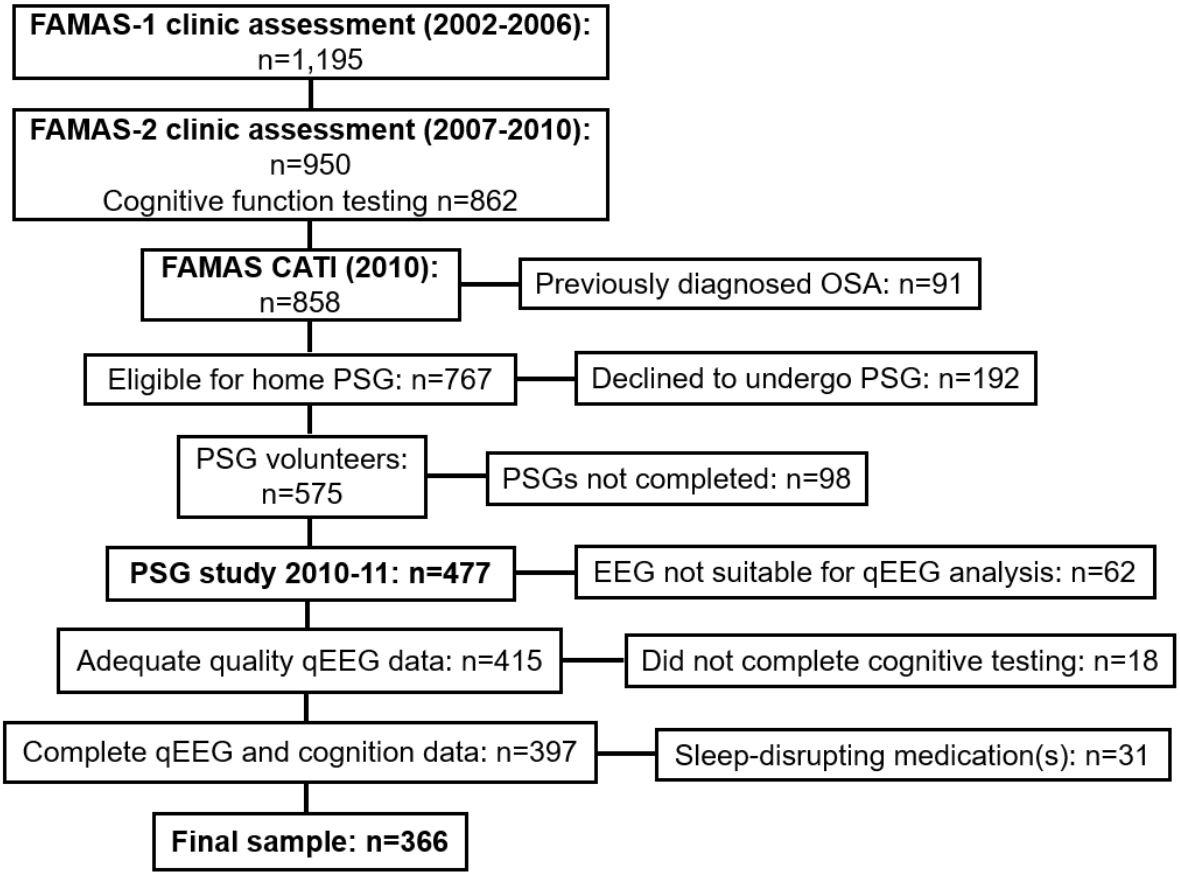
7.3 Methods

7.3.1 Study participants

The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study comprises 2,569 unselected urban community-dwelling men harmonised from two independent prospective community-based cohorts; all participants of the Florey Adelaide Male Ageing Study (FAMAS) and male participants of the North West Adelaide Health Study (NWAHS) (303). The present study includes FAMAS participants (n=1,195) aged 35–80 years at baseline (2002) and living in the northern and western regions of Adelaide, South Australia (304, 320).

During a computer-assisted telephone interview follow-up in 2010 (n=858), FAMAS participants who reported no previous OSA diagnosis (n=767) were invited to undergo unattended home-based eight-channel polysomnography (PSG) (2010–2011) as part of a sub-study of the MAILES Study (98, 303). Approximately 75% of eligible participants (n=575) agreed to undergo PSG. However, 98 PSGs were not completed due to time and budget constraints leading to a final PSG sample of 477 (Figure 7.1). As previously described, there was minor healthy volunteer responder bias among participants who underwent PSG (395). On average, participants who underwent PSG were younger, less obese, and less commonly reported poor general health compared to participants who did not undergo PSG (395). 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.

Figure 7.1 FAMAS clinic and sleep study assessments and cognitive function testing



FAMAS, Florey Adelaide Male Ageing Study. CATI, computer-assisted telephone interview. PSG, polysomnography. qEEG, quantitative electroencephalography.

7.3.2 Sleep study assessment

Participants underwent home-based eight-channel ambulatory PSG (Embletta X100, Embla Systems, Broomfield, Columbia, USA), which recorded electrical brain activity (EEG, F4-M1) and left electrooculography with 12-bit signal resolution, 200 Hz sampling rate, and band-pass filters (0.3–35 Hz) along with submental electromyography (EMG), nasal cannula pressure, thoracic and abdominal motion, finger pulse oximetry, and body position. Before PSG set-up, trained staff obtained anthropometric measurements (height, weight, and body mass index [BMI, kg/m^2]).

A single experienced sleep technician manually scored all PSG measures according to 2007 American Academy of Sleep Medicine (AASM) *Alternative* scoring criteria (32), which was recommended by an expert panel of the Australasian Sleep Association for use in prospective epidemiological studies (251). OSA was identified by an apnea-hypopnea index (AHI) ≥10/h and further categorised as mild (10–19/h), moderate (20–29/h), or severe (AHI ≥30/h). Ruehland et al. (32) have shown that an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* criteria is approximately equivalent to 10/h using the *Alternative* criteria and 15/h using the older 1999 *Chicago* criteria. Therefore, an AHI cut-off of 10/h was chosen to maintain comparability with previous work. Apnea was defined as complete or near-complete airflow cessation (≥90%) measured using nasal cannula pressure excursions with breathing lasting ≥10 seconds. Hypopnea was defined as a ≥50% decrease in nasal cannula pressure excursions and an associated ≥3% oxygen desaturation or EEG arousal (32). Sleep hypoxemia was assessed from the percentage of total sleep time with oxygen saturation <90% (32). Sleep studies were considered acceptable with ≥3.5 h of sleep and ≥5.5 h of total-recorded study time with technically acceptable respiratory and EEG signal quality for the majority of the recording.

7.3.3 EEG data processing

A detailed description of quantitative EEG (qEEG) analysis used in this study has been previously described (372, 396). Synchronised European Data Format and sleep stage files were generated using Embla REMLogic PSG Software (Natus Medical, Inc., Pleasanton, California). Of the 477 men who underwent sleep studies, PSG data were of adequate quality for qEEG analysis in 415. An algorithm identified artefactual EEG data over consecutive non-overlapping 5-second epochs based on previously validated artefact detection amplitude threshold parameters (372). Contaminated 5-second epochs, including arousals where EEG traces went outside the amplitude boundaries, were subsequently excluded from qEEG analysis.

7.3.4 Manual verification of automated artefact scoring accuracy

Automated artefact scoring accuracy was verified by manual review in 10% of randomly selected PSGs (n=36). Four agreement measures were calculated, including accuracy, sensitivity, specificity, and Cohen's Kappa (*k*). Consistent with the original artefact detection validation study (372), the algorithm displayed excellent accuracy (mean ± *SD*) (96.6% ± 4.4%) and specificity (99.9% ± 28.1%) and good to moderate sensitivity (59.1% ± 0.1%) and agreement (*k*= 0.68 ± 0.26).

7.3.5 EEG power spectral analysis

After rejecting artefactual epochs, power spectra were obtained using a standard fast Fourier transform algorithm with a rectangular weighting window for each non-overlapping 5-second epoch of EEG. Absolute spectral power (μV^2) was calculated in the delta, theta, alpha, sigma, and beta frequency bands defined as EEG activity of 0.5–4.5, 4.5–8, 8–12, 12–15, and 15–32 Hz, respectively, during NREM and REM sleep. The EEG power for each sleep-staged 30-second epoch was calculated by averaging data from six artefact-free 5-second epochs comprising each 30-second recording segment. The weighted average spectral power or spectral variance over the frequency interval within the defined frequency bands was computed for NREM (N2 and N3) and REM sleep. Weighted average spectral power is a weighted average, based on sleep stage or type, calculated by averaging the absolute power of 30-second epochs of the EEG. Relative spectral power for each frequency band

during NREM and REM sleep (e.g., delta/delta+theta+alpha+sigma+beta) was calculated. A global measure of NREM and REM EEG slowing (i.e., a ratio of slow to fast EEG frequencies [(delta+theta)/(alpha+sigma+beta)]) was also calculated.

7.3.6 Cognitive assessments

Participants completed four standardised, validated, and well-established cognitive tests outlined below during the 2007–2010 follow-up, previously described in greater detail (338), including the inspection time task, trail-making tests A and B, and the Fuld object memory evaluation (FOME) test. Refer to Chapter 2 for a detailed description of the cognitive tests. The MMSE data has not been included in the present study as it is a measure of global or geriatric cognitive impairment. The average time lag between cognitive and PSG testing was 26 (range, 3–51) months. While both FAMAS and NWAHS participants completed PSG testing, only FAMAS participants completed cognitive and PSG assessments, thus comprising the sample included in all analyses.

7.3.7 Covariate assessments

Self-completed questionnaires determined demographic (age, financial stress [spends >earns versus saves a little/lot], highest educational attainment [≥diploma, certificate, trade, bachelor's degree or higher versus ≤high school], and marital status [married/partner versus other]) and other health-related (smoking status, alcohol risk, and physical activity [low/moderate/vigorous versus sedentary behaviour]) risk factors and quality of life (the 36-item short-form survey instrument [SF-36]). BMI was categorised according to international criteria from the World Health Organisation (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 kg/m^2 [obese]) (308). Relative social disadvantage, based upon participants' residential postcode, was determined with the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-Economic Disadvantage (IRSD) (309). Clinic assessment (2007–2010) included anthropometry (BMI and waist circumference), seated sphygmomanometer blood pressure, and a fasting blood sample to assess blood glucose (304). Composite cardiovascular disease (self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke) and diabetes mellitus (self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0

mmol/L [126 mg/Dl], haemoglobin A1C [≥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 occurring at least three nights/week (Pittsburgh Sleep Quality Index [PSQI] dimensions) and significant daytime fatigue defined as an SF-36 Vitality Scale score one standard deviation (*SD*) below the mean (310). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use (311).

7.3.8 Statistical analysis methodology

Complete case cognition, PSG, and covariate data were available in 366 men. Data were analysed using IBM SPSS version 25.0 (IBM Corporation, Armonk, New York, USA). Descriptive statistics for NREM and REM sleep relative spectral powers, cognitive test scores, and continuous covariates are reported as mean (*SD*). NREM and REM sleep EEG slowing ratio is reported as median (IQR) due to non-normality. For descriptive analyses, dichotomous and categorical risk factor covariates are reported as percentages (proportion).

For analysis of cognitive function in relation to demographic, biomedical, and behavioural risk factors, one-way analysis of variances and independent samples t-tests were performed. Mann-Whitney U-tests were used to test for differences in NREM and REM sleep EEG slowing ratio between middle-aged (<65 years) and older (≥65 years) men. Moreover, independent samples t-tests were used to test for differences in NREM and REM sleep relative spectral powers between middle-aged and older men. Pearson's chi-squared tests were used to examine differences in demographic, biomedical, and behavioural risk factors between middle-aged and older men.

Univariable and multivariable linear regression models determined cross-sectional associations between cognitive dysfunction and NREM and REM sleep relative spectral powers and logarithmically (10-base) transformed EEG slowing ratio. Unstandardised beta (*B*) coefficients (95% confidence interval [CI]) and adjusted R^2 values are reported. For each sleep microarchitecture parameter, three covariate-adjusted regression models were constructed. Model 1 was adjusted for age and

OSA; model 2 was additionally adjusted for demographic (financial stress, highest educational attainment, socio-economic disadvantage, and marital status) risk factors; and model 3 was additionally adjusted for total sleep time (TST) and biomedical and behavioural (BMI, alcohol risk, smoking status, cardiovascular disease, diabetes mellitus, blood glucose, insomnia, and hypertension) risk factors. Adjustment for confounders were performed to determine whether lower NREM sleep delta power, higher power in faster-frequency EEG bands during NREM sleep, and greater REM sleep EEG slowing would be independently associated with worse cognitive function Age, BMI, blood glucose, and TST were treated continuously, with all other covariates treated dichotomously or categorically. The filter function in SPSS was used to ensure only participants with complete case cognition, PSG, and covariate data were included in the final analysis.

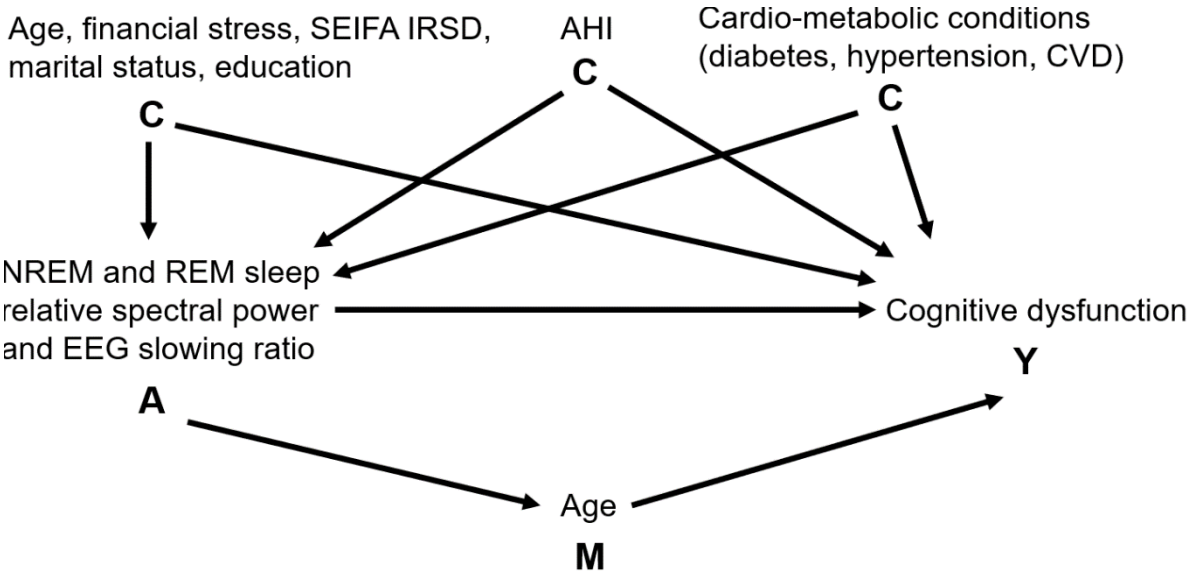
Moderator analysis was performed using age*qEEG as an interaction term to determine if age significantly moderated observed fully adjusted associations between sleep microarchitecture and cognitive dysfunction. After identifying significant moderation, age-stratified (<65 versus ≥65 years) linear regression analyses were performed to determine if sleep microarchitecture parameters were differentially associated with cognitive dysfunction amongst early to middle-aged versus older community-dwelling men.

For age-stratified multivariable linear regression analyses, the purposeful selection of covariates procedure proposed by Hosmer and Lemeshow (325) was applied to construct a robust multivariable model. Accordingly, unadjusted analyses were first performed to examine crude associations between covariates and cognitive function outcomes, with covariates returning p-values <0.25 selected as potential candidates for adjustment. Non-significant covariates were gradually removed until only significant covariates remained. Covariates not initially selected as potential candidates for adjustment were then gradually readded with the significant covariates retained earlier to identify which of these covariates were important in the presence of initially selected covariates. This purposeful covariate selection procedure reduced the final multivariable model to 8 covariates, including age, AHI, financial stress, socio-economic disadvantage, marital status, highest educational attainment, TST,

and cardio-metabolic conditions (one or more of diabetes, hypertension, or cardiovascular disease).

Assumptions of linear regression modelling, including linearity, independence, homoscedasticity, and normality, were met. Furthermore, all variance inflation factor values were near 1, indicating an absence of multicollinearity. For all analyses, a two-sided $p<0.05$ was considered statistically significant. No multiple comparison adjustments were performed (346, 347).

Figure 7.2 Overview of relationships between variables



Legend: A=exposure/treatment/intervention/primary independent variable, C=confounder, M=mediator, Y=outcome variable.

7.4 Results

Of the 477 men who underwent PSG, 397 had adequate quality sleep microarchitecture and cognition data available for analysis. In total, 366 men were included in the analysis after excluding 31 (7.8 %) who reported regularly using psychoactive medication(s), including opiates, antipsychotics, antiepileptics, antidepressants, or benzodiazepines, which may disrupt sleep microarchitecture.

7.4.1 Participant characteristics

Participant characteristics, overall and stratified by age, are reported in Table 7.1. Of the men included in the analysis, 52.5% had at least mild OSA (AHI ≥10/h), and 12.9% had severe OSA (AHI ≥30/h). Approximately one-third (31.7%) were obese (BMI ≥30 kg/m^2). Higher age, lower education, diabetes, and the presence of one or more cardio-metabolic conditions were associated with worse cognitive function (Supplementary Table 7.1).

Men ≥65 years (n=109) had more severe OSA and a higher incidence of cardiovascular disease, diabetes, hypertension, and one or more cardio-metabolic conditions compared to men <65 years (n=257). Men ≥65 years also showed lower TST compared to men <65 years. Furthermore, men ≥65 years showed higher NREM sleep theta power compared to men <65 years. However, there were no other age group differences in sleep microarchitecture.

Table 7.1 Participant characteristics (relative spectral powers, EEG slowing ratio, OSA parameters, and demographic and other risk factors)

Participant characteristics	Overall sample (n=366)	<65 years (n=257)	≥65 years (n=109)
Demographic risk factors			
Age (years), mean (*SD*)	59.0 (10.4)	53.5 (6.4)	71.9 (5.3) *
Financial stress, % (n)			
Spends >earns	15.3 (56)	14.4 (37)	17.4 (19)
Saves a little/lot	84.7 (310)	85.6 (220)	82.6 (90)
Highest educational attainment, % (n)			
≥Diploma, Certificate, Trade, Bachelor's degree or higher	71.3 (261)	73.2 (188)	67.0 (73)
SEIFA IRSD, % (n)			
Quintile 1 (highest disadvantage)	21.6 (79)	24.9 (64)	13.8 (15) $
Quintile 2	10.7 (39)	11.7 (30)	8.3 (9)
Quintile 3	29.0 (106)	32.3 (83)	21.1 (23) $
Quintile 4	26.0 (95)	22.6 (58)	33.9 (37) $
Quintile 5 (lowest disadvantage)	12.8 (47)	8.6 (22)	22.9 (25) $
Married/partner, % (n)	85.0 (311)	85.6 (220)	83.5 (91)
Relative spectral powers, mean (*SD*)			
NREM sleep			
Delta power (0.5–4.5 Hz), %	81.3 (6.9)	81.5 (6.9)	80.8 (6.6)
Theta power (4–8 Hz), %	8.1 (2.7)	7.9 (2.7)	8.5 (2.7) *
Alpha power (8–12 Hz), %	5.3 (2.4)	5.3 (2.5)	5.3 (2.4)
Sigma power (12–15 Hz), %	2.0 (1.0)	2.1 (1.0)	1.9 (1.0)
Beta power (15–32 Hz), %	3.3 (2.0)	3.3 (2.1)	3.5 (1.9)
REM sleep			
Delta power (0.5–4.5 Hz), %	70.1 (9.6)	70 (9.5)	70.3 (10)
Theta power (4.5–8 Hz), %	11.8 (4.1)	11.9 (4.0)	11.6 (4.4)
Alpha power (8–12 Hz), %	6.8 (2.5)	6.8 (2.5)	6.9 (2.7)
Sigma power (12–15 Hz), %	2.9 (1.1)	2.9 (1.1)	2.9 (1.1)
Beta power (15–32 Hz), %	8.4 (3.9)	8.4 (3.9)	8.3 (4.0)
EEG slowing ratios, median (IQR)			
NREM sleep EEG slowing ratio	9.0 (6.8, 12.4)	9.0 (6.7, 12.5)	8.8 (6.8, 12.2)
REM sleep EEG slowing ratio	4.5 (3.4, 6.4)	4.5 (3.4, 6.2)	4.5 (3.2, 6.6)
OSA severity categories (AHI), % (n)			
<10/h	47.5 (162)	50.6 (130)	43.1 (47) $
10–19/h	26.7 (91)	28 (72)	22.0 (24) $
20–29/h	12.9 (44)	11.3 (29)	18.3 (20) $
≥30/h	12.9 (44)	10.1 (26)	16.5 (18) $
Other risk factors			
Medium–very high alcohol risk, % (n)	5.2 (19)	6.6 (17)	1.8 (2) $
Low/moderate/vigorous physical activity, % (n)	77.3 (283)	75.1 (193)	82.6 (90) $
BMI (kg/m^2), % (n)			
<25 (underweight/normal)	19.9 (73)	20.6 (53)	18.3 (20)
25 to <30 (overweight)	48.4 (177)	48.2 (124)	48.6 (53)
≥30 (obese)	31.7 (116)	31.1 (80)	33.0 (36)
Current smokers, % (n)	16.9 (62)	20.2 (52)	9.2 (10) $
Cardiovascular disease, % (n)	6.8 (25)	3.1 (8)	15.6 (17) $
Insomnia, % (n)	12.8 (47)	13.2 (34)	11.9 (13)
Diabetes mellitus, % (n)	17.2 (63)	13.6 (35)	25.7 (28) $
Hypertension, % (n)	47.0 (172)	40.5 (104)	62.4 (68) $
Cardio-metabolic conditions, % (n)	56.6 (204)	48.2 (124)	73.4 (80) $
Total sleep time <360 minutes, % (n)	36.9 (135)	34.6 (89)	42.2 (46) $

Abbreviations: OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; BMI, body mass index; SEIFA IRSD, Socio-Economic Indexes for Areas Index of Relative Socio-Economic Disadvantage; *SD*, standard deviation; IQR, interquartile range.
BMI: body mass index categorised according to international criteria from the World Health Organisation (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 kg/m^2 [obese]).
Cardiovascular disease: self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke.

Diabetes mellitus: self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L (126 mg/Dl), haemoglobin A1C [≥6.5%], or reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).
Insomnia: at least one of two PSQI dimensions (difficulty initiating or maintaining sleep) and significant daytime fatigue defined as an SF-36 Vitality Scale score one *SD* below the mean.
Hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use.
Cardio-metabolic conditions: a combined variable including one or more of diabetes mellitus, hypertension, or cardiovascular disease.
Symbol legends: ***** independent samples t-test $p<0.05$ compared with men <65 years; $^{\#}$Mann-Whitney U-test $p<0.05$ compared with men <65 years; $^{\$}$Pearson's chi-squared test $p<0.05$ compared with men <65 years.
Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

7.4.2 Associations between NREM and REM sleep microarchitecture parameters and cognitive dysfunction in the overall sample

The reported unstandardised beta coefficients represent the change in cognitive test scores corresponding to a 1% increase in relative EEG power and a one-unit increase in logarithmically (10-base) transformed EEG slowing ratio. In the overall sample, worse TMT-A performance was associated with lower NREM and REM sleep delta power, higher NREM and REM sleep theta power, and higher REM sleep alpha power in unadjusted models (Table 7.2). These associations persisted after adjusting for age and OSA (Model 1) and demographic factors (Model 2) and in fully adjusted models (Model 3). Worse TMT-B performance was only associated with higher NREM sleep theta power in an unadjusted model, and this association did not persist after covariate adjustment. Associations between worse TMT-B performance and higher REM sleep theta power were only evident after adjusting for age and OSA and in a fully adjusted model. Associations between worse TMT-B performance and higher REM sleep alpha power were observed in an unadjusted and fully adjusted model (Table 7.3). There were no associations between inspection time (Table 7.4) or FOME performance (Supplementary Table 7.2) and NREM or REM sleep microarchitecture in the overall sample.

7.4.3 Effect moderator analysis

Interaction terms of age*qEEG were included to determine if age moderated significant fully adjusted associations between sleep microarchitecture and cognitive dysfunction. Age significantly moderated fully adjusted associations between lower NREM sleep delta power (*B* = 1.31, 95% CI [-1.93, -0.70], p<0.001), lower REM sleep delta power (*B* = -0.74, 95% CI [-1.36, -0.11], p=0.021), higher NREM sleep theta power (*B*=1.56, 95% CI [0.96, 2.15], p<0.001), higher REM sleep theta power (*B*=0.85, 95% CI [0.26, 1.44], p=0.005), and higher REM sleep alpha power (*B*=1.03, 95% CI [0.36, 1.71], p=0.003) and worse TMT-A performance. Age also significantly moderated fully adjusted associations between higher REM sleep theta power (*B*=6.35, 95% CI [3.46, 9.24], p<0.001) and higher REM sleep alpha power (*B*=7.20, 95% CI [3.89, 10.5], p<0.001) and worse TMT-B performance.

7.4.4 Associations between NREM and REM sleep microarchitecture parameters and cognitive dysfunction in men <65 years

In men <65 years, worse TMT-A performance was only associated with higher REM sleep alpha power in an unadjusted model. Slower inspection time was only associated with lower NREM sleep sigma power after adjusting for demographic factors. No other associations existed between cognitive dysfunction and sleep microarchitecture in men <65 years.

7.4.5 Associations between NREM and REM sleep microarchitecture parameters and cognitive dysfunction in men ≥65 years

In men ≥65 years, worse TMT-A performance was associated with lower NREM sleep delta power and higher NREM sleep theta and alpha power in unadjusted and all three adjusted models. Worse TMT-A performance was only associated with higher NREM sleep sigma power and lower NREM sleep EEG slowing ratio after adjusting for demographic factors.

Regarding REM sleep microarchitecture parameters, worse TMT-A performance was associated with higher REM sleep theta power in unadjusted and all three adjusted models and higher REM sleep alpha power in adjusted models only. Worse TMT-B performance was associated with higher REM sleep theta and alpha power and lower REM sleep delta power in unadjusted and all three adjusted models. However, worse TMT-B performance was only associated with higher REM sleep sigma power after adjusting for demographic factors.

Table 7.2 Covariate unadjusted and adjusted associations between TMT-A performance and NREM and REM sleep relative powers and EEG slowing ratio

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2		Adjusted Model 3	
				Overall sample				
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep								
Delta	-0.14 (-0.24, -0.04)	**0.008**	-0.11 (-0.20, -0.02)	**0.021**	-0.11 (-0.20, -0.02)	**0.022**	-0.11 (-0.20, -0.02)	**0.023**
Adjusted R^2	0.02		0.23		0.27		0.28	
Theta	0.53 (0.27, 0.77)	**<0.001**	0.36 (0.14, 0.59)	**0.002**	0.34 (0.12, 0.57)	**0.003**	0.36 (0.14, 0.59)	**0.002**
Adjusted R^2	0.04		0.24		0.28		0.29	
Alpha	0.28 (-0.02, 0.57)	0.064	0.23 (-0.03, 0.49)	0.081	0.23 (-0.04, 0.49)	0.089	0.22 (-0.05, 0.48)	0.10
Adjusted R^2	0.007		0.23		0.26		0.27	
Sigma	-0.08 (-0.80, 0.65)	0.84	0.34 (-0.31, 0.99)	0.31	0.42 (-0.22, 1.06)	0.20	0.48 (-0.17, 1.13)	0.15
Adjusted R^2	0.003		0.22		0.26		0.27	
Beta	0.22 (-0.13, 0.56)	0.23	0.15 (-0.16, 0.46)	0.35	0.16 (-0.15, 0.46)	0.32	0.13 (-0.18, 0.44)	0.42
Adjusted R^2	0.001		0.22		0.26		0.27	
Slowing ratio	-2.46 (-5.85, 0.92)	0.15	-2.08 (-5.08, 0.92)	0.17	-2.25 (-5.23, 0.73)	0.14	-2.12 (-5.13, 0.88)	0.17
Adjusted R^2	0.003		0.22		0.26		0.27	
REM sleep								
Delta	-0.07 (-0.14, 0.008)	0.081	-0.07 (-0.13, -0.03)	**0.041**	-0.07 (-0.13, -0.003)	**0.042**	-0.08 (-0.14, -0.009)	**0.026**
Adjusted R^2	0.006		0.23		0.27		0.28	
Theta	0.17 (0.01, 0.35)	**0.037**	0.18 (0.03, 0.33)	**0.017**	0.17 (0.03, 0.32)	**0.021**	0.21 (0.06, 0.36)	**0.006**
Adjusted R^2	0.01		0.23		0.27		0.28	
Alpha	0.35 (0.07, 0.63)	**0.013**	0.28 (0.03, 0.53)	**0.027**	0.29 (0.04, 0.53)	**0.021**	0.34 (0.08, 0.59)	**0.009**
Adjusted R^2	0.02		0.23		0.27		0.28	
Sigma	0.27 (-0.38, 0.91)	0.42	0.35 (-0.23, 0.92)	0.23	0.37 (-0.21, 0.95)	0.21	0.45 (-0.16, 1.05)	0.14
Adjusted R^2	0.001		0.22		0.26		0.27	
Beta	0.02 (-0.16, 0.21)	0.80	0.06 (-0.10, 0.22)	0.47	0.06 (-0.11, 0.22)	0.49	0.04 (-0.13, 0.20)	0.67
Adjusted R^2	0.003		0.22		0.26		0.27	
Slowing ratio	-0.09 (-0.22, 0.04)	0.18	-0.07 (-0.19, 0.05)	0.24	-0.08 (-0.19, 0.04)	0.18	-0.07 (-0.19, 0.04)	0.22
Adjusted R^2	0.002		0.22		0.26		0.27	
				Age-stratified sample (<65 years)				
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep								

Delta	-0.06 (-0.14, 0.03)	0.18	-0.04 (-0.12, 0.04)	0.37	-0.03 (-0.12, 0.05)	0.44	-0.008 (-0.10, 0.08)	0.87
Adjusted R^2	0.003		0.07		0.06		0.07	
Theta	0.19 (-0.02, 0.40)	0.082	0.12 (-0.09, 0.33)	0.26	0.12 (-0.10, 0.34)	0.28	0.09 (-0.13, 0.31)	0.42
Adjusted R^2	0.008		0.07		0.07		0.07	
Alpha	0.14 (-0.10, 0.37)	0.26	0.08 (-0.15, 0.31)	0.50	0.67 (-0.17, 0.31)	0.59	0.03 (-0.21, 0.28)	0.79
Adjusted R^2	0.001		0.07		0.06		0.07	
Sigma	0.11 (-0.46, 0.68)	0.71	0.12 (-0.43, 0.68)	0.66	0.08 (-0.49, 0.65)	0.77	-0.07 (-0.68, 0.54)	0.81
Adjusted R^2	0.003		0.07		0.06		0.07	
Beta	0.09 (-0.18, 0.36)	0.51	0.07 (-0.20, 0.33)	0.61	0.05 (-0.22, 0.32)	0.73	-0.20 (-0.60, 0.19)	0.31
Adjusted R^2	0.002		0.07		0.06		0.07	
Slowing ratio	-1.32 (-4.04, 1.41)	0.34	-0.81 (-3.45, 1.84)	0.55	-0.67 (-3.41, 2.08)	0.63	-0.14 (-3.01, 2.72)	0.92
Adjusted R^2	0.000		0.07		0.06		0.07	
REM sleep								
Delta	-0.06 (-0.12, 0.001)	0.055	-0.05 (-0.11, 0.01)	0.13	-0.04 (-0.11, 0.02)	0.17	-0.04 (-0.10, 0.03)	0.23
Adjusted R^2	0.01		0.08		0.07		0.07	
Theta	0.13 (-0.01, 0.28)	0.073	0.10 (-0.05, 0.24)	0.18	0.09 (-0.05, 0.24)	0.20	0.09 (-0.06, 0.24)	0.23
Adjusted R^2	0.009		0.08		0.07		0.07	
Alpha	0.25 (0.02, 0.49)	**0.036**	0.17 (-0.07, 0.40)	0.16	0.18 (-0.06, 0.42)	0.14	0.14 (-0.10, 0.38)	0.26
Adjusted R^2	0.01		0.08		0.07		0.07	
Sigma	0.47 (-0.06, 1.00)	0.082	0.32 (-0.19, 0.84)	0.22	0.32 (-0.23, 0.86)	0.25	0.27 (-0.28, 0.82)	0.33
Adjusted R^2	0.008		0.08		0.07		0.07	
Beta	0.08 (-0.08, 0.23)	0.33	0.08 (-0.07, 0.22)	0.31	0.06 (-0.09, 0.21)	0.43	0.05 (-0.10, 0.21)	0.51
Adjusted R^2	0.000		0.07		0.06		0.07	
Slowing ratio	-0.05 (-0.16, 0.05)	0.32	-0.04 (-0.14, 0.07)	0.50	-0.03 (-0.14, 0.07)	0.55	-0.03 (-0.13, 0.08)	0.63
Adjusted R^2	0.000		0.07		0.06		0.07	
			Age-stratified sample (≥65 years)					
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep								
Delta	-0.39 (-0.67, -0.11)	**0.007**	-0.38 (-0.64, -0.12)	**0.004**	-0.36 (-0.61, -0.12)	**0.004**	-0.34 (-0.59, -0.08)	**0.011**
Adjusted R^2	0.06		0.21		0.34		0.31	
Theta	1.08 (0.48, 1.68)	**0.001**	1.00 (0.44, 1.56)	**0.001**	0.88 (0.34, 1.42)	**0.002**	0.84 (0.29, 1.39)	**0.003**
Adjusted R^2	0.11		0.24		0.35		0.33	
Alpha	0.87 (0.07, 1.68)	**0.034**	0.85 (0.10, 1.59)	**0.027**	0.82 (0.12, 1.52)	**0.022**	0.73 (0.009, 1.45)	**0.047**
Adjusted R^2	0.04		0.18		0.31		0.29	
Sigma	1.10 (-1.19, 3.38)	0.34	1.66 (-0.45, 3.78)	0.12	2.06 (0.07, 4.04)	**0.043**	1.81 (-0.31, 3.93)	0.093
Adjusted R^2	0.001		0.16		0.30		0.28	
Beta	0.56 (-0.52, 1.64)	0.31	0.60 (-0.41, 1.60)	0.24	0.70 (-0.25, 1.65)	0.14	0.63 (-0.59, 1.84)	0.31
Adjusted R^2	0.001		0.15		0.29		0.26	
Slowing ratio	-6.86 (-16.2, 2.51)	0.15	-8.20 (-16.9, 0.45)	0.063	-8.24 (-16.4, -0.12)	**0.047**	-7.07 (-15.7, 1.57)	0.11
Adjusted R^2	0.01		0.17		0.30		0.28	

REM sleep								
Delta	-0.13 (-0.31, 0.05)	0.14	-0.14 (-0.30, 0.03)	0.096	-0.14 (-0.29, 0.01)	0.070	-0.14 (-0.30, 0.02)	0.080
Adjusted R^2	0.01		0.16		0.30		0.28	
Theta	0.39 (0.005, 0.78)	**0.047**	0.39 (0.03, 0.74)	**0.034**	0.38 (0.04, 0.71)	**0.027**	0.41 (0.07, 0.75)	**0.019**
Adjusted R^2	0.03		0.17		0.31		0.30	
Alpha	0.61 (-0.05, 1.27)	0.068	0.65 (0.04, 1.26)	**0.038**	0.68 (0.11, 1.24)	**0.019**	0.66 (0.07, 1.25)	**0.029**
Adjusted R^2	0.02		0.17		0.32		0.29	
Sigma	0.51 (-1.18, 2.21)	0.55	0.79 (-0.78, 2.36)	0.32	0.98 (-0.52, 2.48)	0.20	0.79 (-0.79, 2.37)	0.32
Adjusted R^2	0.007		0.14		0.28		0.26	
Beta	0.008 (-0.47, 0.48)	0.97	0.03 (-0.41, 0.47)	0.90	0.04 (-0.39, 0.46)	0.87	-0.009 (-0.46, 0.44)	0.97
Adjusted R^2	0.01		0.13		0.27		0.25	
Slowing ratio	-0.18 (-0.54, 0.18)	0.33	-0.28 (-0.61, 0.06)	0.10	-0.24 (-0.55, 0.08)	0.14	-0.20 (-0.53, 0.12)	0.22
Adjusted R^2	0.000		0.16		0.29		0.27	

Abbreviations: NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; CI, confidence interval.
Coefficients: unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates: estimates represent the change in cognitive test scores corresponding to a 1% increase in relative spectral power and a one-unit increase in logarithmically (10-base) transformed EEG slowing ratio.
Relative spectral powers: delta: 0.5–4.5 Hz; theta: 4.5–8 Hz; alpha: 8–12 Hz; sigma: 12–15 Hz; beta: 15–32 Hz
EEG slowing ratio: calculated as a ratio of slow to fast EEG frequencies [(delta+theta)/(alpha+sigma+beta)].
Adjusted Model 1: adjusted for age and AHI.
Adjusted Model 2: adjusted for age, AHI, financial stress, highest educational attainment, socio-economic disadvantage, and marital status.
Adjusted Model 3 (overall sample): adjusted for age, AHI, total sleep time, financial stress, highest educational attainment, socio-economic disadvantage, marital status, alcohol risk, BMI, current smoking status, physical activity level, cardiovascular disease, diabetes mellitus, blood glucose, insomnia, and hypertension.
Adjusted Model 3 (age-stratified samples): adjusted for age, AHI, total sleep time, financial stress, highest educational attainment, socio-economic disadvantage, marital status, and cardio-metabolic conditions (one or more of diabetes mellitus, hypertension, or cardiovascular disease).
Legend: p-values representing significant associations boldfaced.
Notes: multicollinearity tests displayed acceptable variance inflation factor for all covariates; AHI was scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

Table 7.3 Covariate unadjusted and adjusted associations between TMT-B performance and NREM and REM sleep relative powers and EEG slowing ratio

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2		Adjusted Model 3	
				Overall sample				
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep								
Delta	-0.51 (-1.03, 0.007)	0.053	-0.35 (-0.81, 0.11)	0.14	-0.28 (-0.74, 0.19)	0.24	-0.31 (-0.77, 0.16)	0.19
Adjusted R^2	0.008		0.22		0.26		0.27	
Theta	1.95 (0.68, 3.21)	**0.003**	1.12 (-0.02, 2.26)	0.054	0.83 (-0.31, 1.97)	0.15	0.90 (-0.25, 2.05)	0.13
Adjusted R^2	0.02		0.22		0.26		0.27	
Alpha	0.69 (-0.79, 2.17)	0.36	0.44 (-0.87, 1.76)	0.51	0.23 (-1.08, 1.53)	0.73	0.32 (-0.99, 1.64)	0.63
Adjusted R^2	0.000		0.22		0.25		0.26	
Sigma	-1.06 (-4.66, 2.54)	0.56	0.90 (-2.32, 4.12)	0.58	0.99 (-2.20, 4.20)	0.54	1.50 (-1.77, 4.77)	0.37
Adjusted R^2	0.002		0.22		0.26		0.27	
Beta	1.40 (-0.33, 3.12)	0.11	1.05 (-0.48, 2.59)	0.18	0.97 (-0.54, 2.48)	0.21	1.01 (-0.54, 2.56)	0.20
Adjusted R^2	0.004		0.22		0.26		0.27	
Slowing ratio	-7.54 (-24.4, 9.34)	0.38	-5.38 (-20.4, 9.59)	0.48	-4.45 (-19.3, 10.4)	0.56	-4.79 (-19.8, 10.3)	0.53
Adjusted R^2	0.001		0.22		0.26		0.26	
REM sleep								
Delta	-0.23 (-0.60, 0.13)	0.20	-0.24 (-0.56, 0.09)	0.15	-0.24 (-0.56, 0.08)	0.14	-0.29 (-0.62, 0.05)	0.091
Adjusted R^2	0.002		0.22		0.26		0.27	
Theta	0.75 (-0.08, 1.59)	0.076	0.75 (0.02, 1.49)	**0.045**	0.68 (-0.04, 1.41)	0.064	0.80 (0.04, 1.55)	**0.039**
Adjusted R^2	0.006		0.22		0.26		0.27	
Alpha	1.43 (0.04, 2.83)	**0.044**	1.04 (-0.20, 2.28)	0.10	1.09 (-0.14, 2.31)	0.082	1.43 (0.15, 2.70)	**0.028**
Adjusted R^2	0.009		0.22		0.26		0.27	
Sigma	0.66 (-2.57, 3.90)	0.69	0.96 (-1.90, 3.82)	0.51	1.14 (-1.75, 4.02)	0.44	1.74 (-1.29, 4.77)	0.26
Adjusted R^2	0.002		0.22		0.26		0.27	
Beta	-0.08 (-1.00, 0.84)	0.86	0.06 (-0.75, 0.88)	0.88	0.12 (-0.69, 0.92)	0.78	0.09 (-0.73, 0.91)	0.83
Adjusted R^2	0.08		0.22		0.25		0.26	
Slowing ratio	-0.23 (-0.89, 0.42)	0.48	-0.13 (-0.71, 0.45)	0.65	-0.11 (-0.69, 0.46)	0.69	-0.09 (-0.67, 0.48)	0.75
Adjusted R^2	0.001		0.22		0.25		0.26	
				Age-stratified sample (<65 years)				
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep								

Delta	-0.26 (-0.71, 0.20)	0.27	-0.13 (-0.57, 0.30)	0.54	-0.06 (-0.51, 0.39)	0.80	0.14 (-0.34, 0.62)	0.57
Adjusted R^2	0.001		0.09		0.09		0.09	
Theta	0.41 (-0.75, 1.58)	0.48	-0.008 (-1.13, 1.11)	0.99	-0.17 (-1.33, 0.99)	0.77	-0.35 (-1.50, 0.80)	0.55
Adjusted R^2	0.002		0.09		0.09		0.09	
Alpha	0.39 (-0.90, 1.67)	0.56	0.06 (-1.18, 1.29)	0.93	-0.16 (-1.43, 1.11)	0.80	-0.33 (-1.62, 0.96)	0.62
Adjusted R^2	0.003		0.09		0.09		0.09	
Sigma	0.70 (-2.35, 3.75)	0.65	0.68 (-2.24, 3.60)	0.65	0.26 (-2.73, 3.26)	0.86	-0.83 (-4.03, 2.37)	0.61
Adjusted R^2	0.003		0.09		0.09		0.09	
Beta	1.36 (-0.09, 2.81)	0.065	1.18 (-0.21, 2.57)	0.096	1.00 (-0.42, 2.42)	0.17	-0.22 (-2.29, 1.84)	0.83
Adjusted R^2	0.01		0.10		0.10		0.09	
Slowing ratio	-5.97 (-20.6, 8.64)	0.42	-2.69 (-16.7, 11.3)	0.71	-0.36 (-14.8, 14.1)	0.96	3.55 (-11.5, 18.6)	0.64
Adjusted R^2	0.001		0.09		0.09		0.09	
REM sleep								
Delta	-0.03 (-0.36, 0.30)	0.86	0.05 (-0.27, 0.37)	0.75	0.09 (-0.24, 0.42)	0.60	0.08 (-0.26, 0.41)	0.65
Adjusted R^2	0.004		0.09		0.09		0.09	
Theta	0.14 (-0.65, 0.92)	0.73	-0.06 (-0.81, 0.68)	0.87	-0.13 (-0.89, 0.64)	0.74	-0.10 (-0.86, 0.67)	0.80
Adjusted R^2	0.004		0.09		0.09		0.09	
Alpha	0.51 (-0.77, 1.80)	0.43	0.006 (-1.23, 1.25)	0.99	-0.05 (-1.31, 1.22)	0.95	-0.06 (-1.33, 1.22)	0.93
Adjusted R^2	0.002		0.09		0.09		0.09	
Sigma	0.26 (-2.61, 3.12)	0.86	-0.60 (-3.35, 2.15)	0.67	-0.98 (-3.84, 1.89)	0.50	-0.96 (-3.83, 1.92)	0.51
Adjusted R^2	0.004		0.09		0.09		0.09	
Beta	-0.20 (-1.02, 0.62)	0.63	-0.20 (-0.98, 0.58)	0.62	-0.29 (-1.09, 0.51)	0.48	-0.25 (-1.06, 0.56)	0.54
Adjusted R^2	0.003		0.09		0.09		0.09	
Slowing ratio	-0.10 (-0.67, 0.47)	0.73	0.02 (-0.52, 0.56)	0.94	0.10 (-0.46, 0.65)	0.74	0.14 (-0.42, 0.70)	0.62
Adjusted R^2	0.004		0.09		0.09		0.06	
			Age-stratified sample (≥65 years)					
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep								
Delta	-1.17 (-2.53, 0.19)	0.092	-1.08 (-2.39, 0.22)	0.10	-1.03 (-2.25, 0.20)	0.10	-0.98 (-2.22, 0.27)	0.12
Adjusted R^2	0.02		0.11		0.25		0.27	
Theta	4.18 (1.28, 7.09)	**0.005**	3.79 (0.99, 6.58)	**0.008**	3.29 (0.60, 5.99)	**0.017**	3.13 (0.50, 5.77)	**0.020**
Adjusted R^2	0.07		0.15		0.27		0.30	
Alpha	2.02 (-1.87, 5.90)	0.31	1.72 (-2.00, 5.44)	0.36	1.72 (-1.77, 5.22)	0.33	1.42 (-2.03, 4.88)	0.42
Adjusted R^2	0.001		0.09		0.23		0.26	
Sigma	0.37 (-10.45, 11.2)	0.95	2.48 (-7.92, 12.9)	0.64	4.17 (-5.69, 14.0)	0.40	2.73 (-7.39, 12.8)	0.59
Adjusted R^2	0.01		0.08		0.23		0.25	
Beta	0.48 (-4.64, 5.60)	0.85	0.57 (-4.32, 5.46)	0.82	1.18 (-3.48, 5.85)	0.62	1.48 (-4.26, 7.22)	0.61
Adjusted R^2	0.01		0.08		0.22		0.25	
Slowing ratio	-13.2 (-58.1, 31.6)	0.56	-17.0 (-59.8, 25.9)	0.43	-17.0 (-57.4, 23.3)	0.40	-12.6 (-53.8, 28.6)	0.55
Adjusted R^2	0.007		0.09		0.23		0.25	

REM sleep								
Delta	-0.95 (-1.78, -0.12)	**0.026**	-0.97 (1.76, -0.17)	**0.017**	-0.94 (-1.67, -0.21)	**0.012**	-0.86 (-1.60, -0.11)	**0.024**
Adjusted R^2	0.04		0.13		0.28		0.29	
Theta	2.51 (0.73, 4.30)	**0.006**	2.51 (0.81, 4.21)	**0.004**	2.32 (0.72, 3.92)	**0.005**	2.17 (0.59, 3.75)	**0.008**
Adjusted R^2	0.07		0.16		0.29		0.31	
Alpha	3.49 (0.37, 6.61)	**0.029**	3.53 (0.56, 6.51)	**0.021**	3.65 (0.92, 6.39)	**0.009**	3.56 (0.82, 6.31)	**0.012**
Adjusted R^2	0.04		0.13		0.28		0.31	
Sigma	5.39 (-2.65, 13.4)	0.19	6.64 (-1.02, 14.3)	0.089	7.80 (0.53, 15.1)	**0.036**	5.51 (-1.87, 12.9)	0.14
Adjusted R^2	0.008		0.11		0.26		0.27	
Beta	0.75 (-1.50, 3.00)	0.51	0.76 (-1.39, 2.91)	0.48	0.90 (-1.15, 2.94)	0.39	0.57 (-1.54, 2.68)	0.59
Adjusted R^2	0.006		0.08		0.23		0.25	
Slowing ratio	-0.47 (-2.19, 1.25)	0.59	-0.80 (-2.45, 0.85)	0.34	-0.56 (-2.11, 1.00)	0.48	-0.31 (-1.87, 1.24)	0.69
Adjusted R^2	0.007		0.09		0.23		0.25	

Abbreviations: NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; CI, confidence interval.
Coefficients: unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates: estimates represent the change in cognitive test scores corresponding to a 1% increase in relative spectral power and a one-unit increase in logarithmically (10-base) transformed EEG slowing ratio.
Relative spectral powers: delta: 0.5–4.5 Hz; theta: 4.5–8 Hz; alpha: 8–12 Hz; sigma: 12–15 Hz; beta: 15–32 Hz
EEG slowing ratio: calculated as a ratio of slow to fast EEG frequencies [(delta+theta)/(alpha+sigma+beta)].
Adjusted Model 1: adjusted for age and AHI.
Adjusted Model 2: adjusted for age, AHI, financial stress, highest educational attainment, socio-economic disadvantage, and marital status.
Adjusted Model 3 (overall sample): adjusted for age, AHI, total sleep time, financial stress, highest educational attainment, socio-economic disadvantage, marital status, alcohol risk, BMI, current smoking status, physical activity level, cardiovascular disease, diabetes mellitus, blood glucose, insomnia, and hypertension.
Adjusted Model 3 (age-stratified samples): adjusted for age, AHI, total sleep time, financial stress, highest educational attainment, socio-economic disadvantage, marital status, and cardio-metabolic conditions (one or more of diabetes mellitus, hypertension, or cardiovascular disease).
Legend: p-values representing significant associations boldfaced.
Notes: multicollinearity tests displayed acceptable variance inflation factor for all covariates; AHI was scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

Table 7.4 Unadjusted and adjusted associations between inspection time and NREM and REM sleep relative powers and EEG slowing ratio

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2		Adjusted Model 3	
				Overall sample				
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep								
Delta	-0.01 (-0.47, 0.47)	0.99	0.10 (-0.35, 0.55)	0.67	0.29 (-0.17, 0.74)	0.22	0.32 (-0.11, 0.76)	0.15
Adjusted R^2	0.003		0.11		0.13		0.24	
Theta	0.66 (-0.50, 1.82)	0.26	0.13 (-0.98, 1.24)	0.82	-0.32 (-1.44, 0.80)	0.57	-0.60 (-1.68, 0.48)	0.28
Adjusted R^2	0.001		0.11		0.13		0.24	
Alpha	-0.58 (-1.92, 0.77)	0.40	-0.72 (-1.99, 0.55)	0.27	-1.22 (-2.50, 0.06)	0.061	-1.16 (-2.38, 0.11)	0.064
Adjusted R^2	0.001		0.11		0.14		0.24	
Sigma	-2.78 (-6.06, 0.50)	0.097	-1.45 (-4.59, 1.70)	0.37	-2.45 (-5.60, 0.71)	0.13	-2.59 (5.66, 0.49)	0.099
Adjusted R^2	0.005		0.11		0.13		0.24	
Beta	0.22 (-1.37, 1.81)	0.78	0.02 (-1.49, 1.53)	0.98	-0.32 (-1.82, 1.18)	0.67	-0.29 (-1.76, 1.17)	0.69
Adjusted R^2	0.003		0.11		0.13		0.23	
Slowing ratio	4.66 (-10.8, 20.1)	0.55	5.77 (-8.81, 20.4)	0.44	11.0 (-3.66, 25.6)	0.14	12.1 (-1.99, 26.2)	0.092
Adjusted R^2	0.002		0.11		0.13		0.24	
REM sleep								
Delta	0.05 (-0.29, 0.38)	0.78	0.04 (-0.27, 0.36)	0.79	0.09 (-0.23, 0.41)	0.57	0.16 (-0.15, 0.47)	0.31
Adjusted R^2	0.003		0.11		0.13		0.24	
Theta	0.07 (-0.70, 0.83)	0.87	0.07 (-0.66, 0.79)	0.86	-0.05 (-0.77, 0.67)	0.89	-0.28 (-0.99, 0.44)	0.45
Adjusted R^2	0.003		0.11		0.13		0.24	
Alpha	0.34 (-0.93, 1.62)	0.60	0.10 (-1.11, 1.31)	0.87	-0.07 (-1.28, 1.14)	0.91	-0.19 (-1.39, 1.01)	0.76
Adjusted R^2	0.002		0.11		0.13		0.23	
Sigma	-0.44 (-3.39, 2.51)	0.77	-0.18 (-2.96, 2.61)	0.90	-0.78 (-3.62, 2.07)	0.59	-1.13 (-3.98, 1.73)	0.44
Adjusted R^2	0.003		0.11		0.13		0.24	
Beta	-0.49 (-1.33, 0.35)	0.25	-0.38 (-1.18, 0.41)	0.35	-0.43 (-1.22, 0.37)	0.29	-0.49 (-1.27, 0.28)	0.21
Adjusted R^2	0.001		0.11		0.13		0.24	
Slowing ratio	0.12 (-0.47, 0.72)	0.69	0.18 (-0.38, 0.74)	0.53	0.35 (-0.21, 0.91)	0.22	0.44 (-0.10, 0.98)	0.11
Adjusted R^2	0.002		0.11		0.13		0.24	
				Age-stratified sample (<65 years)				
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep								

Delta	-0.09 (-0.49, 0.32)	0.67	-0.02 (-0.43, 0.39)	0.93	0.17 (-0.25, 0.58)	0.44	0.03 (-0.39, 0.45)	0.88
Adjusted R^2	0.003		0.02		0.05		0.06	
Theta	0.97 (-0.07, 2.00)	0.066	0.76 (-0.28, 1.80)	0.15	0.31 (-0.76, 1.38)	0.57	0.75 (-0.25, 1.74)	0.14
Adjusted R^2	0.01		0.03		0.05		0.07	
Alpha	-0.18 (-1.33, 0.97)	0.76	-0.38 (-1.54, 0.77)	0.51	-0.89 (-2.06, 0.28)	0.13	-0.49 (-1.61, 0.62)	0.38
Adjusted R^2	0.004		0.02		0.05		0.06	
Sigma	-1.89 (-4.65, 0.87)	0.18	-1.94 (-4.68, 0.80)	0.16	-2.82 (-5.57, -0.06)	**0.045**	-2.47 (-5.26, 0.31)	0.082
Adjusted R^2	0.003		0.03		0.06		0.07	
Beta	0.04 (-1.29, 1.36)	0.96	-0.07 (-1.39, 1.25)	0.92	-0.37 (-1.69, 0.95)	0.58	-0.74 (-2.54, 1.06)	0.42
Adjusted R^2	0.004		0.02		0.05		0.06	
Slowing ratio	2.17 (-11.1, 15.4)	0.75	4.10 (-9.10, 17.3)	0.54	9.44 (-3.93, 22.8)	0.17	5.13 (-8.00, 18.3)	0.44
Adjusted R^2	0.004		0.02		0.05		0.06	
REM sleep								
Delta	-0.03 (-0.34, 0.27)	0.83	0.009 (-0.29, 0.31)	0.96	0.04 (-0.27, 0.34)	0.80	-0.15 (-0.44, 0.14)	0.32
Adjusted R^2	0.004		0.02		0.05		0.06	
Theta	0.37 (-0.33, 1.08)	0.30	0.28 (-0.43, 0.98)	0.44	0.15 (-0.55, 0.86)	0.67	0.55 (-0.11, 1.22)	0.10
Adjusted R^2	0.001		0.02		0.05		0.07	
Alpha	0.50 (-0.66, 1.66)	0.40	0.24 (-0.92, 1.41)	0.68	0.08 (-1.09, 1.26)	0.89	0.78 (-0.33, 1.88)	0.17
Adjusted R^2	0.001		0.02		0.05		0.07	
Sigma	-0.38 (-2.98, 2.21)	0.77	-0.82 (-3.41, 1.78)	0.54	-1.25 (-3.91, 1.41)	0.36	0.15 (-2.36, 2.67)	0.91
Adjusted R^2	0.004		0.02		0.05		0.06	
Beta	-0.39 (-1.13, 0.35)	0.30	-0.38 (-1.12, 0.35)	0.31	-0.34 (-1.08, 0.41)	0.37	-0.07 (-0.77, 0.64)	0.85
Adjusted R^2	0.001		0.02		0.05		0.06	
Slowing ratio	0.02 (-0.49, 0.53)	0.94	0.09 (-0.42, 0.60)	0.74	0.26 (-0.25, 0.78)	0.32	0.05 (-0.44, 0.55)	0.83
Adjusted R^2	0.004		0.02		0.05		0.06	
			Age-stratified sample (≥65 years)					
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep								
Delta	0.34 (-1.00, 1.68)	0.62	0.41 (-0.90, 1.72)	0.54	0.63 (-0.69, 1.96)	0.34	0.82 (-0.52, 2.17)	0.23
Adjusted R^2	0.008		0.04		0.07		0.12	
Theta	-0.93 (-3.86, 2.01)	0.53	-1.27 (-4.14, 1.60)	0.38	-2.21 (-5.13, 0.71)	0.14	-2.15 (-5.03, 0.73)	0.14
Adjusted R^2	0.006		0.05		0.09		0.13	
Alpha	-1.42 (-5.20, 2.37)	0.46	1.63 (-5.32, 2.07)	0.38	-2.05 (-5.78, 1.69)	0.28	-2.41 (-6.09, 1.27)	0.20
Adjusted R^2	0.005		0.05		0.08		0.13	
Sigma	-0.13 (-10.7, 10.4)	0.98	1.46 (-8.87, 11.8)	0.78	1.08 (-9.51, 11.7)	0.84	-1.52 (-12.4, 9.36)	0.78
Adjusted R^2	0.01		0.04		0.07		0.11	
Beta	0.43 (-4.58, 5.43)	0.87	0.47 (-4.41, 5.35)	0.85	0.73 (-4.29, 5.74)	0.77	-0.30 (-6.47, 5.88)	0.92
Adjusted R^2	0.01		0.04		0.07		0.11	
Slowing ratio	10.3 (-33.2, 53.8)	0.64	7.72 (-34.9, 50.3)	0.72	9.00 (-34.2, 52.2)	0.68	18.7 (-25.5, 62.9)	0.40
Adjusted R^2	0.008		0.04		0.07		0.12	

REM sleep								
Delta	0.05 (-0.77, 0.87)	0.91	0.05 (-0.77, 0.87)	0.91	0.08 (-0.72, 0.88)	0.85	0.30 (-0.52, 1.12)	0.47
Adjusted R^2	0.01		0.04		0.07		0.11	
Theta	-0.16 (-1.97, 1.64)	0.86	-0.18 (-1.94, 1.58)	0.84	-0.32 (-2.09, 1.46)	0.72	-0.51 (-2.28, 1.25)	0.57
Adjusted R^2	0.01		0.04		0.07		0.11	
Alpha	0.16 (-2.93, 3.24)	0.92	0.15 (-2.87, 3.18)	0.92	-0.14 (-3.16, 2.88)	0.93	-0.41 (-3.47, 2.65)	0.79
Adjusted R^2	0.01		0.04		0.07		0.11	
Sigma	2.10 (-5.70, 9.91)	0.59	2.94 (-4.69, 10.6)	0.45	2.72 (-5.15, 10.6)	0.49	-0.30 (-8.32, 7.73)	0.94
Adjusted R^2	0.007		0.05		0.07		0.11	
Beta	-0.35 (-2.53, 1.83)	0.75	-0.37 (-2.50, 1.77)	0.74	-0.24 (-2.43, 1.95)	0.83	-1.19 (-3.45, 1.07)	0.30
Adjusted R^2	0.009		0.04		0.07		0.12	
Slowing ratio	0.52 (-1.15, 2.18)	0.54	0.31 (-1.34, 1.95)	0.71	0.31 (-1.35, 1.97)	0.71	0.74 (-0.93, 2.40)	0.38
Adjusted R^2	0.006		0.04		0.07		0.12	

Abbreviations: NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; CI, confidence interval.
Coefficients: unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates: estimates represent the change in cognitive test scores corresponding to a 1% increase in relative spectral power and a one-unit increase in logarithmically (10-base) transformed EEG slowing ratio.
Relative spectral powers: delta: 0.5–4.5 Hz; theta: 4.5–8 Hz; alpha: 8–12 Hz; sigma: 12–15 Hz; beta: 15–32 Hz
EEG slowing ratio: calculated as a ratio of slow to fast EEG frequencies [(delta+theta)/(alpha+sigma+beta)].
Adjusted Model 1: adjusted for age and AHI.
Adjusted Model 2: adjusted for age, AHI, financial stress, highest educational attainment, socio-economic disadvantage, and marital status.
Adjusted Model 3 (overall sample): adjusted for age, AHI, total sleep time, financial stress, highest educational attainment, socio-economic disadvantage, marital status, alcohol risk, BMI, current smoking status, physical activity level, cardiovascular disease, diabetes mellitus, blood glucose, insomnia, and hypertension.
Adjusted Model 3 (age-stratified samples): adjusted for age, AHI, total sleep time, financial stress, highest educational attainment, socio-economic disadvantage, marital status, and cardio-metabolic conditions (one or more of diabetes mellitus, hypertension, or cardiovascular disease).
Legend: p-values representing significant associations boldfaced.
Notes: multicollinearity tests displayed acceptable variance inflation factor for all covariates; AHI was scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

7.5 Discussion

This community-based cohort study is one of the first to examine cross-sectional associations between Qeeg sleep microarchitecture and cognitive dysfunction while accounting for OSA and other potential confounders. In this sample of community-dwelling middle-aged and older men (n=366), worse visual attention and processing speed (TMT-A performance) was associated with higher NREM sleep theta and REM sleep theta and alpha power and lower REM sleep delta power in the overall sample and men ≥65 years. Worse executive function (TMT-B performance) was also associated with higher REM sleep theta and alpha power in the overall sample and men ≥65 years. These results contribute to and strengthen the emerging community-based cohort literature suggesting that sleep microarchitecture may represent an important brain-specific cognitive dysfunction marker.

Previous literature has documented that sleep microarchitecture parameters are associated with neurocognitive disorders. For example, analysis of sleep microarchitecture has been applied in clinical settings to diagnose epilepsy, stroke, traumatic brain injury, depression, learning and attention disorders, and Alzheimer's disease (301, 397-399). Furthermore, several small case-controlled studies have examined differences in NREM and REM sleep microarchitecture parameters between older patients with MCI and matched controls. Reported findings include higher NREM sleep delta and theta power (42), greater REM sleep EEG slowing ratio (40), and slower NREM sleep parietal spindle density (41) in patients with MCI compared to matched controls. However, case-controlled studies have not thoroughly examined associations between sleep microarchitecture and cognitive dysfunction.

A recent community-based cohort study (45) investigated the link between sleep architecture and cognitive dysfunction using over 150 objectively measured sleep architecture parameters to identify 23 associated with cognitive function. Regarding executive function, Djonlagic et al. (45) found that lower NREM sleep delta activity was associated with worse TMT-B performance. When combined with the findings of the present study that worse visual attention and processing speed (TMT-A performance) was associated with lower delta power in the overall sample (NREM and REM sleep) and men ≥65 years (NREM sleep) and REM sleep delta power in

men ≥65 years, these results support the notion that slow-wave activity (0.5–4.5 Hz) is important for cognitive function.

In contrast with the findings of Djonlagic et al. (45), the present study did not observe any independent associations between lower NREM sleep delta power with worse TMT-B performance. The contrasting findings may be due to electrode positioning. While Djonlagic et al. (45) used multiple electrode sites with statistical adjustment, the present study used only one frontal EEG derivation (F4-M1). The multiple electrode sites used by Djonlagic et al. (45) may partly explain their reported association between lower NREM sleep delta power and worse TMT-B performance. Their contrasting findings with the present study could also reflect the inclusion of women participants from the MESA cohort. Nevertheless, the present and Djonlagic et al. (45) studies provide evidence that NREM sleep microarchitecture is independently associated with worse executive function, particularly in older community-dwelling men.

Previous case-controlled studies report greater frontal REM sleep EEG slowing in patients with MCI compared to matched controls (301). A similar pattern of frontal REM sleep EEG slowing has been reported in patients with mild-moderate Alzheimer's disease (285, 301). While the present study did not observe associations between cognitive dysfunction and REM sleep EEG slowing, worse TMT-A performance was associated with lower NREM EEG slowing in men ≥65 years. Although it has been reported that REM sleep EEG slowing may be linked with worse cognitive function (285, 287), NREM sleep EEG slowing reflects the predominance of slower versus faster EEG frequencies, typically associated with better cognitive function. However, Waser et al. (390) identified greater NREM sleep EEG slowing in men with cognitive decline from early to late adulthood, contrasting with the results of the present study in community-dwelling men and other small studies in patients with MCI or Alzheimer's disease (301, 400, 401). The contrasting findings may be due to the different study populations and warrant further exploration in longitudinal studies.

In men ≥65 years in the present study, worse TMT-A performance was associated with higher NREM sleep theta power, conflicting with previous findings in older women. Women ≥65 years of the Study of Osteoporotic Fractures who had

developed MCI five years after a baseline sleep study exhibited lower NREM sleep theta power compared to age- and gender-matched controls (43). Previous literature has reported that women typically show higher power in slower frequency bands during NREM sleep compared to age-matched men (402). Consequently, discrepancies between the findings of the present study and the Study of Osteoporotic Fractures may be primarily driven by gender differences, and associations between cognitive dysfunction and sleep microarchitecture may differ in women compared to men. Therefore, as the present study was only conducted in men, the generalisability of the results to women remains unknown. Furthermore, MCI reflects significantly greater and broader cognitive dysfunction compared to relatively normal performance on a single task (TMT-A) in the FAMAS cohort of men, which may also account for the different findings. Therefore, further studies are warranted to investigate gender differences in sleep microarchitecture in relation to cognitive dysfunction.

In the present study, there were no associations between memory performance (FOME test) and sleep microarchitecture, contrasting with previous small studies assessing different types of memory (42, 403). Westerberg et al. (42) studied patients with aMCI and controls and assessed sleep-dependent declarative memory. The authors found correlations of higher NREM sleep delta and theta power with better declarative memory in controls but not in patients with aMCI. (42). Moreover, Ferrarelli et al. (403) found a strong correlation between higher NREM sleep delta power and better working memory performance. However, previous small studies could not adjust for potential confounders, a key advantage of the comparatively larger FAMAS cohort. Therefore, the present community-based cohort study provides more robust evidence suggesting that memory performance is not independently associated with sleep microarchitecture. Nevertheless, further evidence from community samples controlling for potentially important confounders remains warranted to extend these findings.

Regarding visual processing speed, an association of slower inspection time with lower NREM sleep sigma power in men <65 years was observed after adjusting for demographic factors. However, this significant association is unable to be compared to small studies given the assessed cognitive function domains. Small studies have

not examined associations between visual processing speed and sleep microarchitecture. Thus, further studies in large samples are needed to extend these findings.

Preliminary evidence from small studies suggests sleep spindle metrics, including occurrence, frequency, density, and amplitude, may be associated with cognitive function (51, 281-283, 388, 404). The adjusted association of worse TMT-A performance with higher NREM sleep sigma power in men ≥65 years could reflect disrupted thalamocortical network integrity with advancing age. Therefore, further community-based cohort studies are warranted to determine whether sleep spindle metrics are independently associated with cognitive function. Moreover, the non-oscillatory component of 1/f function or noise-like temporal brain activity should be considered in future studies, given the potential links with cognitive processing speed (405). Accurate application of this EEG analysis approach requires multiple electrode derivations (frontal, temporal, and occipital) (406), which was impracticable in the present study.

The key strengths of this study are 1) the comparatively large and well-characterised sample of community-dwelling men with data available on objectively measured sleep microarchitecture parameters and multiple standardised, validated, and well-established cognitive tests (306, 312), and 2) the extensive OSA, survey, and biomedical data (303), allowing for control of confounders that influence cortical activity and cognitive function. The main limitation of this study is a cross-sectional design from which causality cannot be inferred. Another limitation is the average time lag of 26 months between cognitive (2007–2010) and PSG (2010–2011) assessment, with potential changes in sleep microarchitecture over that period. However, this is unlikely given the evidence that sleep microarchitecture is relatively stable within individuals and represents a trait fingerprint of electrical brain activity (267, 407). Furthermore, given that cognition has been reported to decline over time, particularly in older community-dwelling participants (19, 338), assessing cognitive function before sleep microarchitecture could have underestimated the observed associations. Assessing cognitive function and sleep microarchitecture at the same time point could have increased the significance of the observed associations.

Several additional study limitations need to be acknowledged. As the EEG montage did not include recording of leg EMG signals, sleep-associated movement disorders such as REM sleep behaviour disorder, restless legs syndrome, and periodic limb movements of sleep could have introduced changes in sleep microarchitecture and could not be controlled. However, any leg movement-related artefacts in the EEG crossing the artefact detection boundaries would have been excluded from the analysis. Also, sleep microarchitecture parameters were identified using only a single frontal EEG derivation (F4-M1), and consequently, potentially important topographical differences may have been missed (408). Nonetheless, over 85% of EEG traces were of sufficient quality for Qeeg analysis and not rejected due to artefacts by the Qeeg algorithm, as having 85% clean artefact-free EEG was the threshold for any PSG Qeeg included in the analysis. Although this study comprehensively adjusted for multiple relevant potential confounders, several residual and unknown factors could have influenced the findings. Lastly, this sleep sub-study was conducted exclusively in men, and consequently, independent associations of sleep microarchitecture parameters with cognitive dysfunction in women remain unknown.

In summary, in this sample of community-dwelling middle-aged and older men, NREM and REM sleep microarchitecture parameters derived from Qeeg power spectral analysis were independently associated with cognitive dysfunction. Worse TMT-A performance was independently associated with higher NREM sleep theta and REM sleep theta and alpha but lower delta power in the overall sample and men ≥65 years. Furthermore, worse TMT-B performance was independently associated with higher REM sleep theta and alpha power in the overall sample and men ≥65 years. These novel findings suggest that sleep microarchitecture parameters determined by quantitative power spectral analysis of the EEG derived from routine overnight sleep studies may represent important brain-specific cognitive dysfunction markers beyond standard PSG indices of OSA and sleep timing, particularly in older community-dwelling men. Prospective community-based cohort studies ideally conducted in large samples of randomly selected community-dwelling men and women are warranted to determine if sleep microarchitecture parameters in mid-life are independently associated with future cognitive decline in older age.

7.6 Supplementary Tables

Supplementary Table 7.1 Cognitive function outcomes in relation to participant demographic and other risk factors and OSA parameters

	Inspection time (milliseconds)	TMT-A (seconds)	TMT-B (seconds)	FOME (number/10)
Demographic risk factors				
Age (years)	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**	**Mean (*SD*)**
<50	55.5 (16.0)	13.1 (3.9)	63.8 (22.3)	7.1 (1.5)
50–59	58.9 (25.6)	14.1 (4.5)	70.2 (22.2)	6.6 (1.6)
60–69	68.4 (23.5)	16.5 (5.1)	83.4 (28.9)	6.0 (1.7)
≥70	83.6 (47.8)	21.5 (9.9)	99.9 (46.2)	5.4 (1.5)
p	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Financial stress				
Spends >earns	65.6 (32.1)	17.6 (6.6)	85.4 (29.6)	6.2 (1.6)
Save a little/lot	63.4 (21.0)	15.6 (6.6)	76.3 (32.6)	6.4 (1.7)
p	0.70	**0.014**	**0.040**	0.41
Highest educational attainment				
≥Diploma, certificate, trade, bachelor's degree or higher	62.4 (21.5)	15.4 (5.5)	74.1 (27.1)	6.4 (1.8)
≤High school	72.3 (45.4)	17.2 (8.7)	86.7 (41.6)	6.1 (1.6)
p	**0.009**	**0.013**	**0.002**	**0.030**
SEIFA IRSD				
Quintile 1 (highest disadvantage)	67.3 (37.7)	16.1 (8.9)	79.1 (41.1)	6.2 (1.7)
Quintile 2	61.6 (23.7)	15.8 (6.0)	75.3 (29.0)	6.5 (1.7)
Quintile 3	63.9 (35.0)	15.8 (5.6)	77.7 (28.3)	6.6 (1.8)
Quintile 4	66.4 (27.4)	15.5 (5.5)	73.5 (29.9)	6.1 (1.7)
Quintile 5 (lowest disadvantage)	65.3 (14.9)	16.7 (7.0)	85.8 (31.2)	6.3 (1.7)
p	0.27	0.85	0.27	0.18
Married/partner				
No	64.4 (23.1)	18.4 (11.1)	85.5 (49.6)	6.2 (1.9)
Yes	65.4 (31.8)	15.4 (5.4)	76.3 (28.1)	6.4 (1.7)
p	0.96	**0.026**	0.21	0.62
Other risk factors				
OSA severity categories (AHI)				
<10/h	63.9 (27.7)	15.5 (5.7)	74.5 (28.3)	6.4 (1.7)
10–19/h	64.8 (34.9)	15.2 (5.2)	78.5 (29.6)	6.4 (1.7)
20–29/h	61.2 (13.5)	16.3 (4.8)	74.1 (22.1)	6.3 (1.5)
≥30/h	76.1 (42.1)	18.8 (11.9)	92.8 (53.4)	6.0 (1.9)
p	0.80	0.38	0.56	0.91
Alcohol risk				
Non–low	59.1 (14.2)	15.0 (6.3)	72.2 (21.3)	7.1 (1.7)
Medium–very high	65.6 (31.2)	16.0 (6.6)	78.0 (32.8)	6.3 (1.7)
p	0.87	0.17	0.62	**0.033**
Physical activity				
Sedentary behaviour	63.2 (32.1)	15.0 (5.6)	77.0 (29.2)	6.5 (1.8)
Low/moderate/vigorous	65.8 (30.2)	16.2 (6.9)	77.9 (33.2)	6.3 (1.7)
p	0.095	0.10	0.69	0.45
BMI (kg/m^2)				
<25 (underweight/normal)	61.0 (18.1)	16.1 (6.4)	77.7 (28.0)	6.0 (1.9)
25 to <30 (overweight)	63.5 (21.5)	15.7 (5.6)	78.3 (31.1)	6.4 (1.5)
≥30 (obese)	70.5 (44.9)	16.2 (8.1)	76.8 (36.6)	6.4 (1.8)
p	0.24	0.86	0.88	0.25
Current smoking status				
Never/former	66.6 (32.9)	15.8 (6.7)	77.9 (33.4)	6.3 (1.7)
Current smoker	58.7 (13.7)	16.4 (6.1)	76.5 (26.5)	6.5 (1.7)
p	0.073	0.65	0.49	0.32

Cardiovascular disease				
No	64.5 (30.1)	15.5 (5.6)	76.1 (28.5)	6.3 (1.7)
Yes	75.6 (36.3)	21.0 (13.8)	98.6 (62.0)	6.2 (1.7)
p	0.18	**0.008**	**0.013**	0.51
Insomnia				
No	64.6 (29.7)	15.8 (6.6)	76.9 (32.1)	6.3 (1.7)
Yes	69.6 (36.1)	16.9 (6.3)	83.0 (33.8)	6.6 (1.6)
p	0.21	0.30	0.32	0.14
Diabetes mellitus				
No	63.6 (27.5)	15.4 (5.5)	74.6 (28.2)	6.4 (1.7)
Yes	73.0 (42.2)	18.6 (10.1)	92.7 (44.9)	6.1 (1.7)
p	**<0.001**	**<0.001**	**<0.001**	0.16
Hypertension				
No	62.6 (31.9)	15.7 (5.4)	75.4 (26.7)	6.4 (1.7)
Yes	68.1 (29.0)	16.2 (7.8)	80.3 (37.6)	6.3 (1.7)
p	**0.002**	0.89	0.12	0.56
Cardio-metabolic conditions				
No	60.5 (28.4)	15.3 (5.3)	72.8 (26.3)	6.3 (1.7)
Yes	68.5 (32.5)	16.3 (7.3)	81.5 (39.0)	6.4 (1.7)
p	**0.013**	0.17	**0.011**	0.76
Total sleep time (minutes)				
<360	62.2 (20.3)	17.1 (8.1)	79.7 (38.2)	6.4 (1.7)
≥360	67.0 (35.4)	15.2 (5.4)	76.6 (28.3)	6.3 (1.7)
p	0.15	**0.015**	0.38	0.85

Abbreviations: OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; BMI, body mass index; 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; FOME, Fuld object memory evaluation; *SD*, standard deviation.
BMI: body mass index categorised according to international criteria from the World Health Organisation (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 kg/m^2 [obese]).
Cardiovascular disease: self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke.
Diabetes mellitus: self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L (126 mg/Dl), haemoglobin A1C ≥6.5%, or reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).
Insomnia: at least one of two PSQI dimensions (difficulty initiating or maintaining sleep) and significant daytime fatigue defined as an SF-36 Vitality Scale score one *SD* below the mean.
Hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use.
Cardio-metabolic conditions: a combined variable including one or more of diabetes mellitus, hypertension, or cardiovascular disease.
Legend: p-values representing statistically significant between-group differences boldfaced.
Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

Supplementary Table 7.2 Unadjusted and adjusted associations between FOME performance and NREM and REM sleep relative powers and EEG slowing ratio

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2		Adjusted Model 3	
				Overall sample				
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep								
Delta	0.01 (-0.02, 0.04)	0.36	0.01 (-0.02, 0.03)	0.60	0.002 (-0.02, 0.03)	0.89	0.01 (-0.02, 0.03)	0.74
Adjusted R^2	0.001		0.12		0.12		0.15	
Theta	-0.06 (-0.13, 0.01)	0.079	-0.03 (-0.09, 0.04)	0.40	-0.02 (-0.08, 0.05)	0.64	-0.02 (-0.08, 0.05)	0.62
Adjusted R^2	0.006		0.12		0.12		0.15	
Alpha	-0.04 (-0.12, 0.04)	0.30	-0.03 (-0.11, 0.04)	0.37	-0.02 (-0.09, 0.06)	0.62	-0.03 (-0.10, 0.05)	0.52
Adjusted R^2	0.001		0.12		0.12		0.15	
Sigma	0.08 (-0.11, 0.27)	0.40	-0.003 (-0.18, 0.18)	0.98	0.02 (-0.16, 0.20)	0.83	0.01 (-0.18, 0.19)	0.94
Adjusted R^2	0.001		0.12		0.12		0.15	
Beta	0.008 (-0.08, 0.10)	0.87	0.02 (-0.07, 0.11)	0.65	0.03 (-0.06, 0.12)	0.52	0.01 (-0.08, 0.10)	0.77
Adjusted R^2	0.003		0.12		0.12		0.15	
Slowing ratio	0.17 (-0.73, 1.06)	0.72	0.10 (-0.74, 0.94)	0.81	-0.05 (-0.90, 0.80)	0.91	0.08 (-0.78, 0.95)	0.85
Adjusted R^2	0.003		0.12		0.12		0.15	
REM sleep								
Delta	-0.004 (-0.02, 0.02)	0.69	-0.004 (-0.02, 0.01)	0.69	-0.007 (-0.03, 0.01)	0.46	-0.01 (-0.03, 0.01)	0.50
Adjusted R^2	0.002		0.12		0.12		0.15	
Theta	-0.005 (-0.05, 0.04)	0.84	-0.01 (-0.05, 0.04)	0.82	-0.001 (-0.04, 0.01)	0.98	-0.01 (-0.04, 0.04)	0.99
Adjusted R^2	0.003		0.12		0.12		0.15	
Alpha	-0.03 (-0.11, 0.04)	0.41	-0.02 (-0.09, 0.05)	0.64	-0.005 (-0.08, 0.07)	0.90	-0.005 (-0.08, 0.07)	0.89
Adjusted R^2	0.001		0.12		0.12		0.15	
Sigma	0.04 (-0.13, 0.21)	0.64	0.03 (-0.13, 0.19)	0.76	0.08 (-0.09, 0.24)	0.37	0.08 (-0.10, 0.25)	0.38
Adjusted R^2	0.002		0.12		0.12		0.15	
Beta	0.04 (-0.007, 0.09)	0.097	0.03 (-0.01, 0.08)	0.14	0.04 (-0.005, 0.09)	0.083	0.04 (-0.01, 0.08)	0.13
Adjusted R^2	0.005		0.13		0.13		0.15	
Slowing ratio	0.008 (-0.03, 0.04)	0.63	0.01 (-0.03, 0.04)	0.76	0.001 (-0.03, 0.03)	0.99	0.005 (-0.03, 0.04)	0.79
Adjusted R^2	0.002		0.12		0.12		0.15	
				Age-stratified sample (<65 years)				
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep								

Delta	0.02 (-0.01, 0.05)	0.27	0.01 (-0.02, 0.04)	0.42	0.01 (-0.02, 0.04)	0.67	0.01 (-0.02, 0.04)	0.58
Adjusted R^2	0.001		0.04		0.04		0.06	
Theta	-0.07 (-0.15, 0.008)	0.080	-0.05 (-0.13, 0.03)	0.19	-0.04 (-0.11, 0.05)	0.39	-0.04 (-0.12, 0.04)	0.35
Adjusted R^2	0.008		0.05		0.05		0.06	
Alpha	-0.08 (-0.16, 0.01)	0.084	-0.06 (-0.15, 0.02)	0.15	-0.05 (-0.13, 0.04)	0.29	-0.05 (-0.14, 0.04)	0.26
Adjusted R^2	0.008		0.05		0.05		0.06	
Sigma	0.002 (-0.20, 0.21)	0.98	-0.007 (-0.21, 0.20)	0.95	0.009 (-0.20, 0.22)	0.93	0.01 (-0.21, 0.24)	0.91
Adjusted R^2	0.004		0.04		0.04		0.06	
Beta	0.03 (-0.07, 0.13)	0.54	0.04 (-0.06, 0.13)	0.47	0.04 (-0.06, 0.14)	0.39	0.07 (-0.07, 0.22)	0.31
Adjusted R^2	0.002		0.04		0.05		0.06	
Slowing ratio	0.43 (-0.56, 1.41)	0.40	0.31 (-0.66, 1.28)	0.53	0.17 (-0.83, 1.17)	0.74	0.23 (-0.81, 1.28)	0.66
Adjusted R^2	0.001		0.04		0.04		0.06	
REM sleep								
Delta	0.003 (-0.02, 0.03)	0.82	-0.002 (-0.02, 0.02)	0.87	-0.006 (-0.03, 0.02)	0.62	-0.008 (-0.03, 0.02)	0.47
Adjusted R^2	0.004		0.04		0.04		0.06	
Theta	-0.02 (-0.07, 0.03)	0.47	-0.009 (-0.06, 0.04)	0.75	0.001 (-0.05, 0.05)	0.97	0.006 (-0.05, 0.06)	0.83
Adjusted R^2	0.002		0.04		0.04		0.06	
Alpha	-0.06 (-0.14, 0.03)	0.19	-0.03 (-0.12, 0.05)	0.45	-0.02 (-0.11, 0.07)	0.65	-0.02 (-0.11, 0.07)	0.69
Adjusted R^2	0.003		0.04		0.04		0.06	
Sigma	-0.04 (-0.23, 0.16)	0.70	0.007 (-0.18, 0.20)	0.94	0.06 (-0.14, 0.26)	0.57	0.05 (-0.15, 0.25)	0.61
Adjusted R^2	0.001		0.04		0.05		0.07	
Beta	0.03 (-0.02, 0.09)	0.25	0.03 (-0.02, 0.09)	0.23	0.04 (-0.02, 0.09)	0.19	0.05 (-0.009, 0.10)	0.098
Adjusted R^2	0.001		0.05		0.05		0.07	
Slowing ratio	0.02 (-0.02, 0.06)	0.25	0.02 (-0.02, 0.06)	0.35	0.01 (-0.02, 0.05)	0.47	0.02 (-0.02, 0.06)	0.43
Adjusted R^2	0.001		0.04		0.05		0.06	
			Age-stratified sample (≥65 years)					
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep								
Delta	-0.005 (-0.06, 0.05)	0.85	-0.005 (-0.06, 0.05)	0.85	-0.01 (-0.07, 0.05)	0.70	-0.02 (-0.08, 0.04)	0.53
Adjusted R^2	0.01		0.02		0.07		0.03	
Theta	0.02 (-0.10, 0.13)	0.78	0.02 (-0.10, 0.13)	0.76	0.03 (-0.09, 0.15)	0.62	0.04 (-0.09, 0.16)	0.57
Adjusted R^2	0.009		0.02		0.06		0.03	
Alpha	0.04 (-0.11, 0.19)	0.57	0.04 (-0.11, 0.19)	0.59	0.06 (-0.09, 0.22)	0.43	0.06 (-0.09, 0.22)	0.44
Adjusted R^2	0.007		0.01		0.06		0.03	
Sigma	0.01 (-0.40, 0.42)	0.96	-0.01 (-0.43, 0.41)	0.96	0.03 (-0.41, 0.48)	0.88	0.10 (-0.36, 0.56)	0.67
Adjusted R^2	0.01		0.02		0.07		0.03	
Beta	-0.05 (-0.25, 0.14)	0.59	-0.06 (-0.25, 0.14)	0.57	-0.05 (-0.26, 0.16)	0.61	0.02 (-0.24, 0.28)	0.90
Adjusted R^2	0.007		0.01		0.06		0.03	
Slowing ratio	-0.54 (-2.25, 1.16)	0.53	-0.46 (-2.17, 1.25)	0.60	-0.70 (-2.50, 1.10)	0.44	-1.00 (-2.85, 0.85)	0.29
Adjusted R^2	0.006		0.01		0.06		0.02	

REM sleep								
Delta	-0.007 (-0.04, 0.03)	0.66	-0.006 (-0.04, 0.03)	0.71	-0.005 (-0.04, 0.03)	0.76	-0.01 (-0.05, 0.02)	0.44
Adjusted R^2	0.008		0.02		0.07		0.03	
Theta	-0.001 (-0.07, 0.07)	0.98	-0.002 (-0.07, 0.07)	0.98	-0.009 (-0.08, 0.07)	0.80	0.004 (-0.07, 0.08)	0.93
Adjusted R^2	0.01		0.02		0.07		0.03	
Alpha	0.01 (-0.11, 0.14)	0.82	0.009 (-0.11, 0.13)	0.88	0.01 (-0.11, 0.14)	0.85	0.02 (-0.10, 0.15)	0.71
Adjusted R^2	0.01		0.02		0.07		0.03	
Sigma	0.09 (-0.22, 0.39)	0.58	0.08 (-0.23, 0.38)	0.63	0.10 (-0.23, 0.43)	0.53	0.18 (-0.16, 0.51)	0.30
Adjusted R^2	0.007		0.01		0.06		0.02	
Beta	0.04 (-0.05, 0.12)	0.38	0.04 (-0.05, 0.12)	0.42	0.04 (-0.05, 0.13)	0.40	0.07 (-0.02, 0.17)	0.14
Adjusted R^2	0.002		0.01		0.06		0.007	
Slowing ratio	0.02 (-0.02, 0.06)	0.25	-0.04 (-0.10, 0.03)	0.29	-0.05 (-0.11, 0.02)	0.19	-0.06 (-0.13, 0.01)	0.11
Adjusted R^2	0.005		0.005		0.05		0.002	

Abbreviations: NREM, non-rapid eye movement; REM, rapid eye movement; CI, confidence interval.
Coefficients: unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable linear regression models are reported.
Estimates: estimates represent the change in cognitive test scores corresponding to a 1% increase in relative spectral power and a one-unit increase in logarithmically (10-base) transformed EEG slowing ratio.
Relative spectral powers: delta: 0.5–4.5 Hz; theta: 4.5–8 Hz; alpha: 8–12 Hz; sigma: 12–15 Hz; beta: 15–32 Hz.
EEG slowing ratio: calculated as a ratio of slow to fast EEG frequencies [(delta+theta)/(alpha+sigma+beta)].
Adjusted Model 1: adjusted for age and AHI.
Adjusted Model 2: adjusted for age, AHI, financial stress, highest educational attainment, socio-economic disadvantage, and marital status.
Adjusted Model 3 (overall sample): adjusted for age, AHI, total sleep time, financial stress, highest educational attainment, socio-economic disadvantage, marital status, alcohol risk, BMI, current smoking status, physical activity level, cardiovascular disease, diabetes mellitus, blood glucose, insomnia, and hypertension.
Adjusted Model 3 (age-stratified samples): adjusted for age, AHI, total sleep time, financial stress, highest educational attainment, socio-economic disadvantage, marital status, and cardio-metabolic conditions (one or more of diabetes mellitus, hypertension, or cardiovascular disease).
Notes: multicollinearity tests displayed acceptable variance inflation factor for all covariates; AHI was scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

CHAPTER 8. LONGITUDINAL ASSOCIATIONS OF SLEEP MICROARCHITECTURE WITH FUTURE COGNITIVE FUNCTION IN MIDDLE-AGED AND OLDER MEN FROM A COMMUNITY-BASED COHORT STUDY

8.1 Abstract

Study objectives: Prospective observational studies examining associations between baseline sleep microarchitecture and future cognitive function predominantly recruited from small samples with relatively short follow-up. Therefore, this study examined sleep microarchitecture predictors of cognitive function (visual attention, processing speed, and executive function) after 8–10 years among community-dwelling middle-aged and older men.

Methods: Florey Adelaide Male Ageing Study participants (n=477) underwent home-based polysomnography (2010–2011), with 157 completing baseline (2007–2010) and follow-up (2018–2019) cognitive testing (trail-making tests A [TMT-A] and B [TMT-B]). Whole-night F4-M1 sleep electroencephalography (EEG) recordings were processed following artefact exclusion, and quantitative EEG characteristics obtained using previously validated algorithms. Multivariable linear regression models were adjusted for baseline obstructive sleep apnea, demographic, biomedical, and behavioural factors, and cognitive task performance.

Results: At baseline, participants were aged (mean [*SD*]) 58.9 (8.9) years with normal cognitive function. In unadjusted analyses, lower REM sleep relative delta and higher REM sleep relative alpha power were associated with worse TMT-A performance at follow-up (delta, *B*= -0.02, 95% CI [-0.04, -0.001], p=0.042; alpha, *B*=0.08, 95% CI [0.01, 0.15], p=0.024). Lower overall and slow N2 and N3 sleep spindle density were associated with worse TMT-A performance at follow-up (all p<0.05). The significant adjusted association of higher N3 sleep fast spindle density

with worse TMT-B performance at follow-up (*B* =1.06, 95% CI [0.13, 2.00], p=0.026) did not persist following adjustment for baseline cognition.

Conclusions: In this sample of community-dwelling middle-aged and older men with normal baseline performance, sleep microarchitecture was not independently associated with 8–10 year cognitive function.

8.2 Introduction

The normal ageing process is associated with cognitive function decline in many individuals (3). With rising years of life expectancy, there is an increase in age-associated mild cognitive impairment (MCI) and an approximate 20–30% conversion rate from MCI to clinical dementia and Alzheimer's disease (AD) (3). Disrupted conventional sleep electroencephalography (EEG) macroarchitecture parameters and obstructive sleep apnea (OSA), a highly prevalent sleep-related breathing disorder (12), show associations with cognitive impairment (13, 338). However, these associations are often weak and inconsistent, underlining the importance of establishing more robust cognitive function markers.

Emerging evidence, predominantly from small experimental laboratory studies, supports that finer-grained sleep EEG microarchitecture parameters assessed through quantitative EEG (qEEG) power spectral analysis (PSA) of EEGs could represent valuable brain-specific cognitive function markers (44). Chapter 7 of this thesis reported independent cross-sectional associations between lower rapid eye movement (REM) sleep relative delta and higher REM and non-REM (NREM) sleep relative theta and alpha power with worse visual attention and processing speed (trail-making test A [TMT-A] performance) and executive function (trail-making test B [TMT-B] performance) (339). These associations were observed among older (≥65 years) but not younger (<65 years) community-dwelling men. These findings from a community-based cohort study suggest that sleep qEEG may have prognostic value as a brain-specific cognitive function marker among older community-dwelling populations. However, longitudinal evidence from community-based cohort studies remains warranted to provide more robust evidence on the prognostic utility of qEEG markers of cognitive function.

Prospective observational studies examining associations between qEEG markers and future cognitive function either included short follow-up (1–2 years) or recruited smaller samples of older participants (≥60 years), many with baseline impairment (MCI, AD, or clinical dementia) (52-55, 301). Moreover, these studies examined qEEG markers during wakefulness, limiting the longitudinal evidence on the association between sleep qEEG markers at baseline and cognitive function at follow-up. Luckhaus et al. (52) recruited patients with MCI (n=88, mean age at baseline = 65.9 ± 9.6 years) and mild probable AD (n=42, mean age at baseline = 69.1 ± 10.7 years) and found that lower alpha power during wakefulness was associated with a 1-year transition from MCI to AD (52). Jelic et al. (53) recruited patients with MCI (n=27) categorised into stable MCI (S MCI) or progressed MCI (P MCI) after 21 months of follow-up and found that lower theta power was associated with further cognitive decline after 21 months in patients with S MCI and P MCI compared to healthy controls (n=16) (53). In older (≥70 years) participants with subjective cognitive complaints (SCC) (n=44), Prichep et al. (54) found that higher theta power was associated with conversion to MCI or dementia after 7–9 years. Hamilton et al. (55) recruited patients with MCI (n=92, age at baseline ≥60 years) and found that greater EEG slowing (theta/alpha ratio) was associated with a transition from MCI to dementia after 1.5 years (55). In older (≥65 years) community-dwelling women from the Study of Osteoporotic Fractures, Djonlagic et al. (43) demonstrated that higher theta and alpha power during NREM and alpha and sigma power during REM were associated with MCI over 5 years.

Limited preliminary evidence from small studies in healthy participants (409, 410) and patients with MCI (281) suggests that sleep spindles may be associated with cognitive function decline. Sleep spindles are brief bursts of neural oscillatory activity (sigma frequency range: 11–16 Hz, duration threshold ≥0.5 and ≤3 seconds) generated by the interplay of thalamic and thalamocortical nuclei and are believed to play an important role in cortical reorganisation processes contributing to learning capability and overnight declarative memory consolidation (269, 276). Several studies have reported an age-associated decline in spindle density (11–16 Hz, number/minute), average frequency (Hz, oscillations/second), and amplitude (μV) in healthy and disease populations (409-411). Taillard et al. (281) recruited participants with SCC and patients with MCI (n=29, mean age 71 years) and cognitively normal

controls (n=29 mean age 68 years) and reported that spindle maximal amplitude was significantly lower across NREM sleep in people with SCC compared to the control group. Gorgoni et al. (41) recruited patients with MCI (n=15) and AD (n=15) and a healthy control group (n=15) and reported associations of MCI and AD with lower parietal fast spindle density, suggesting that advancing age may be associated with spindle deficits. Despite the evidence linking sleep spindle abnormalities with cognitive function decline, longitudinal analyses in larger community-based studies remain warranted to determine the prognostic value of sleep spindles as brain-specific cognitive function markers.

While the emerging literature from a community-based cross-sectional cohort study (338) and smaller observational and clinical studies (52-55, 281, 301, 409) supports that qEEG sleep microarchitecture (EEG spectral power, sleep spindles, and EEG slowing) may represent a valuable brain-specific cognitive function marker, no community-based cohort studies are available to determine the prognostic value of sleep qEEG markers for predicting cognitive impairment. Identifying a link between sleep qEEG markers and future cognitive function would contribute to the evidence regarding potentially modifiable markers of cognitive impairment (341, 412). Therefore, the aim of this study was to investigate independent longitudinal associations between sleep microarchitecture parameters and cognitive function 8–10 years later among a sample of community-dwelling middle-aged and older men. It was hypothesised that sleep microarchitecture would be independently associated with cognitive function at 8–10 years follow-up after controlling for baseline obstructive sleep apnea and other relevant risk factors and cognitive task performance.

8.3 Methods

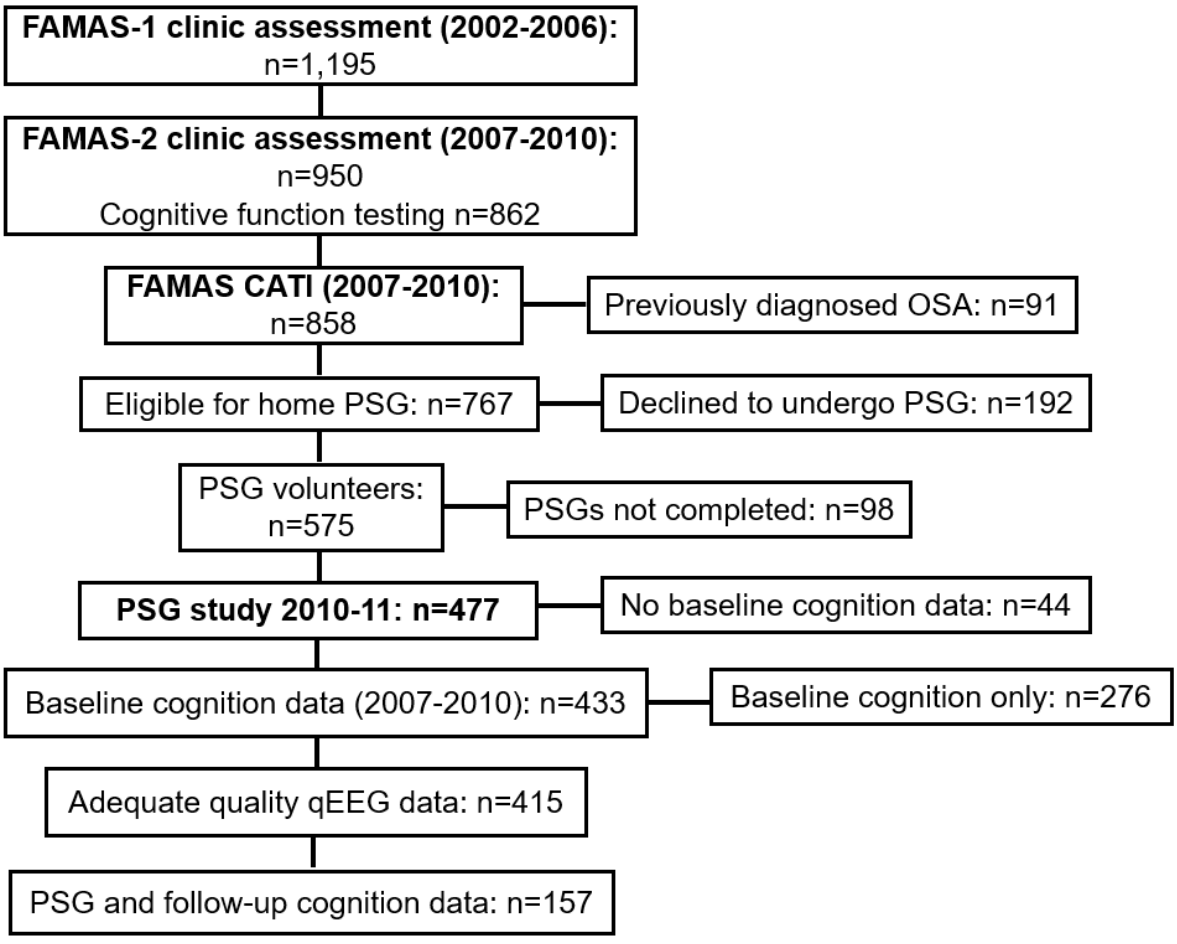
8.3.1 Study participants

The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study includes 2,569 urban community-dwelling men harmonised from two prospective community-based cohort studies: all Florey Adelaide Male Ageing Study (FAMAS) and male North West Adelaide Health Study (NWAHS) participants. The present longitudinal community-based cohort study includes FAMAS participants aged 35–

80 years at baseline (2002–2006) residing in the north-west regions of Adelaide, South Australia (304, 320).

During a computer-assisted telephone interview follow-up in 2010 (n=858), FAMAS participants who reported no previous OSA diagnosis (n=767) were invited to undergo home-based polysomnography (PSG) (2010–2011) as part of a sub-study of the MAILES Study (98, 303). Approximately 75% of eligible participants (n=575) agreed to participate, with time and budget constraints resulting in a final sample of n=477 (Figure 8.1). 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.

Figure 8.1 FAMAS clinic and sleep study assessments and cognitive function testing



FAMAS, Florey Adelaide Male Ageing Study. CATI, computer-assisted telephone interview. PSG, polysomnography. Qeeg, quantitative electroencephalography.

8.3.2 Baseline sleep study assessment

As previously described (338-340), participants underwent home-based eight-channel ambulatory PSG (Embletta X100, Embla Systems, Broomfield, Colorado, USA), which recorded electrical brain activity (EEG, F4-M1) and left electrooculography 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 measurements.

A single experienced sleep technician manually scored all PSG measures according to 2007 American Academy of Sleep Medicine (AASM) *Alternative* scoring criteria (32), recommended by an expert panel of the Australasian Sleep Association for use in prospective epidemiological studies (321). OSA was identified by an apnea-hypopnea index (AHI) ≥10/h and further categorised as mild (10–19/h), moderate (20–29/h), or severe (≥30/h). An AHI ≥5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria is approximately equivalent to ≥10/h using the AASM 2007 *Alternative* and ≥15/h using the older 1999 *Chicago* criteria (32). Therefore, an AHI cut-off of 10/h was chosen to maintain comparability with previous work. Apnea was defined as complete or near-complete airflow cessation (≥90%) measured using nasal cannula pressure excursions lasting ≥10 seconds. Hypopnea was defined as a ≥50% decrease in nasal cannula pressure excursions and an associated ≥3% oxygen desaturation or EEG arousal (32). Nocturnal hypoxemia was assessed from the oxygen desaturation index 3% (ODI 3%) and the percentage of total sleep time with oxygen saturation <90% (TST90). Acceptable sleep studies included ≥3.5 h of sleep and ≥5.5 h of total-recorded study time with technically acceptable respiratory and EEG signal quality.

8.3.3 EEG data processing

A detailed description of Qeeg analysis used in the present study has been previously described (38, 372). Synchronised European Data Format and sleep stage files were generated using Embla REMLogic PSG Software (Natus Medical, Inc., Pleasanton, California). An algorithm identified artefactual EEG data over consecutive non-overlapping 5-second epochs based on previously validated artefact detection amplitude threshold parameters (372). Contaminated 5-second epochs, including arousals where EEG traces went outside the amplitude boundaries, were subsequently excluded from Qeeg analysis.

8.3.4 EEG power spectral analysis

After rejecting artefactual epochs, power spectra were obtained using a standard fast Fourier transformation algorithm with a rectangular weighting window for each non-overlapping 5-second EEG epoch. Absolute spectral power (μV^2) was calculated in the delta, theta, alpha, sigma, and beta frequency bands defined as EEG activity of 0.5–4.5, 4.5–8, 8–12, 12–15, and 15–32 Hz, respectively, during NREM and REM sleep. The EEG power for each sleep-staged 30-second epoch was calculated by averaging data from six artefact-free 5-second epochs comprising each 30-second recording segment (372). Weighted average spectral power or variance over the frequency interval within the defined bands was computed for NREM (N2 and N3) and REM sleep. Weighted average spectral power, based on sleep stage or type, was calculated by averaging the absolute power of 30-second EEG epochs. Relative spectral power for each frequency band during NREM and REM sleep (e.g., delta/delta+theta+alpha+sigma+beta) was calculated. A global measure of NREM and REM sleep EEG slowing (i.e., a ratio of slow to fast EEG frequencies [(delta+theta)/(alpha+sigma+beta)]) was also calculated. As previously reported (367), manual verification of automated artefact scoring accuracy performed in 10% of randomly selected PSGs showed excellent accuracy and specificity and good to moderate sensitivity and agreement.

8.3.5 Sleep spindle detection algorithm and spindle metrics of interest

All PSGs were exported to Standardised European Data format, from which overnight F4-M1 EEG recordings underwent automated artefact detection using a validated algorithm. Spindle events were visually identified using an automated detection tool developed and written in Java, version 1.6 (Oracle, Santa Clara, California, USA), and previously validated in OSA samples (382). A 128-order band-passing Finite-Impulse-Response filter was applied to the raw EEG signal, yielding a time course of sigma activity (11–16 Hz, ≥0.5 and ≤3 seconds) (383). Reference standard spindle events were marked from onset to offset and exported with start time and duration details. The onset and offset of spindle events were determined by the first and second amplitude threshold crossings. Spindle events were recorded where the edges of the amplitude threshold crossings showed a threshold of 20% and tolerance of 50% of spindle amplitude. Spindles meeting criteria of duration 0.5–3 seconds and an inter-event interval >1 second were counted as events. Spindle occurrence (11–16 Hz, total overall spindle events), average frequency (Hz) of overall spindle events, spindle amplitude (μV), and overall (11–16 Hz), slow (11 ≤ fz ≤ 13 Hz; fz: frequency), and fast (13 < fz ≤ 16 Hz) spindle densities (spindle events per minute of sleep) were the spindle metrics of interest calculated during N2 and N3 sleep (340).

8.3.6 Baseline and follow-up cognitive assessments

Three standardised, validated, and well-established cognitive tests, previously described in greater detail (65, 66, 306, 338), were administered during the 2007–2010 follow-up and repeated at the 2018–2019 examination, including trail-making tests A (TMT-A) and B (TMT-B) and the 30-point mini-mental state examination (MMSE). Refer to Chapter 2 for a detailed description of the cognitive tests. Although FAMAS participants also completed the inspection time task and Fuld object memory evaluation (FOME) test at baseline, these participants only completed TMT-A, TMT-B, and the MMSE at follow-up, and therefore the number of cognitive tests that could be examined was limited for the longitudinal analysis.

8.3.7 Baseline covariate assessments

Self-completed questionnaires assessed demographic factors (age, financial stress, highest educational attainment, and marital status). Relative social disadvantage, based on participants' residential postcode, was determined with the Australian Bureau of Statistics Socio-Economic Indexes for Areas (SEIFA) Index of Relative Socio-Economic Disadvantage (IRSD) (309). Clinic assessments (2007–2010) included anthropometry, seated sphygmomanometer blood pressure, and a fasting blood sample to assess blood glucose and haemoglobin A1C (304). Composite cardiovascular disease (self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke) and diabetes mellitus (self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L [126 mg/dL], haemoglobin A1C ≥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 at least three nights/week (Pittsburgh Sleep Quality Index [PSQI] 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 (310). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or reported antihypertensive medication use (311). Self-completed questionnaires assessed chronic disease risk factors (smoking status, alcohol risk, and physical activity) and health-related quality of life (SF-36). Body mass index (BMI) was categorised according to international criteria (308).

8.3.8 Statistical analysis methodology

Data were analysed using IBM SPSS version 25.0 (IBM Corporation, Armonk, New York, USA). Baseline participant characteristics are reported as mean (*SD*) for normally distributed continuous variables, median (interquartile range [IQR]) for skewed continuous variables, and percentages (frequencies) for dichotomous and categorical variables. Baseline participant characteristics are stratified by follow-up cognitive examination participation and performance status. As previously reported (313), impaired performance was defined as a ≥0.5 *SD* change in TMT score between the baseline and follow-up examinations. Between-group differences were

assessed using Pearson's chi-squared tests for dichotomous and categorical variables, independent samples t-tests for normally distributed continuous variables, and Mann-Whitney U-tests for skewed continuous variables.

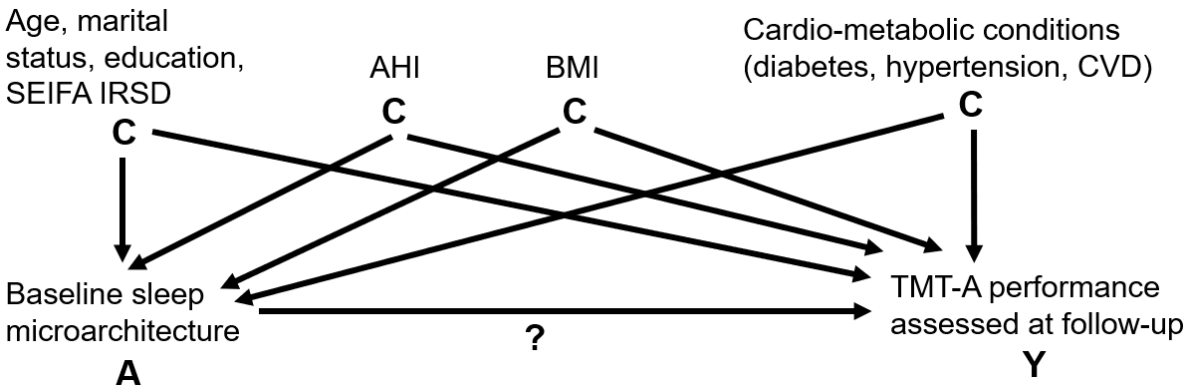
Mann-Whitney U and Kruskal-Wallis tests examined differences in cognitive performance across covariate categories. Standardised z-scores were calculated using the logarithmic base 10 test scores, subtracting the mean, and dividing by the sample *SD* (26, 31, 313, 314). Differences in z-scores were assessed using independent samples t-tests and one-way analysis of variance with Bonferroni correction for multiple comparisons.

Linear regression models determined longitudinal associations between sleep microarchitecture parameters (NREM and REM sleep EEG relative spectral power, EEG slowing ratio, and sleep spindle metrics) and standardised TMT-A and TMT-B performance at 8–10 years follow-up, with results presented as unstandardised beta (*B*) coefficients (95% confidence interval [CI]). EEG slowing ratio was normalised by applying a logarithmic base 10 transformation. Three regression models were constructed, including 1) unadjusted, 2) models adjusted for age, AHI, highest educational attainment, socio-economic disadvantage, marital status, BMI, and cardio-metabolic conditions (one or more of hypertension, diabetes mellitus, or cardiovascular disease), and 3) additionally adjusted for baseline cognitive performance. These analyses were performed to determine if sleep microarchitecture parameters assessed at baseline were independently associated with future cognitive function. Purposeful covariate selection (325, 339) ensured robust covariates were retained for multivariable adjustment. Furthermore, covariates in multivariable adjustment are previously reported risk factors for cognitive decline (306, 341-343). The principal assumptions of linear regression modelling were satisfied, including linearity, normality, and homoscedasticity. Multicollinearity was assessed by examining the variance inflation factor. The filter function in SPSS was used to ensure only participants with complete case cognition, PSG, and covariate data were included in the final analysis.

Binary logistic regression models determined longitudinal associations and sleep microarchitecture parameters and dichotomised values of change in TMT times (cut-offs for cognitive change; normal [≤0.5 *SD*] and impaired [>0.5 *SD*] performers (313))

and MMSE scores <28/30 at follow-up corresponding to cognitive impairment (316). Results are presented as odds ratios (OR) 95% CI. Covariates in multivariable adjustment were consistent with linear regression analyses. For all analyses, a two-sided p<0.05 was considered statistically significant. Based on previously reported practical considerations and given the exploratory nature of the analyses, multiple comparison adjustments were not performed (346, 347).

Figure 8.2 Overview of relationships between variables



Legend: A=exposure/treatment/intervention/primary independent variable, C=confounder, Y=outcome variable.

8.4 Results

Of the 433 men with PSG and cognitive data at baseline, 36.3% (n=157) participated in the 2018–2019 follow-up cognitive examination (Figure 8.1). The mean (*SD*) age at baseline of those who participated in the 2018–2019 follow-up examination was 58.9 (8.9) (range, 41–81) years.

8.4.1 Baseline participant characteristics stratified by follow-up status

Relative to non-participants, those who participated in the follow-up cognitive examination were younger (Table 8.1) and showed higher N3 sleep average spindle frequency (Table 8.2). However, there were no differences in disease or chronic disease risk factors.

Table 8.1 Baseline participant characteristics stratified by cognitive follow-up examination participation status

	Cognitive follow-up examination participation		
Baseline participant characteristics	**Participants (n=157)**	**Non-participants (n=276)**	***p*-values**
Demographic risk factors			
% (n)			
Age (years)			
<50	18.5 (29)	25.7 (71)	
50–59	34.4 (54)	29.3 (81)	
60–69	33.1 (52)	21.7 (60)	**0.006**
≥70	14.0 (22)	23.2 (64)	
Financial stress			
Spends >earns	14.6 (23)	17.0 (47)	0.52
Highest educational attainment			
≥Diploma, certificate, trade, bachelor's degree or higher	75.2 (118)	70.3 (194)	0.28
Biomedical risk factors			
BMI (kg/m^2)			
<25 (underweight/normal)	19.1 (30)	21.4 (59)	
25 to <30 (overweight)	45.9 (72)	45.7 (126)	0.83
≥30 (obese)	35.0 (55)	33.0 (91)	
Behavioural risk factors			
Current smokers	14.6 (23)	20.2 (55)	0.15
Physical activity level – sedentary behaviour	18.5 (29)	25.0 (69)	0.86
Mean (*SD*)			
Cognitive baseline data			
TMT-A, secs	15.4 (5.2)	16.2 (7.1)	0.14
TMT-B, secs	75.3 (26.1)	80.0 (37.6)	0.12

Abbreviations: BMI, body mass index; *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.
BMI: body mass index categorised according to international criteria from the World Health Organisation (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 kg/m^2 [obese]).
Cardiovascular disease: self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke.
Diabetes mellitus: self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), haemoglobin A1C ≥6.5%, or reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).
Insomnia: difficulty initiating or maintaining sleep occurring at least three nights/week (PSQI dimensions) and significant daytime fatigue defined as a score one *SD* 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.

Table 8.2 Sleep microarchitecture parameters stratified by cognitive follow-up examination participation status

	Cognitive follow-up examination participation	
Baseline participant characteristics	**Participants (n=157)**	**Non-Participants (n=276)**
Sleep microarchitecture parameters		
Mean (*SD*)		
NREM		
Delta	81.2 (6.4)	81.5 (7.1)
Theta	8.2 (2.8)	8.0 (2.7)
Alpha	5.3 (2.4)	5.2 (2.5)
Sigma	2.0 (0.9)	2.0 (1.0)
Beta	3.3 (1.6)	3.3 (2.3)
REM		
Delta	69.7 (8.7)	70.5 (10.3)
Theta	11.9 (3.5)	11.6 (4.4)
Alpha	6.9 (2.4)	6.7 (2.6)
Sigma	3.0 (1.1)	2.8 (1.1)
Beta	8.4 (3.4)	8.3 (4.2)
Median (IQR)		
NREM EEG slowing ratio	9.0 (6.4, 12.7)	9.0 (6.9, 12.2)
REM EEG slowing ratio	4.5 (3.4, 6.2)	4.5 (3.6, 6.6)
Mean (*SD*)		
N2 sleep spindle metrics		
Occurrence	213.8 (157.0)	221 (165.6)
Overall density	1.0 (0.7)	1.1 (0.7)
Fast density	0.4 (0.3)	0.4 (0.3)
Slow density	0.7 (0.5)	0.7 (0.5)
Average frequency	12.8 (0.3)	12.8 (0.3)
Amplitude	13.8 (3.1)	13.8 (4.4)
N3 sleep spindle metrics		
Occurrence	43.9 (64.4)	34.0 (43.0)
Overall density	0.6 (0.7)	0.5 (0.6)
Fast density	0.1 (0.2)	0.1 (0.2)
Slow density	0.5 (0.6)	0.4 (0.5)
Average frequency	12.4 (1.5) *****	11.9 (2.9)
Amplitude	12.7 (4.7)	13.3 (7.8)

Abbreviations: *SD*, standard deviation; IQR, interquartile range. NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; N2, stage 2 sleep; N3, stage 3 sleep
EEG relative spectral powers: delta: 0.5–4 Hz; theta: 4.5–8 Hz; alpha: 8–12 Hz; sigma: 12–15 Hz; beta: 15–32 Hz
EEG slowing ratio: calculated as a ratio of slow to fast EEG frequencies [(delta+theta)/(alpha+sigma+beta)].
Spindle metrics: occurrence (11–16 Hz, total events), overall density (11–16 Hz, number/minute), fast density (13–16 Hz, number/minute), slow density (11–13 Hz, number/minute), average frequency (Hz, oscillations/second), and amplitude (μV).
Symbol legends: *****independent samples t-test $p<0.05$ compared to men without follow-up cognition data.

Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

8.4.2 Prevalence of cognitive impairment and incident MCI

Regarding MMSE performance, 13.4% (n=21) of participants showed cognitive impairment (<28/30) at baseline, whereas 14% (n=22) showed cognitive impairment (<28/30) at follow-up. Furthermore, 8.9% (n=14) showed incident MCI (≥28/30 at baseline but <28/30 at follow-up). Refer to Chapter 4 for baseline and follow-up TMT performance relative to normative values of age and highest educational attainment.

8.4.3 Sleep microarchitecture stratified by change in cognitive function from baseline to follow-up

Participants who showed a ≥0.5 *SD* reduction on TMT-A and TMT-B were older (Table 8.3) compared to participants who did not show a ≥0.5 *SD* reduction. Participants who showed a ≥0.5 *SD* reduction on TMT-A recorded lower N2 sleep spindle occurrence and N2 and N3 sleep overall and slow spindle density compared to participants who did not show a ≥0.5 *SD* reduction (Table 8.4). Participants who showed a ≥0.5 *SD* reduction on TMT-B recorded lower N2 sleep spindle amplitude compared to participants who did not show a ≥0.5 *SD* reduction (Table 8.4).

Table 8.3 Baseline participant characteristics stratified by standard deviation reduction in TMT performance from baseline to follow-up

	Follow-up examination					
Follow-up cognitive performance domains	**Visual attention and processing speed (TMT-A)**			**Executive function (TMT-B)**		
Cognitive performance subgroups	**<0.5 *SD* reduction(n =129)**	**≥0.5 *SD* reduction (n=28)**	***p*-values**	**<0.5 *SD* reduction (n=122)**	**≥0.5 *SD* reduction (n=35)**	***p*-values**
Demographic risk factors						
% (n)						
Age (years)						
<50	22.4 (29)	3.6 (1)		21.5 (26)	11.4 (4)	
50–59	38.8 (50)	14.3 (4)	**<0.001**	35.5 (43)	31.4 (11)	**0.009**
60–69	31.0 (40)	39.3 (11)		34.7 (42)	25.7 (9)	
≥70	7.8 (10)	42.9 (12)		9.1 (11)	31.4 (11)	
Financial stress						
Spends >earns	85.8 (115)	67.9 (19)	**0.005**	87.6 (106)	82.9 (29)	0.56
Highest educational attainment						
≥Diploma, certificate, trade, bachelor's degree or higher	72.9 (94)	78.6 (22)	0.66	77.0 (94)	71.4 (25)	0.51
SEIFA IRSD						
Quintile 1 (most socio-economic disadvantage)	19.4 (25)	28.6 (8)		22.1 (27)	20.0 (7)	
Quintile 2	8.5 (11)	17.9 (5)	0.21	7.4 (9)	22.9 (8)	0.057
Quintile 3	31.8 (41)	14.3 (4)		31.4 (38)	14.3 (5)	
Quintile 4	27.8 (35)	28.6 (8)		26.4 (32)	31.4 (11)	
Quintile 5 (least socio-economic disadvantage)	13.5 (17)	10.7 (3)		13.2 (16)	11.4 (4)	
Married/partner	87.6 (113)	96.4 (27)	0.16	88.5 (108)	91.4 (32)	0.62
Biomedical risk factors						
BMI (kg/m^2)						
% (n)						
<25 (underweight/normal)	21.7 (28)	7.1 (2)		20.5 (25)	14.3 (5)	
25 to <30 (overweight)	45.0 (58)	53.6 (15)	0.22	42.6 (52)	60.0 (21)	0.18
≥30 (obese)	33.3 (43)	39.3 (11)		37.2 (45)	25.7 (9)	
Current smokers	16.3 (21)	7.1 (2)	0.20	13.9 (17)	17.1 (6)	0.65
Cardiovascular disease	3.9 (5)	10.7 (3)	0.15	4.1 (5)	8.6 (3)	0.29
Diabetes mellitus	15.5 (20)	17.9 (5)	0.80	14.8 (18)	25.7 (9)	0.14
Insomnia	9.3 (12)	17.9 (5)	0.20	8.2 (10)	20.0 (7)	0.050
Hypertension	56.6 (73)	67.9 (19)	0.23	58.2 (71)	60.0 (21)	0.82
Cardio-metabolic conditions	58.9 (76)	71.4 (20)	0.19	59.8 (73)	65.7 (23)	0.51
Behavioural risk factors						
Physical activity level – sedentary behaviour	18.6 (24)	17.9 (5)	0.88	21.3 (26)	8.6 (3)	0.084
Alcohol risk – medium to very high	7.0 (9)	7.1 (2)	0.99	6.6 (8)	11.4 (4)	0.35
Mean (*SD*)						
ESS	6.8 (4.2)	7.1 (4.5)	0.76	6.6 (4.3)	7.7 (3.6)	0.18
% (n)						
ESS ≥11 (excessive daytime sleepiness)	14.7 (19)	17.9 (5)	0.68	14.8 (18)	20.0 (7)	0.49
Psychotropic medication(s)	10.1 (13)	3.6 (1)	0.28	7.4 (9)	14.3 (5)	0.21

Abbreviations: SEIFA IRSD, Socio-Economic Indexes for Areas Index of Relative Socio-Economic Disadvantage; BMI, body mass index; ESS, Epworth Sleepiness Scale; *SD*, standard deviation; IQR, interquartile range.
BMI: body mass index categorised according to international criteria from the World Health Organisation (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 kg/m^2 [obese]).
Cardiovascular disease: self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke.

Diabetes mellitus: self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), haemoglobin A1C ≥6.5%, or reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).
Insomnia: difficulty initiating or maintaining sleep occurring at least three nights/week (PSQI 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): Use of one or more of opiates, antipsychotics, antiepileptics, antidepressants, or benzodiazepines.
Legend: p-values representing significant between-group differences boldfaced.
Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

Table 8.4 Sleep microarchitecture parameters stratified by standard deviation reduction in TMT performance

	Cognitive follow-up examination participants			
Follow-up cognitive performance domains	**Visual attention and processing speed (TMT-A)**		**Executive function (TMT-B)**	
Cognitive performance subgroups	**<0.5 *SD* reduction (n=129)**	**≥0.5 *SD* reduction (n=28)**	**<0.5 *SD* reduction (n=122)**	**≥0.5 *SD* reduction (n=35)**
Sleep microarchitecture parameters				
Mean (*SD*)				
NREM				
Delta	80.9 (6.4)	82.7 (5.6)	81.1 (6.5)	81.4 (6.2)
Theta	8.1 (2.5)	7.7 (2.0)	8.2 (2.9)	8.1 (2.4)
Alpha	5.4 (2.4)	4.8 (2.5)	5.3 (2.4)	5.3 (2.5)
Sigma	2.1 (1.0)	1.8 (0.7)	2.1 (0.9)	2.0 (1.0)
Beta	3.4 (1.7)	3.1 (0.9)	3.3 (1.6)	3.2 (1.4)
REM				
Delta	70.2 (9.0)	67.2 (6.7)	69.6 (8.9)	70.4 (7.8)
Theta	11.8 (3.6)	12.6 (3.0)	11.9 (3.5)	11.9 (3.2)
Alpha	6.5 (2.5)	7.6 (2.2)	6.9 (2.4)	6.9 (2.5)
Sigma	3.0 (1.2)	3.3 (1.0)	3.0 (1.1)	2.9 (1.2)
Beta	8.3 (3.5)	9.2 (2.8)	8.5 (3.6)	8.0 (2.9)
Median (IQR)				
NREM sleep EEG slowing ratio	8.9 (6.3, 11.9)	10.3 (7.6, 14.5)	8.9 (6.4, 12.5)	9.5 (6.7, 13.1)
REM sleep EEG slowing ratio	4.6 (3.4, 6.6)	3.9 (3.0, 5.4)	4.3 (3.3, 6.6)	4.8 (3.6, 6.1)
Mean (*SD*)				
N2 sleep spindle metrics				
Occurrence	229.7 (161.2)	151.9 (121.0) *	219.4 (153.8)	200.6 (166.8)
Overall density	1.1 (0.7)	0.8 (0.6) *	1.1 (0.7)	1.0 (0.8)
Fast density	0.4 (0.3)	0.3 (0.3)	0.4 (0.3)	0.4 (0.4)
Slow density	0.7 (0.5)	0.5 (0.4) *	0.7 (0.5)	0.6 (0.5)
Average frequency	12.8 (0.3)	12.8 (0.2)	12.8 (0.3)	12.8 (0.3)
Amplitude	14.0 (3.0)	13.5 (3.5)	14.2 (3.2)	12.8 (2.6) *
N3 sleep spindle metrics				
Occurrence	47.0 (67.7)	32.3 (48.6)	45.9 (67.5)	38.2 (53.9)
Overall density	0.7 (0.7)	0.4 (0.5) *	0.7 (0.7)	0.6 (0.7)
Fast density	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)	0.1 (0.2)
Slow density	0.6 (0.6)	0.3 (0.3) *	0.5 (0.6)	0.5 (0.6)
Average frequency	12.4 (1.2)	12.7 (0.4)	12.4 (1.3)	12.2 (2.2)
Amplitude	4.6 (6.6)	13.1 (4.9)	13.1 (4.9)	11.3 (3.8)

Abbreviations: SEIFA IRSD, Socio-Economic Indexes for Areas Index of Relative Socio-Economic Disadvantage; BMI, body mass index; ESS, Epworth Sleepiness Scale; *SD*, standard deviation; IQR, interquartile range; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; N2, stage 2 sleep; N3, stage 3 sleep.
BMI: body mass index categorised according to international criteria from the World Health Organisation (<25 [underweight/normal], 25 to <30 [overweight], and ≥30 kg/m^2 [obese]).
Cardiovascular disease: self-reported, doctor-diagnosed myocardial infarction, angina, transient ischemic attack, or stroke.
Diabetes mellitus: self-reported, doctor-diagnosed, fasting plasma glucose ≥7.0 mmol/L (126 mg/dL), haemoglobin A1C ≥6.5%, or reported antidiabetic medication use (oral hypoglycaemic agents and/or insulin).
Insomnia: difficulty initiating or maintaining sleep occurring at least three nights/week (PSQI 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): Use of one or more of opiates, antipsychotics, antiepileptics, antidepressants, or benzodiazepines.
EEG relative spectral powers: delta: 0.5–4 Hz; theta: 4.5–8 Hz; alpha: 8–12 Hz; sigma: 12–15 Hz; beta: 15–32 Hz
EEG slowing ratio: calculated as a ratio of slow to fast EEG frequencies [(delta+theta)/(alpha+sigma+beta)].

Spindle metrics: occurrence (11–16 Hz, total events), overall density (11–16 Hz, number/minute), fast density (13–16 Hz, number/minute), slow density (11–13 Hz, number/minute), average frequency (Hz, oscillations/second), and amplitude (μV).
Legend: p-values representing significant between-group differences boldfaced.
Notes: all PSG measures were scored according to AASM 2007 *Alternative* scoring criteria in which an AHI of 10/h is approximately equivalent to an AHI of 5/h used to define sleep-disordered breathing by the AASM 2007 *Recommended* scoring criteria.

8.4.4 Associations between sleep microarchitecture and future cognitive function

In unadjusted models, worse standardised TMT-A performance at follow-up was associated with lower baseline REM sleep relative delta power, higher baseline REM sleep relative alpha power, and lower baseline N2 and N3 sleep overall and slow spindle density and N2 sleep spindle occurrence (Table 8.5). However, these associations did not persist in adjusted models. In an adjusted model only (Model 1), worse standardised TMT-B performance at follow-up was associated with greater baseline N3 sleep fast spindle density. However, this association did not persist after adjusting for baseline TMT-B performance (Table 8.6). MMSE performance at follow-up was not associated with baseline NREM and REM sleep microarchitecture parameters in unadjusted or adjusted models (Supplementary Table 8.1).

Table 8.5 Covariate unadjusted and adjusted associations between baseline sleep microarchitecture parameters and standardised (z-score) follow-up TMT-A performance

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep relative power						
Delta	0.002 (-0.02, 0.03)	0.86	0.001 (-0.02, 0.03)	0.97	0.006 (-0.02, 0.03)	0.61
Theta	0.008 (-0.05, 0.07)	0.79	0.008 (-0.05, 0.07)	0.78	-0.004 (-0.06, 0.05)	0.87
Alpha	-0.008 (-0.08, 0.06)	0.82	-0.005 (-0.07, 0.06)	0.89	-0.02 (-0.08, 0.04)	0.42
Sigma	-0.13 (-0.31, 0.06)	0.18	-0.05 (-0.23, 0.12)	0.54	-0.07 (-0.23, 0.08)	0.34
Beta	-0.004 (-0.11, 0.011)	0.94	-0.005 (-0.11, 0.10)	0.92	-0.002 (-0.09, 0.09)	0.97
EEG slowing ratio	0.07 (-0.78, 0.91)	0.87	0.005 (-0.77, 0.78)	0.99	0.18 (-0.52, 0.88)	0.61
REM sleep relative power						
Delta	-0.02 (-0.04, -0.001)	**0.042**	-0.01 (-0.03, 0.006)	0.19	-0.004 (-0.02, 0.01)	0.61
Theta	0.05 (-0.001, 0.09)	0.057	0.04 (-0.005, 0.08)	0.081	0.02 (-0.02, 0.06)	0.32
Alpha	0.08 (0.01, 0.15)	**0.024**	0.04 (-0.02, 0.11)	0.21	0.02 (-0.04, 0.08)	0.54
Sigma	0.10 (-0.05, 0.24)	0.21	0.03 (-0.11, 0.17)	0.69	-0.004 (-0.13, 0.12)	0.95
Beta	0.03 (-0.02, 0.08)	0.25	0.01 (-0.03, 0.06)	0.60	-0.003 (-0.05, 0.04)	0.88
EEG slowing ratio	-0.004 (-0.04, 0.03)	0.80	-0.005 (-0.04, 0.03)	0.76	0.003 (-0.03, 0.03)	0.86
N2 sleep spindle metrics						
Occurrence	-0.001 (-0.002, -0.0002)	**0.017**	0.0007 (-0.001, 0.001)	0.90	-0.0002 (-0.001, 0.001)	0.74
Overall density	-0.29 (-0.52, -0.06)	**0.014**	0.005 (-0.24, 0.25)	0.97	-0.03 (-0.25, 0.20)	0.80
Fast density	-0.30 (-0.79, 0.18)	0.22	0.23 (-0.24, 0.71)	0.33	0.15 (-0.30, 0.58)	0.52
Slow density	-0.43 (-0.76, -0.11)	**0.010**	-0.11 (-0.44, 0.23)	0.54	-0.13 (-0.43, 0.18)	0.42
Average frequency	0.30 (-0.33, 0.92)	0.35	0.43 (-0.16, 1.02)	0.15	0.48 (-0.05, 1.02)	0.077
Maximum amplitude	-0.03 (-0.08, 0.03)	0.33	0.03 (-0.03, 0.08)	0.29	0.02 (-0.03, 0.07)	0.44
N3 sleep spindle metrics						
Occurrence	-0.001 (-0.004, 0.001)	0.33	0.0002 (-0.002, 0.003)	0.86	0.0005 (-0.002, 0.003)	0.68
Overall density	-0.25 (-0.49, -0.009)	**0.042**	-0.01 (-0.26, 0.23)	0.92	0.002 (-0.22, 0.23)	0.98
Fast density	-0.14 (-1.11, 0.82)	0.77	0.64 (-0.28, 1.56)	0.17	0.62 (-0.22, 1.46)	0.15
Slow density	-0.33 (-0.61, -0.05)	**0.023**	-0.08 (-0.36, 0.21)	0.60	-0.06 (-0.32, 0.21)	0.68
Average frequency	0.03 (-0.08, 0.14)	0.59	0.06 (-0.04, 0.15)	0.28	0.05 (-0.04, 0.14)	0.30
Maximum amplitude	-0.02 (-0.06, 0.02)	0.27	0.01 (-0.02, 0.05)	0.43	0.007 (-0.02, 0.04)	0.66

Abbreviations: CI, confidence interval; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; N2, stage 2 sleep; N3, stage 3 sleep.
Coefficients: unstandardised beta (*B*) coefficients (95% CI) from univariable and multivariable regression models are reported.
Estimates: estimates represent the change in follow-up TMT-A and TMT-B scores corresponding to a 1% increase in baseline relative EEG spectral power and a one-unit increase in baseline logarithmically (10-base) transformed EEG slowing ratio.
EEG relative spectral powers: delta: 0.5–4 Hz; theta: 4.5–8 Hz; alpha: 8–12 Hz; sigma: 12–15 Hz; beta: 15–32 Hz.
EEG slowing ratio: calculated as a ratio of slow to fast EEG frequencies [(delta+theta)/(alpha+sigma+beta)].
Spindle metrics: occurrence (11–16 Hz, total events), overall density (11–16 Hz, number/minute), fast density (13–16 Hz, number/minute), slow density (11–13 Hz, number/minute), average frequency (Hz, oscillations/second), and amplitude (μV).
Adjusted Model 1: adjusted for baseline age, AHI, highest educational attainment, socio-economic disadvantage, marital status, BMI, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes mellitus, or hypertension).
Adjusted Model 2: additionally adjusted for baseline cognitive task performance.
Spindle occurrence (adjusted Model 1 and 2): additionally adjusted for total sleep time.
Legend: p-values representing significant associations boldfaced.

Table 8.6 Covariate unadjusted and adjusted associations between baseline sleep microarchitecture parameters and standardised (z-score) follow-up TMT-B performance

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
NREM sleep relative power						
Delta	0.01 (-0.02, 0.04)	0.47	0.01 (-0.02, 0.04)	0.40	0.009 (-0.01, 0.03)	0.40
Theta	-0.02 (-0.09, 0.04)	0.43	-0.03 (-0.09, 0.03)	0.27	-0.02 (-0.07, 0.03)	0.43
Alpha	-0.01 (-0.08, 0.06)	0.75	-0.02 (-0.09, -0.05)	0.62	-0.02 (-0.07, 0.04)	0.59
Sigma	-0.11 (-0.29, 0.07)	0.23	-0.06 (-0.24, 0.12)	0.49	-0.07 (-0.22, 0.08)	0.38
Beta	-0.02 (-0.13, 0.09)	0.70	-0.02 (-0.12, 0.09)	0.78	-0.03 (-0.12, 0.06)	0.46
EEG slowing ratio	0.19 (-0.67, 1.00)	0.69	0.18 (-0.63, 0.98)	0.66	0.20 (-0.47, 0.87)	0.55
REM sleep relative power						
Delta	-0.005 (-0.02, 0.02)	0.64	0.002 (-0.02, 0.02)	0.80	0.007 (-0.009, 0.02)	0.41
Theta	0.004 (-0.05, 0.05)	0.87	-0.007 (-0.06, 0.04)	0.79	-0.002 (-0.04, 0.04)	0.91
Alpha	0.03 (-0.04, 0.10)	0.47	-0.009 (-0.08, 0.06)	0.80	-0.02 (-0.08, 0.04)	0.45
Sigma	0.02 (-0.13, 0.17)	0.82	-0.04 (-0.19, 0.11)	0.60	-0.07 (-0.19, 0.06)	0.28
Beta	0.01 (-0.04, 0.06)	0.67	-0.0004 (-0.05, 0.05)	0.99	-0.02 (-0.06, 0.02)	0.28
EEG slowing ratio	0.002 (-0.03, 0.04)	0.90	0.004 (-0.03, 0.04)	0.80	0.004 (-0.02, 0.03)	0.76
N2 sleep spindle metrics						
Occurrence	-0.001 (-0.002, 0.0004)	0.24	0.0005 (-0.001, 0.002)	0.43	0.0002 (-0.001, 0.001)	0.74
Overall density	-0.16 (-0.40, 0.08)	0.18	0.09 (-0.16, 0.34)	0.49	0.03 (-0.18, 0.24)	0.77
Fast density	-0.17 (-0.65, 0.32)	0.50	0.34 (-0.15, 0.83)	0.17	0.16 (-0.26, 0.57)	0.46
Slow density	-0.24 (-0.57, 0.09)	0.16	-0.0005 (-0.35, 0.35)	0.99	-0.02 (-0.31, 0.28)	0.91
Average frequency	-0.11 (-0.74, 0.52)	0.72	0.09 (-0.52, 0.70)	0.76	-0.06 (-0.57, 0.46)	0.83
Maximum amplitude	-0.02 (-0.08, 0.03)	0.38	0.01 (-0.04, 0.07)	0.67	-0.002 (-0.05, 0.04)	0.92
N3 sleep spindle metrics						
Occurrence	-0.001 (-0.003, 0.002)	0.69	0.0004 (-0.002, 0.003)	0.78	-0.0004 (-0.002, 0.002)	0.97
Overall density	-0.04 (-0.29, 0.21)	0.74	0.15 (-0.10, 0.40)	0.23	0.08 (-0.14, 0.29)	0.49
Fast density	0.26 (-0.71, 1.23)	0.59	1.06 (0.13, 2.00)	**0.026**	0.57 (-0.24, 1.38)	0.17
Slow density	-0.08 (-0.36, 0.21)	0.59	0.11 (-0.19, 0.40)	0.48	0.05 (-0.20, 0.30)	0.70
Average frequency	0.004 (-0.10, 0.11)	0.94	0.03 (-0.07, 0.13)	0.56	0.01 (-0.08, 0.10)	0.80
Maximum amplitude	-0.03 (-0.06, 0.006)	0.11	-0.005 (-0.04, 0.03)	0.77	-0.02 (-0.05, 0.01)	0.27

Abbreviations: NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; CI, confidence interval.
Coefficients: unstandardised beta (*B*) coefficients (95% confidence interval) from univariable and multivariable regression models are reported.
Estimates: estimates represent the change in follow-up TMT-A and TMT-B scores corresponding to a 1% increase in baseline relative EEG spectral power and a one-unit increase in baseline logarithmically (10-base) transformed EEG slowing ratio.
EEG relative spectral powers: delta: 0.5–4 Hz; theta: 4.5–8 Hz; alpha: 8–12 Hz; sigma: 12–15 Hz; beta: 15–32 Hz.
EEG slowing ratio: calculated as a ratio of slow to fast EEG frequencies [(delta+theta)/(alpha+sigma+beta)].
Spindle metrics: occurrence (11–16 Hz, total events), overall density (11–16 Hz, number/minute), fast density (13–16 Hz, number/minute), slow density (11–13 Hz, number/minute), average frequency (Hz), and amplitude (μV).
Adjusted Model 1: adjusted for baseline age, AHI, highest educational attainment, socio-economic disadvantage, marital status, BMI, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes mellitus, or hypertension).
Adjusted Model 2: additionally adjusted for baseline cognitive task performance.
Spindle occurrence (adjusted Model 1 and 2): additionally adjusted for total sleep time.
Legend: p-values representing significant associations boldfaced

8.4.5 Covariate unadjusted and adjusted associations between sleep microarchitecture and change in cognitive function from baseline to follow-up

In unadjusted models, higher N2 and N3 sleep overall and slow spindle density and spindle occurrence (N2 sleep only) were associated with reduced odds of significant decline in TMT-A performance, defined as a ≥0.5 *SD* reduction from baseline to follow-up (Table 8.7). Furthermore, higher N2 and N3 sleep spindle amplitude was associated with reduced odds of significant decline in TMT-B performance (Table 8.8). These associations did not persist in models adjusted for age and other covariates and adjusting for baseline standardised TMT time did not attenuate these associations further.

Table 8.7 Covariate unadjusted and adjusted associations between baseline sleep microarchitecture parameters and change in TMT-A performance from baseline to follow-up

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
NREM sleep relative power						
Delta	1.05 (0.97, 1.13)	0.21	1.06 (0.97, 1.16)	0.19	1.06 (0.97, 1.16)	0.19
Theta	0.93 (0.77, 1.12)	0.43	0.91 (0.73, 1.15)	0.45	0.92 (0.73, 1.16)	0.47
Alpha	0.89 (0.73, 1.08)	0.24	0.86 (0.67, 1.09)	0.20	0.86 (0.68, 1.09)	0.20
Sigma	0.62 (0.36, 1.07)	0.087	0.62 (0.32, 1.20)	0.15	0.62 (0.32, 1.20)	0.16
Beta	0.86 (0.62, 1.19)	0.36	0.73 (0.46, 1.15)	0.17	0.73 (0.46, 1.15)	0.17
EEG slowing ratio	3.84 (0.44, 33.2)	0.22	5.68 (0.42, 77.7)	0.19	5.56 (0.40, 76.6)	0.20
REM sleep relative power						
Delta	0.96 (0.91, 1.01)	0.12	0.97 (0.91, 1.04)	0.38	0.97 (0.91, 1.04)	0.36
Theta	1.07 (0.95, 1.21)	0.28	1.11 (0.94, 1.31)	0.20	1.12 (0.95, 1.33)	0.18
Alpha	1.16 (0.97, 1.38)	0.12	1.11 (0.89, 1.39)	0.37	1.11 (0.89, 1.39)	0.35
Sigma	1.36 (0.93, 1.99)	0.12	1.10 (0.69, 1.73)	0.70	1.09 (0.69, 1.73)	0.70
Beta	1.08 (0.96, 1.23)	0.22	1.02 (0.87, 1.18)	0.83	1.02 (0.87, 1.19)	0.83
EEG slowing ratio	1.04 (0.96, 1.13)	0.37	1.05 (0.95, 1.15)	0.39	1.04 (0.95, 1.15)	0.40
N2 sleep spindle metrics						
Occurrence	0.996 (0.99, 1.00)	**0.025**	1.001 (0.997, 1.005)	0.66	1.001 (0.997, 1.006)	0.63
Overall density	0.42 (0.19, 0.93)	**0.031**	1.16 (1.08, 1.26)	0.75	1.17 (0.47, 2.90)	0.73
Fast density	0.40 (0.08, 1.88)	0.24	2.36 (0.45, 12.5)	0.31	2.51 (0.47, 13.6)	0.28
Slow density	0.25 (0.07, 0.84)	**0.025**	0.84 (0.21, 3.29)	0.80	0.84 (0.21, 3.32)	0.81
Average frequency	2.19 (0.42, 11.4)	0.35	5.39 (0.55, 53.3)	0.15	5.31 (0.53, 53.1)	0.16
Amplitude	0.95 (0.82, 1.10)	0.48	1.10 (0.91, 1.33)	0.32	1.10 (0.91, 1.32)	0.33
N3 sleep spindle metrics						
Occurrence	0.99 (0.98, 1.00)	0.29	1.001 (0.99, 1.01)	0.84	1.001 (0.99, 1.01)	0.86
Overall density	0.37 (0.14, 0.99)	**0.047**	0.83 (0.30, 2.34)	0.73	0.82 (0.29, 2.33)	0.71
Fast density	0.57 (0.04, 8.16)	0.68	7.73 (0.34, 175.2)	0.20	8.38 (0.36, 193.5)	0.18
Slow density	0.24 (0.07, 0.85)	**0.027**	0.56 (0.14, 2.27)	0.42	0.55 (0.13, 2.23)	0.40
Average frequency	2.29 (0.84, 6.23)	0.10	2.82 (0.83, 9.54)	0.096	3.01 (0.87, 10.5)	0.083
Amplitude	0.88 (0.76, 1.01)	0.065	0.97 (0.82, 1.15)	0.73	0.97 (0.82, 1.15)	0.73

Abbreviations: CI, confidence interval; OR, odds ratio; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; N2, stage 2 sleep; N3, stage 3 sleep.
Coefficients: odds ratios (95% CI) from univariable and multivariable binary logistic regression models are reported.
Estimates: estimates represent odds of decline in TMT-A and TMT-B scores corresponding to a 1% increase in relative EEG spectral power at baseline and a one-unit increase in logarithmically (10-base) transformed EEG slowing ratio at baseline.
EEG relative spectral powers: delta: 0.5–4 Hz; theta: 4.5–8 Hz; alpha: 8–12 Hz; sigma: 12–15 Hz; beta: 15–32 Hz.
EEG slowing ratio: calculated as a ratio of slow to fast EEG frequencies [(delta+theta)/(alpha+sigma+beta)].
Spindle metrics: occurrence (11–16 Hz, total events), overall density (11–16 Hz, number/minute), fast density (13–16 Hz, number/minute), slow density (11–13 Hz, number/minute), average frequency (Hz, oscillations/second), and amplitude (μV).
Adjusted Model 1: adjusted for baseline age, AHI, highest educational attainment, socio-economic disadvantage, marital status, BMI, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes mellitus, or hypertension).
Adjusted Model 2: additionally adjusted for baseline cognitive task performance
Spindle occurrence (Adjusted Model 1 and 2): additionally adjusted for total sleep time.
Legend: p-values representing significant associations boldfaced.

Table 8.8 Covariate unadjusted and adjusted associations between baseline sleep microarchitecture parameters and change in TMT-B performance from baseline to follow-up

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
NREM sleep relative power						
Delta	1.01 (0.95, 1.07)	0.81	1.00 (0.93, 1.07)	0.95	1.00 (0.92, 1.07)	0.89
Theta	0.99 (0.86, 1.14)	0.88	1.01 (0.86, 1.20)	0.87	1.02 (0.87, 1.21)	0.80
Alpha	1.00 (0.85, 1.17)	0.96	1.00 (0.82, 1.21)	0.97	1.00 (0.82, 1.22)	0.97
Sigma	0.89 (0.58, 1.38)	0.60	1.01 (0.61, 1.68)	0.97	1.02 (0.61, 1.70)	0.94
Beta	0.96 (0.74, 1.24)	0.75	1.00 (0.74, 1.36)	0.98	1.00 (0.74, 1.35)	0.99
Slowing ratio	1.34 (0.19, 9.18)	0.77	1.08 (0.11, 10.3)	0.95	1.03 (0.11, 9.99)	0.98
REM sleep relative power						
Delta	1.01 (0.97, 1.06)	0.66	1.03 (0.97, 1.09)	0.30	1.03 (0.98, 1.10)	0.25
Theta	0.99 (0.89, 1.12)	0.95	0.99 (0.86, 1.14)	0.93	0.99 (0.86, 1.15)	0.94
Alpha	0.99 (0.85, 1.17)	0.95	0.92 (0.75, 1.12)	0.39	0.91 (0.74, 1.11)	0.35
Sigma	0.92 (0.65, 1.30)	0.62	0.77 (0.50, 1.16)	0.21	0.75 (0.49, 1.15)	0.18
Beta	0.95 (0.84, 1.07)	0.40	0.90 (0.78, 1.04)	0.16	0.89 (0.77, 1.03)	0.12
Slowing ratio	1.01 (0.94, 1.09)	0.79	1.01 (0.92, 1.10)	0.95	1.00 (0.92, 1.10)	0.98
N2 sleep spindle metrics						
Occurrence	1.00 (0.997, 1.002)	0.55	1.002 (0.99, 1.005)	0.24	1.002 (0.99, 1.005)	0.25
Overall density	0.82 (0.46, 1.48)	0.51	1.47 (0.72, 2.99)	0.29	1.46 (0.71, 2.98)	0.30
Fast density	0.66 (0.19, 2.30)	0.52	2.05 (0.49, 8.57)	0.33	1.98 (0.47, 8.38)	0.35
Slow density	0.82 (0.36, 1.87)	0.64	1.47 (0.57, 3.78)	0.43	1.48 (0.57, 3.82)	0.42
Frequency	0.40 (0.09, 1.75)	0.22	0.46 (0.07, 2.87)	0.41	0.44 (0.07, 2.73)	0.38
Amplitude	0.85 (0.74, 0.99)	**0.036**	0.89 (0.75, 1.06)	0.19	0.89 (0.75, 1.06)	0.25
N2 sleep spindle metrics						
Occurrence	1.00 (0.99, 1.005)	0.55	1.00 (0.99, 1.01)	0.90	1.00 (0.99, 1.01)	0.89
Overall density	0.88 (0.48, 1.62)	0.69	1.37 (0.69, 2.72)	0.37	1.36 (0.68, 2.69)	0.39
Fast density	0.90 (0.09, 8.98)	0.93	5.53 (0.41, 74.6)	0.20	4.93 (0.35, 69.2)	0.24
Slow density	0.85 (0.42, 1.74)	0.66	1.32 (0.59, 2.94)	0.50	1.31 (0.59, 2.93)	0.51
Average frequency	0.91 (0.74, 1.14)	0.42	0.89 (0.70, 1.13)	0.35	0.89 (0.70, 1.13)	0.33
Amplitude	0.89 (0.79, 1.00)	**0.043**	0.91 (0.80, 1.05)	0.20	0.91 (0.79, 1.04)	0.17

Abbreviations: CI, confidence interval; OR, odds ratio; NREM, non-rapid eye movement sleep; REM, rapid eye movement sleep; N2, stage 2 sleep; N3, stage 3 sleep.
Coefficients: odds ratios (95% CI) from univariable and multivariable binary logistic regression models are reported.
Estimates: estimates represent odds of decline in TMT-A and TMT-B scores corresponding to a 1% increase in relative EEG spectral power at baseline and a one-unit increase in logarithmically (10-base) transformed EEG slowing ratio at baseline.
EEG relative spectral powers: delta: 0.5–4 Hz; theta: 4.5–8 Hz; alpha: 8–12 Hz; sigma: 12–15 Hz; beta: 15–32 Hz.
EEG slowing ratio: calculated as a ratio of slow to fast EEG frequencies [(delta+theta)/(alpha+sigma+beta)].
Spindle metrics: occurrence (11–16 Hz, total events), overall density (11–16 Hz, number/minute), fast density (13–16 Hz, number/minute), slow density (11–13 Hz, number/minute), average frequency (Hz), and amplitude (μV).
Adjusted Model 1: adjusted for baseline age, AHI, highest educational attainment, socio-economic disadvantage, marital status, BMI, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes mellitus, or hypertension).
Adjusted Model 2: additionally adjusted for baseline cognitive task performance
Spindle occurrence (Adjusted Model 1 and 2): additionally adjusted for total sleep time.
Legend: p-values representing significant associations boldfaced.

8.5 Discussion

This community-based cohort study is the first to examine prospective associations between sleep microarchitecture and future cognitive function and decline among community-dwelling middle-aged and older men. Sleep microarchitecture parameters (sleep EEG relative spectral power, global EEG slowing ratio, and sleep spindle metrics) were not associated with any cognitive function outcomes (visual attention and processing speed [TMT-A] and executive function [TMT-B] performance) at 8–10 years follow-up. These findings extend smaller prospective observational studies of sleep microarchitecture assessed through quantitative EEG (qEEG) power spectral analysis (44, 52-55, 301, 409), suggesting sleep qEEG has limited prognostic value as an early brain-specific cognitive function marker.

Chapter 7 of this thesis (339) reported independent cross-sectional associations between sleep microarchitecture (lower NREM sleep delta power and higher REM sleep theta and alpha power) with cognitive dysfunction (worse TMT-A [lower NREM sleep delta power only] and TMT-B performance) among older (≥65 years) community-dwelling men. Other authors (40-42, 44, 45, 301) reported differences in sleep microarchitecture between patients with mild cognitive impairment and age- and gender-matched controls. However, prospective observational studies examining associations between sleep microarchitecture and future cognitive function and decline have predominantly been conducted in smaller samples of older participants (≥60 years), many with mild cognitive impairment/Alzheimer's disease at baseline (52-55, 301) or a comparatively larger study including older community-dwelling women (≥65 years) (43). The novel contribution of the present study is the inclusion of a comparatively larger and younger sample of community-dwelling men to capture the prognostic value of sleep qEEG as a valuable early brain-specific cognitive impairment marker.

Unadjusted associations between lower REM sleep delta and greater REM sleep alpha power and worse TMT-A performance at follow-up did not persist in adjusted analyses. Small observational studies report associations between higher NREM sleep alpha and theta power and future cognitive decline (52-54, 302). Conversely, in the present study, relative NREM sleep EEG spectral power was not associated

with any domains of cognitive function in unadjusted or adjusted analyses. Djonlagic et al. (43) reported significant differences in baseline NREM sleep qEEG markers between older (≥65 years) community-dwelling women who developed mild cognitive impairment five years after their baseline sleep study compared to women who did not develop mild cognitive impairment. Therefore, the present analysis of community-dwelling men expands on findings derived from a prospective study by Djonlagic et al. (43), as longitudinal associations between sleep microarchitecture and future cognitive function were examined. In contrast, Djonlagic et al. (43) only investigated between-group differences in sleep microarchitecture and cognitive decline.

Given that the FAMAS cohort consists exclusively of community-dwelling men who are, on average, younger compared to participants of previous smaller observational studies (52-54, 302) and the Study of Osteoporotic Fractures (413), previously reported age and gender differences in sleep microarchitecture could account for the discrepant findings between the present study and previous studies. Previous reports suggest that women typically show higher slow frequency EEG activity during NREM sleep, particularly in the delta and theta frequency ranges, compared to age-matched men (401, 413). Previous reports also suggest that with ageing, slow-wave activity (0.5–4 Hz) typically decreases, and ageing is also associated with higher power in the fast-frequency beta range (15–32 Hz) (414, 415). Collectively, previous literature supports age, gender, and cognitive status differences, potentially accounting for the discrepant findings.

Although the FAMAS cohort of men was largely free of mild cognitive impairment and Alzheimer's disease at baseline (median MMSE score = 29/30), most scored worse compared to previously reported normative values of age and highest educational attainment on TMT-A and TMT-B (306) at follow-up as reported in Chapter 4. Therefore, unadjusted associations between lower REM sleep delta and greater REM sleep alpha power with worse TMT-A performance could relate to the sample overall showing cognitive impairment at follow-up as sleep qEEG markers may have been more sensitive for detecting impairment. However, these associations were no longer significant after adjustment for baseline cognitive task performance and other potential confounders. Therefore, the findings suggest a limited prognostic value of

qEEG markers for identifying individuals at risk of cognitive dysfunction and decline in older age.

Along with EEG spectral power, it is important to investigate the prognostic value of sleep spindles as markers of cognitive decline. Observational studies have identified potential links between ageing and sleep spindle abnormalities, including lower occurrence, densities, frequency, and amplitude, with cognitive impairment (281, 409-411). While the present study observed several unadjusted associations of higher overall and slow spindle density during N2 sleep with worse TMT-A performance at follow-up, these did not persist in adjusted analyses, suggesting these metrics might not be important markers of future cognitive impairment.

The adjusted association between higher N3 sleep fast spindle density and worse TMT-B performance at follow-up did not persist after adjustment for baseline cognitive task performance. No other adjusted associations were observed between sleep spindle metrics and future cognitive function. An observational study examined the topographical distribution of fast spindle density in healthy controls and patients with mild cognitive impairment and Alzheimer's disease and identified lower parietal N2 sleep fast spindle density in patients with mild cognitive impairment and Alzheimer's disease compared to healthy controls (41). Fast spindles are typically studied during N2 sleep, particularly prominent in the centroparietal brain region, and believed to be important for cognitive function (269). Further community-based longitudinal studies remain warranted to provide more consistent robust evidence of the presence or absence of associations between fast spindle density during N2 and N3 sleep and future cognitive decline.

While healthy volunteer responder bias was not observed in men who consented to follow-up assessments compared to non-participants who only undertook the baseline cognitive examination, considerable loss to follow-up could have significantly reduced the power to detect significant longitudinal associations between baseline sleep qEEG markers and future TMT performance. Another potential explanation for the lack of significant longitudinal associations is the influence of uncontrollable factors, including OSA treatment modality (continuous positive airway pressure [CPAP], mandibular advancement splint [MAS], or

pharyngeal surgery and participant adherence) and participant selection bias (e.g., death or lack of consent for follow-up assessments). It will be necessary for further longitudinal community-based studies to carefully consider the potential influence of these factors on associations observed or not observed between baseline sleep microarchitecture and future cognitive function.

This study has several strengths. It includes a comparatively younger community-based sample representative of an understudied adult male population. Data included cognitive function at baseline and follow-up assessed by standardised and validated tests with well-established test and performance parameters (306, 312, 338). Extensive survey and biomedical data (303, 304, 320) provided the means to control for multiple relevant potential confounders. Along with these strengths, several study limitations need to be acknowledged. Sleep microarchitecture parameters were acquired using a single frontal EEG derivation (F4–M1). Consequently, potentially important topographical differences in sleep microarchitecture parameters may have been missed. The sleep sub-study was performed in men, with results in women remaining unknown. Due to the low follow-up study response rate over 8–10 years, multivariable regression models were not adjusted for waist circumference, which is reported to impact cognitive function (416, 417). However, in the sample, body mass index and waist circumference were highly correlated (Pearson's r=0.89). Although this study adjusted for multiple potential confounders, residual and unknown factors could have affected the findings. As a limited number of cognitive tests were completed at follow-up, it remains unknown whether sleep microarchitecture was associated with future cognitive function and decline in domains that were not assessed, which requires further longitudinal investigation.

In summary, among this sample of community-dwelling men with normal baseline cognitive function, sleep microarchitecture parameters assessed through qEEG power spectral analysis at baseline were not independently associated with cognitive function 8–10 years later. These findings suggest that qEEG has limited prognostic value as an early brain-specific cognitive function marker. If associations exist between baseline sleep microarchitecture and future cognitive function, then further prospective investigation in studies with a longer follow-up to capture greater

cognitive decline and more extensive cognitive tests that could be more sensitive to nocturnal hypoxemia or sleep disruption might reveal these associations. Therefore, further longitudinal qEEG studies in larger samples of community-dwelling men and women with a longer follow-up and more extensive cognitive tests remain warranted.

8.6 Supplementary Tables

Supplementary Table 8.1 Unadjusted and adjusted binary logistic regression analyses of associations between sleep microarchitecture parameters at baseline with impaired MMSE performance at follow-up

	Unadjusted Model		Adjusted Model 1		Adjusted Model 2	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
NREM sleep relative power						
Delta	0.99 (0.93, 1.07)	0.85	1.02 (0.93, 1.12)	0.71	1.01 (0.90, 1.12)	0.91
Theta	1.08 (0.92, 1.25)	0.35	1.01 (0.84, 1.23)	0.89	1.04 (0.85, 1.28)	0.72
Alpha	1.02 (0.85, 1.23)	0.82	0.95 (0.74, 1.23)	0.70	0.99 (0.76, 1.30)	0.95
Sigma	0.78 (0.46, 1.33)	0.37	0.72 (0.34, 1.50)	0.37	0.76 (0.32, 1.78)	0.52
Beta	0.89 (0.64, 1.24)	0.48	0.80 (0.47, 1.35)	0.40	0.73 (0.38, 1.40)	0.35
EEG slowing ratio	1.34 (0.14, 12.8)	0.80	2.94 (0.15, 56.2)	0.48	2.58 (0.09, 76.8)	0.58
REM sleep relative power						
Delta	0.99 (0.93, 1.04)	0.58	1.01 (0.94, 1.09)	0.74	1.04 (0.96, 1.13)	0.38
Theta	1.03 (0.90, 1.16)	0.69	1.02 (0.85, 1.21)	0.84	0.97 (0.80, 1.18)	0.77
Alpha	1.09 (0.91, 1.32)	0.36	1.00 (0.77, 1.30)	0.99	0.96 (0.70, 1.30)	0.77
Sigma	1.01 (0.68, 1.51)	0.95	0.77 (0.46, 1.32)	0.34	0.65 (0.35, 1.21)	0.18
Beta	1.02 (0.90, 1.17)	0.74	0.94 (0.78, 1.13)	0.49	0.87 (0.70, 1.09)	0.22
EEG slowing ratio	1.01 (0.92, 1.10)	0.87	1.04 (0.93, 1.16)	0.48	1.04 (0.92, 1.19)	0.52
N2 sleep spindle metrics						
Occurrence	1.00 (0.99, 1.001)	0.99	1.00 (0.99, 1.004)	0.66	1.00 (0.995, 1.006)	0.91
Overall density	0.57 (0.27, 1.24)	0.16	0.90 (0.34, 2.42)	0.84	1.05 (0.36, 3.06)	0.93
Fast density	0.20 (0.03, 1.41)	0.11	0.44 (0.04, 4.65)	0.50	0.60 (0.06, 6.52)	0.68
Slow density	0.63 (0.22, 1.77)	0.38	1.10 (0.32, 3.84)	0.88	1.33 (0.33, 5.33)	0.91
Average frequency	0.33 (0.06, 1.87)	0.21	0.22 (0.02, 2.37)	0.21	0.20 (0.02, 2.75)	0.23
Amplitude	0.84 (0.70, 1.01)	0.065	0.88 (0.68, 1.13)	0.31	0.90 (0.69, 1.17)	0.42
N3 sleep spindle metrics						
Occurrence	1.00 (0.99, 1.01)	0.48	1.00 (0.99, 1.01)	0.84	1.00 (0.99, 1.01)	0.64
Overall density	0.63 (0.27, 1.46)	0.28	0.87 (0.35, 2.16)	0.77	0.90 (0.35, 2.31)	0.82
Fast density	0.06 (0.001, 3.29)	0.17	0.14 (0.001, 19.2)	0.44	0.10 (0.00, 19.4)	0.39

Slow density	0.67 (0.26, 1.71)	0.40	0.92 (0.34, 2.52)	0.87	0.97 (0.34, 2.76)	0.96
Average frequency	1.96 (0.69, 5.58)	0.21	3.23 (0.72, 14.5)	0.13	2.07 (0.39, 11.1)	0.40
Amplitude	0.94 (0.83, 1.06)	0.32	1.00 (0.85, 1.17)	0.95	0.97 (0.79, 1.18)	0.74

Abbreviations: CI, confidence interval; OR, odds ratio; NREM, non-rapid eye movement; REM, rapid eye movement; N2, stage 2 sleep; N3, stage 3 sleep.
Estimates: estimates represent the odds of scoring <28/30 on the MMSE at follow-up corresponding to a 1% increase in relative EEG spectral power at baseline and a one-unit increase in logarithmically (10-base) transformed EEG slowing ratio at baseline.
EEG relative spectral powers: delta: 0.5–4.5 Hz; theta: 4.5–8 Hz; alpha: 8–12 Hz; sigma: 12–15 Hz; beta: 15–32 Hz.
EEG slowing ratio: calculated as a ratio of slow to fast EEG frequencies [(delta+theta)/(alpha+sigma+beta)].
Spindle metrics: occurrence (11–16 Hz, total events), overall density (11–16 Hz, number/minute), fast density (13–16 Hz, number/minute), slow density (11–13 Hz, number/minute), average frequency (Hz, oscillations/second), and amplitude (μV).
Adjusted Model 1: adjusted for baseline age, AHI, highest educational attainment, socio-economic disadvantage, marital status, BMI, and cardio-metabolic conditions (one or more of cardiovascular disease, diabetes mellitus, or hypertension).
Adjusted Model 2: additionally adjusted for baseline MMSE performance.
Spindle occurrence (Adjusted Model 1 and 2): additionally adjusted for total sleep time.

CHAPTER 9. SUMMARY, FUTURE DIRECTIONS, AND CONCLUSIONS

9.1 OSA and advancing age are fundamental risk factors for cognitive function decline

Advancing age is associated with measurable cognitive function decline across multiple domains (1-4), disrupted conventional sleep electroencephalography (EEG) macroarchitecture, including greater non-rapid eye movement (NREM) light stage 1 (N1) and 2 (N2) sleep and reduced deep or slow-wave stage 3 (N3) and rapid eye movement (REM) sleep (5-8), and an increased risk of obstructive sleep apnea (OSA) (9-11). OSA is the most common sleep-related breathing disorder (12), characterised by repetitive pharyngeal collapse leading to intermittent nocturnal hypoxemia (oxyhemoglobin desaturation) and sleep fragmentation (81, 82). Furthermore, OSA is associated with daytime cognitive dysfunction, including attentional problems, vigilance failure, memory impairments (declarative, working, and verbal), and executive dysfunction (13-17, 418).

9.2 Cohort studies investigating associations between OSA, sleep macroarchitecture, and cognitive function are clinical or select

Available evidence supporting cognitive dysfunction in patients with OSA primarily comes from small experimental laboratory studies (193, 199-202, 206, 209, 226, 235, 251, 419-421). Cohort studies investigating independent cross-sectional associations between conventional polysomnography (PSG)-derived OSA disease severity and intermittent hypoxemia and sleep macroarchitecture parameters and daytime cognitive function outcomes predominantly recruited from clinical (previous OSA diagnosis or incident mild cognitive impairment [MCI]) (18, 24, 25, 250) or select community-based (populations classified as at heightened risk of OSA [Berlin screening questionnaire] or older age [≥65 years]) (19-23) populations. The clinical and select community-based cohort samples potentially account for often weak and inconsistent associations between routine OSA and sleep macroarchitecture

parameters and cognitive function outcomes due to different participant characteristics and differing severities of OSA and health conditions. Consequently, the scope, magnitude, and generalisability of OSA- and disrupted sleep macroarchitecture-associated cognitive dysfunction among the broader population remains uncertain and requires further investigation.

9.3 Research motivations

Together with determining the scope, magnitude, and generalisability of OSA- and disrupted sleep macroarchitecture-associated cognitive dysfunction among the broader unselected population, additional community-based cohort studies are necessary to determine the prognostic value of finer-grained quantitative EEG (qEEG) sleep microarchitecture as a valuable brain-specific cognitive function marker. Establishing these associations would considerably enhance our understanding of the contributing role of sleep to cognitive function and provide data on potential target interventions (e.g., sleep slow-wave activity [SWA] enhancement) to help prevent or slow cognitive function decline in older age.

9.4 Restatement of original contribution to knowledge

This doctoral research has made several significant original contributions to knowledge by *utilising an analytic epidemiologic approach to investigate independent cross-sectional and longitudinal associations between OSA, sleep macroarchitecture, and sleep microarchitecture parameters or qEEG markers (relative EEG spectral power, EEG slowing ratio, and sleep spindle metrics), and daytime cognitive function outcomes among a sample of unselected community-dwelling middle-aged and older men from a prospective community-based study of Australian Men, the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) Study, one of the most comprehensive and longest-running longitudinal community-based cohort studies of male health and wellbeing with ageing in Australia (303).* The novel findings from this thesis enhance our understanding of the contributing role of various sleep parameters to daytime cognitive function and the possibility of utilising target interventions (e.g., sleep slow-wave activity enhancement) to improve sleep architecture and slow cognitive function decline in older age.

9.5 Summary of findings from Study 1 (CHAPTER 3)

In **Study 1 (CHAPTER 3)** of this thesis, it was postulated that parameters indicative of greater OSA severity and disrupted sleep macroarchitecture would show modest independent cross-sectional associations with worse cognitive function in the complete sample and men ≥65 years in age-stratified analysis based on previous reports (6, 19-21). **Age-stratified analyses demonstrated that a higher percentage of N1 sleep was independently associated with worse visual attention and processing speed (trail-making test A [TMT-A] performance [slower completion times]) in older (≥65 years) community-dwelling men. Conversely, a higher percentage of N3 sleep was independently associated with better TMT-A performance (faster completion times) in men ≥65 years.** These significant independent cross-sectional associations support findings from the Apnea Positive Pressure Long-term Efficacy Study (APPLES) in a middle-aged (mean age approximately 50 years) highly educated clinical sample of patients with previously diagnosed OSA (18), the Osteoporotic Fractures in Men (MrOS) Sleep Study in older (≥67 years) community-dwelling men (19, 20), and the community-based HypnoLaus Study in older (>65 years) community-dwelling men and women (21). Therefore, the findings from **Study 1 (CHAPTER 3)** in a randomly selected community-based sample extend previous literature reporting on findings from clinical and select community-based cohort samples and imply a potentially important link between disrupted conventional sleep EEG macroarchitecture through lighter, more fragmented sleep and impaired daytime attentional performance, highlighting the importance of slow-wave sleep for daytime cognitive function among older community-dwelling men.

9.6 Future research suggestions building on Study 1 (CHAPTER 3)

Further studies remain warranted to investigate and determine the prognostic value of conventional OSA disease severity parameters and disrupted sleep EEG macroarchitecture for identifying prospective cognitive dysfunction and decline and general alternations in finer-grained sleep EEG microarchitectural characteristics. Establishing a link between sleep EEG microarchitecture and prospective cognitive dysfunction and decline would provide an opportunity to utilise targeted interventions, for example, slow-wave sleep enhancement through non-invasive closed-loop

targeted auditory/acoustic stimulation (422), to attempt to improve sleep microarchitecture through reducing lighter, more fragmented sleep and enhancing slow-wave sleep to promote deeper more restorative sleep, improve daytime cognitive function and slow cognitive function decline in older age.

Given that the MAILES Study consists exclusively of community-dwelling middle-aged and older men, investigating associations between conventional OSA disease severity parameters, sleep EEG macroarchitecture, and cognitive function among community-dwelling women remains essential. Qiu et al. (423) recently examined associations between OSA and visuospatial, prospective, and short numeric memory, fluid intelligence, and reaction time among 267,889 male and female participants from the UK Biobank Study. Older (≥65 years) female patients with OSA showed a higher risk of poor prospective memory, which was not observed in younger (<65 years) female patients with OSA or male patients with OSA (423). However, the UK Biobank Study identified OSA by a physician diagnosis or electronic record. The UK Biobank Study also relied on diagnosed OSA, a largely under-recognised and under-diagnosed sleep-related breathing disorder (424). Consequently, in the UK Biobank Study, reliance on diagnosed OSA may have influenced the severity and/or presentation of OSA in women who often present with atypical symptoms and are less likely to be diagnosed than men (425). The inability to generalise the findings of **Study 1 (CHAPTER 3)** of this thesis to women underlines the importance of further studies investigating associations between OSA, sleep macroarchitecture, and cognitive function among community-dwelling women.

9.7 Associations between OSA and sleep macroarchitecture at baseline and cognitive function at follow-up

Clinical and community-based cohort studies investigating longitudinal associations between baseline conventional OSA disease severity and sleep EEG macroarchitecture parameters and prospective cognitive function predominantly recruited from older populations (≥60 years at baseline), with many participants showing baseline impairment (MCI or Alzheimer's disease [AD]) (26-31). Several studies also included a relatively short follow-up period (4–8 years) between the baseline PSG and follow-up cognitive assessments (26, 30, 31). Consequently, whether OSA and sleep macroarchitecture independently predict prospective

cognitive dysfunction among a community-based cohort who are on average younger than 60 years at baseline, predominantly free of cognitive impairment, and with a longer follow-up duration between the baseline PSG and follow-up cognitive examinations remains undetermined and requires investigation.

9.8 Summary of findings from Study 2 (CHAPTER 4)

In **Study 2 (CHAPTER 4)** of this thesis, this research question was addressed by assessing OSA and sleep macroarchitecture parameters as predictors of cognitive function examined 8–10 years after baseline home-based PSG (2010–2011) while controlling for baseline cognitive task performance (2007–2010). **Interestingly, higher mean oxygen saturation (SaO_2) (less hypoxemia) was independently associated with worse TMT-A performance 8–10 years later. Furthermore, a higher percentage of N1 sleep was independently associated with better TMT-A performance 8–10 years later**. These unexpected, counterintuitive associations contrast with the findings in **Study 1 (CHAPTER 3)** of a significant independent cross-sectional association between a higher percentage of N1 sleep and worse TMT-A performance at baseline. Furthermore, the longitudinal findings from **Study 2** (**CHAPTER 4)** contrast with the cross-sectional findings as **Study 1 (CHAPTER 3)** did not report any independent cross-sectional associations between OSA parameters (obstructive breathing episodes, intermittent nocturnal hypoxemia, and mean SaO_2) and cognitive function. The findings in **Study 2 (CHAPTER 4)** also contradict previous clinical and community-based cohort studies reporting longitudinal associations of OSA (AHI ≥15/h) with future cognitive decline (incident MCI and AD) in older community-dwelling participants from the Alzheimer's Disease Neuroimaging Initiative Study and Study of Osteoporotic Fractures (27, 30) and longitudinal associations between a lower percentage of REM sleep and an increased risk of developing AD and dementia. In contrast, N1 sleep was not associated with the risk of cognitive function decline in the community-based Framingham Heart Study (29).

9.9 Possible explanations for the significant longitudinal associations reported in Study 2 (CHAPTER 4)

In **Study 2 (CHAPTER 4)**, a sensitivity analysis was performed to examine cross-sectional associations between the percentage of N1 sleep and mean SaO_2 and cognitive function among men who volunteered and participated in the follow-up PSG and cognitive examinations (n=157) and men who were unwilling or unable to participate (n=276). This sensitivity analysis was performed to attempt to resolve the conflicting significant cross-sectional and longitudinal associations. This sensitivity analysis revealed that the percentage of N1 sleep and mean SaO_2 at baseline were not cross-sectionally associated with baseline TMT-A performance regardless of follow-up examination participation status. A possible factor influencing the unexpected, counterintuitive longitudinal N1 association could be OSA treatment status between the baseline and follow-up periods. Some evidence suggests that CPAP treatment in individuals with lighter, more fragmented sleep or more arousals and lower oxygen saturation at baseline may perform better compared to untreated individuals (361). Indeed, the results showed that men who self-indicated that they were treated with CPAP >4 hours/night, mandibular advancement splint, or pharyngeal surgery recorded significantly better TMT-A performance (faster completion times) 8–10 years after baseline PSG compared to untreated men.

Several additional potential explanations exist for the longitudinal N1 sleep and mean SaO_2 associations with TMT-A performance at follow-up. The significantly smaller sample of men who completed follow-up assessments may represent self-selection bias and different participant characteristics in men willing versus unwilling to undergo follow-up examinations. For example, volunteer responder bias was observed in men who volunteered to undergo a second follow-up examination as more were partnered/married compared to men who were unable or unwilling to participate. Previous community-based cohort literature demonstrates a higher prevalence and risk of cognitive impairment among participants who reported being single compared to married (362-364), supporting that significant between-group differences in marital status at baseline could have influenced the observed associations. Another potential explanation for the N1 sleep and mean SaO_2 findings is greater disrupted and fragmented sleep during the baseline sleep examination in

men who did not participate in the follow-up examination, potentially lengthening their N1 sleep, lowering their mean SaO_2 levels, and possibly contributing to worse cognitive function. If these men experienced greater disrupted and fragmented sleep, this might have discouraged them from volunteering to undergo a second PSG. Furthermore, men who did not participate in the follow-up examinations could have been experiencing increased amyloid-beta protein deposition and accumulation, which has been reported to adversely affect sleep and arterial SaO_2, potentially leading to deterioration in cognitive function (426).

Men who volunteered to complete the follow-up assessments (n=157) may represent a relatively healthier population (survivor effect) compared to men who did not volunteer to participate (n=243) or passed away (n=33), who may have experienced more significant deterioration in sleep architecture, physical health, and cognitive function. Mortality may have strongly influenced the longitudinal associations as men who passed away showed a significantly higher prevalence of cardio-metabolic health conditions, including cardiovascular disease and diabetes mellitus hypertension at baseline compared to men who did not pass away. These men also recorded a higher percentage of N1 sleep at baseline, suggesting that adverse health conditions may have contributed to more disrupted and fragmented sleep, cognitive dysfunction, and poorer physical health. One or a combination of these factors may have resulted in many men choosing not to participate or also passing away, resulting in low participant numbers at follow-up and potentially influencing the associations observed between OSA and sleep macroarchitecture at baseline and cognitive function at follow-up.

9.10 Additional physiological sleep measures and OSA-specific hypoxic burden should be investigated in future studies

Analyses in **Study 2** (**CHAPTER 4)** relied on traditional clinical PSG parameters, which are unable to capture the magnitude of physiological changes associated with arousal events, including microarousal events and apneas versus hypopneas and their durations. Moreover, flow limitation and different OSA phenotypes, including arousal thresholds and non-routine hypoxemia measures such as total oxygen desaturation specific to OSA or the total area under the respiratory event-related

desaturation curve for individual apneas and hypopneas (OSA-specific hypoxic burden) (335) were not captured.

Hypoxic burden has been reported to predict multiple health outcomes, including cardiovascular disease-related mortality (335) and incident heart failure (365) in the prospective community-based MrOS and Sleep Heart Health studies and all-cause mortality in the French Pays de la Loire Sleep Cohort (366). Very recent work by Azarbarzin and colleagues investigated the separate influence of desaturation and arousal components of the AHI on associations with OSA-related comorbidities (hypertension, diabetes, and excessive daytime sleepiness) and clinical outcomes (incident CVD and car crash) in participants from the MESA, MrOS, and SHHS cohorts. Findings demonstrated that AHI events with arousals but without desaturation were not associated with any OSA-related comorbidities or clinical outcomes. In contrast, AHI events with ≥4% oxygen desaturations and no arousals demonstrated the strongest associations with hypertension, diabetes, sleepiness, and CVD (Ali Azarbarzin, "personal communication," September 2, 2022). Accordingly, this emerging data suggests that arousals do not add predictive value for a variety of cardio-metabolic conditions and subjective daytime sleepiness, with a strongly emerging consensus recognising intermittent hypoxemia as a major risk factor contributing to the pathogenesis of OSA-related comorbidities, cardio-metabolic conditions, metabolic dysfunction, and cognitive function decline (427, 428).

These very recent findings suggest that very frequent cortical arousals may, over time, reduce the level of hypoxia and promote less severe hypoxic events and arousal intensity. Moreover, previous literature suggests that frequent cortical arousals typically result in a higher percentage of N1 sleep compared to other sleep stages (357). Consequently, the findings from Azarbarzin and colleagues may, in part, explain the contradicting associations of a higher percentage of N1 sleep and lower mean SaO_2 with better TMT-A performance at follow-up. However, this is speculative as previous studies have not investigated the predictive value of arousals for cognitive function. In the MAILES cohort, arousals at baseline were not associated with TMT-A performance at follow-up (Pearson's r=0.00, p=1.00). Consequently, it is challenging to determine the underlying physiological mechanisms driving the longitudinal associations presented in this thesis. Assessment of hypoxic burden requires utilisation of an emerging algorithm, which was unavailable in the MAILES cohort.

9.11 Future research suggestions building on Study 2 (CHAPTER 4)

Given that many of the associations between OSA and sleep macroarchitecture with future TMT performance were non-significant, future longitudinal community-based cohort studies should assess a broader range of cognitive function domains. Specifically, it would be useful to examine OSA and sleep macroarchitecture parameters at baseline in relation to performance on episodic memory and learning (FOME performance) and information processing speed (inspection time task performance) at follow-up. In this thesis it was not possible to perform these analyses as FAMAS participants had only completed the FOME test and inspection time task at baseline and not at follow-up.

Future prospective studies should also carefully consider the above-mentioned factors and examine performance across more comprehensive cognitive function domains to generate consistent robust data on the longitudinal associations between OSA and sleep macroarchitecture and future cognitive function. Importantly, examining sleep EEG microarchitecture or brain neuronal oscillatory activity through quantitative EEG (qEEG) power spectral analysis (PSA) of EEG waveforms by utilising the fast Fourier transform algorithm enables a more detailed fine-grained analysis of sleep EEG that may be associated with OSA parameters and reveal valuable brain-specific cognitive function markers and was the focus of subsequent experimental chapters.

9.12 Summary of findings from Study 3 (CHAPTER 5)

In **Study 3 (CHAPTER 5)** and subsequent chapters, this thesis explored associations between baseline sleep qEEG markers, OSA parameters, and cognitive function outcomes. In **Study 3 (CHAPTER 5)** of this thesis, it was hypothesised that more severe OSA would be independently associated with spindle metrics. The results showed that **more frequent obstructive breathing episodes (AHI) and greater intermittent hypoxemia (TST90) were independently associated with N2 and N3 sleep spindle abnormalities (decreased densities but increased frequency and amplitude).** Therefore, this community-based cohort study is the first to determine independent cross-sectional associations between spindle abnormalities, obstructive breathing events, and arterial oxygen saturation levels. These findings expand preliminary evidence from small clinical studies supporting associations between OSA parameters and spindle metrics (370, 371). The novel results of **Study 3**

(CHAPTER 5) support differential associations between OSA and hypoxemia measures and sleep spindle metrics assessed during N2 and N3 sleep.

9.13 Future research suggestions building on Study 3 (CHAPTER 5)

Preliminary evidence from small clinical studies (368, 369, 383) suggests that CPAP treatment partially normalises spindle abnormalities commonly observed in patients with OSA, including reduced spindle densities, average frequency, and occurrence (46-48). In these small clinical studies, CPAP treatment increased spindle density (368, 383), overall spindle occurrence (369), and spindle amplitude (383). Nonetheless, additional studies remain warranted to assess whether OSA-related spindle abnormalities are independently associated with cross-sectional and prospective cognitive impairment and whether OSA treatment effectively improves OSA-related spindle abnormalities and cognitive function. Future studies should also investigate sleep spindles during N3 sleep separately as they may represent discrete functional associations with OSA-related sleep disruption.

9.14 Associations between sleep spindle metrics and cognitive function outcomes and the potential moderating influence of OSA

Although there has been some previous research, the majority of studies that examined associations between sleep spindle metrics and cognitive function outcomes in healthy and sleep-disordered populations (49-51, 281, 283, 284) were small experimental laboratory studies. These studies identified associations between higher spindle occurrence, average frequency, and overall and fast spindle density and better memory performance (49, 50, 279), attention, vigilance, and verbal fluency (51). Furthermore, a recent community-based cohort study by Djonlagic et al. (45) examined associations between sleep spindle metrics and cognitive function outcomes in 3,819 participants harmonised from two independent community-based cohort studies, the Multi-Ethnic Study of Atherosclerosis (MESA) Study and MrOS Study, reporting an association of higher fast spindle density with better executive function (TMT-B performance). However, the potential moderating influence of OSA in associations between sleep spindle metrics and cognitive function outcomes remains undetermined.

9.15 Summary of findings from Study 4 (CHAPTER 6)

In **Study 4 (CHAPTER 6)** of this thesis, this knowledge gap was addressed by investigating independent cross-sectional associations between sleep spindle metrics and cognitive function outcomes, with interaction analysis determining the moderating influence of OSA. **Associations between lower N2 sleep spindle occurrence (11–16 Hz, count) and slower visual processing speed (inspection times), and higher N3 sleep fast spindle density (13–16 Hz, number/minute) and average frequency (Hz, oscillations/second) and worse executive function (TMT-B performance) were observed.** Significant associations between N2 and N3 sleep spindle metrics and performance in distinct cognitive function domains suggest that spindles assessed during N2 and N3 sleep may represent different neurobiological phenomena in relation to cognitive function, and future studies should investigate these separately.

In interaction analyses**,** with a decrease in N2 sleep spindle frequency (slower spindles), there was an increase in TMT-A completion times (worse performance) in men with severe OSA (AHI ≥30/h). Furthermore, with an increase in N2 sleep spindle amplitude (μV), there was an increase in TMT-B completion times (worse performance) in men with mild OSA (AHI 10–19/h). Lastly, with an increase in N3 sleep spindle occurrence, there was an improvement in episodic memory and learning (higher Fuld object memory evaluation [FOME] scores) in men with mild OSA but a decline in memory performance in men with moderate OSA (AHI 20–29/h). These significant interaction effects support that OSA plays a critical moderating role in the associations between spindle metrics and cognitive function outcomes. The potential mechanism linking mild OSA with an improvement in memory performance remains uncertain. One explanation may be hypoxic preconditioning, referring to continued exposure to mild levels of OSA and hypoxia, which may lead to a compensatory response and resistance to subsequent hypoxia (429).

9.16 Future research suggestions building on Study 4 (CHAPTER 6)

Randomised controlled trials (RCTs) should investigate whether CPAP treatment can reverse spindle abnormalities and determine whether daytime performance is enhanced in participants with improved spindle measures. RCTs would extend the limited evidence from small studies suggesting that CPAP partially reverses spindle abnormalities, specifically occurrence, densities, and amplitude, in patients with OSA (368, 369, 383). Longitudinal studies are also warranted to determine if sleep spindle metrics in mid-life predict cognitive function decline in older age and can be modified by OSA treatment.

9.17 Exploring sleep quantitative EEG markers of cognitive function

It has been proposed by D'Rozario et al. (44) that NREM and REM sleep EEG spectral power determined by qEEG power spectral analysis may represent valuable brain-specific cognitive function markers. Multiple case-controlled studies have identified differences in NREM and REM sleep EEG spectral power between patients with MCI and age-matched controls (40-43). Furthermore, Djonlagic et al. (45) examined cross-sectional associations between sleep microarchitecture and cognitive function in a community-based cohort (45), reporting an association of lower NREM sleep delta power with worse TMT-B performance. However, Djonlagic et al. (45) recruited community-dwelling men and women ≥54 years from the MESA Study and community-dwelling men ≥65 years from the MrOS Study. Consequently, the study was predominantly enriched with older participants (overall sample age (54–97 years), leaving cross-sectional associations between sleep microarchitecture and cognitive function among early-to-middle-aged community-dwelling participants unclear.

9.18 Summary of findings from Study 5 (CHAPTER 7)

In **Study 5 (CHAPTER 7)** of this thesis, associations between sleep microarchitecture and cognitive function in the overall and age-stratified samples of community-dwelling men were examined. The advantage of the analysis, adding to the existing community-based cohort literature, is the relatively wide age range of participants, which allowed for age-stratification (<65 versus ≥65 years).

Associations between lower NREM relative delta power and greater REM theta and alpha relative spectral power and worse TMT-A and TMT-B performance were observed in older (≥65 years) men but not in younger (<65 years) men. These findings extend the emerging community-based cohort literature suggesting sleep microarchitecture may represent an important brain-specific cognitive dysfunction marker, particularly in older community-dwelling men. **Study 5 (CHAPTER 7)** of this thesis did not determine the potential moderation of associations between sleep microarchitecture and cognitive function by OSA severity because although it has previously been reported that OSA was significantly associated with increased EEG power and REM sleep EEG slowing in the MAILES cohort, OSA did not strongly influence qEEG power bands in overall sleep (34).

9.19 Future research suggestions building on Study 5 (CHAPTER 7)

An important research question is whether CPAP treatment normalises sleep microarchitecture abnormalities commonly observed in patients with OSA, including greater REM sleep EEG slowing (285, 287), greater fast-frequency (beta) EEG activity during NREM sleep (294), and reduced slow-frequency (delta) EEG activity during NREM sleep (44) compared to age- and gender-matched controls. Findings from small clinical studies suggest that CPAP treatment can partially these sleep microarchitecture abnormalities in patients with OSA (287, 292). Large interventional trials would offer the opportunity to determine whether CPAP is an efficacious treatment for reversing sleep microarchitecture abnormalities in patients with OSA and link this to improvements in cognitive function. Non-invasive closed-loop targeted auditory/acoustic stimulation may be another valuable intervention for SWA enhancement (422, 430) and improving cognitive function, particularly memory consolidation (431-436) and executive function (437). However, the effect of SWA enhancement on cognitive function in patients with OSA has not been examined. Accordingly, future interventional trials should investigate the effect of SWA enhancement via targeted auditory stimulation on cognitive function in patients with OSA.

9.20 Longitudinal associations between sleep microarchitecture parameters at baseline and future cognitive function outcomes

Literature investigating sleep microarchitecture predictors of cognitive function remains limited to smaller observational studies in older populations (43, 52-55). Therefore, longitudinal associations between sleep microarchitecture parameters and future cognitive dysfunction and decline remain uncertain. **In Study 6 (CHAPTER 8)** of this thesis**,** the next logical research step was addressed by investigating if sleep microarchitecture parameters described in the cross-sectional analysis chapters (relative EEG spectral power, sleep spindle metrics, and EEG slowing ratio) assessed during the baseline 2010–2011 home-based baseline PSG assessment independently predicted cognitive function after 8–10 years while controlling for baseline cognitive task performance. **Only lower REM delta and higher REM sleep alpha power were associated with worse TMT-A performance 8–10 years later in unadjusted analyses. These associations did not persist following adjustment for baseline cognitive task performance, and no significant associations were observed between NREM sleep qEEG variables at baseline and TMT performance at follow-up**.

9.21 Possible explanations for the absence of significant longitudinal associations reported in Study 6 (CHAPTER 8)

Several potential factors may help explain the findings. The community-based cohort was relatively younger compared to previous small samples, possibly meaning the degree of cognitive impairment was considerably minimal in this population despite a reasonably long follow-up period relative to previous smaller observational studies. Furthermore, the significant number of participants lost to follow-up due to death or lack of consent to follow-up assessments meant the power to detect significant associations, likely of small effect size, was reduced. Finally, the characteristics of participants who completed follow-up cognitive assessments may have been subject to self-selection bias. For example, participants who experienced greater cognitive function decline may have chosen not to participate in the follow-up sleep and cognitive assessment. Consequently, men who participated in the follow-up assessments may have been more resilient sleepers with less cognitive function decline and better overall general health with a lower prevalence of health conditions.

These factors and other uncontrollable factors, including the impact of OSA treatment modality and participant adherence, OSA patient phenotypes, and OSA-related measures, including flow limitations, apneas and hypopneas and their durations, and the degree of hypoxic burden could, in part, explain the findings. Therefore, the prognostic value of qEEG as an early brain-specific cognitive impairment marker requires further prospective investigation in studies with longer follow-up durations to capture greater cognitive function decline and more extensive cognitive tests that may be more sensitive to nocturnal hypoxemia or sleep disruption.

9.22 Limitations of experimental chapters of the thesis

Although study limitations are detailed in the respective experimental chapters, major ones are discussed below.

Cross-sectional analyses of MAILES data do not enable conclusions regarding causal inference. The significant independent cross-sectional associations highlight the importance of future causal investigations between OSA, sleep macroarchitecture, and sleep microarchitecture with cognitive function.

Traditional sleep quality measures, including sleep onset latency and sleep efficiency, depend on lights out. Due to the data collection methodology, this data was unavailable in the MAILES cohort. Consequently, potential associations between traditional sleep quality measures that rely on lights out information (sleep onset latency and sleep efficiency) and cognitive function could not be determined.

Only single-night PSG was conducted as multiple-night sleep testing in an epidemiological study is impracticable concerning time and cost. Therefore, whether night-to-night variability in OSA severity or sleep macro and microarchitecture would have influenced the reported associations remains unclear.

Although sleep spindles are believed to be a putative marker of thalamocortical network activity and important for learning capability and overnight declarative memory consolidation, the results presented in this thesis do not clarify whether there is a cause-effect relationship between sleep spindles and cognitive function, which requires investigation.

Of the original 433 FAMAS participants who underwent baseline PSG (2010–2011) and cognitive assessment (2007–2010), only 157 completed the follow-up cognitive examination (2018–2019). Self-selection bias and death (n=33 FAMAS participants) may have largely contributed to the low participant numbers at follow-up.

A limited number of cognitive domains (visual attention, processing speed, and executive function) were assessed at follow-up. Consequently, it remains uncertain whether OSA and sleep macro and sleep microarchitecture parameters are associated with future cognitive function and decline in cognitive domains that were not assessed, including visual processing speed and working memory.

The MAILES Study cohort consists exclusively of community-dwelling middle-aged and older men. Consequently, results may not be generalisable to women, which requires further investigation.

The MAILES Study cohort included middle-aged and older community-dwelling men predominantly of Australian or European descent (96%). Consequently, generalisability of the findings in this thesis to other ethnic populations remains questionable. Given the participant characteristics in the MAILES Study cohort, validation of the findings in other more diverse populations remains warranted.

It is acknowledged that it is possible that several of the significant findings reported in this thesis may be due to chance alone due to multiple physiologic parameters having been studied. However, the decision not to adjust for multiple comparisons was made on the basis of the analysis being exploratory in nature and the fact that there are several practical considerations for multiple comparisons in exploratory analyses (347). Therefore, further studies in other community-based cohorts remain warranted to confirm the findings reported in this thesis.

9.23 Broader future research directions

Future studies should investigate the potential impact of night-to-night variability on observed associations between sleep parameters and cognitive function. Lechat et al. (438) recently utilised validated novel non-invasive under-mattress sensory sleep tracker technology (Withings) in a large, global, non-randomly selected community

sample (n=67,278) to assess the impact of night-to-night variability in OSA severity on diagnostic classification, reporting that multiple-night diagnosis of OSA showed substantially better predictive value compared to single-night diagnosis. These findings underline the importance of assessing associations between OSA and sleep macro and microarchitecture parameters and cognitive function over multiple nights of sleep testing.

While sleep spindles are believed to be important for cognitive function, the analyses undertaken in this thesis do not provide the means to establish causality. Furthermore, although this thesis has demonstrated the moderating role of OSA in the association between sleep spindle metrics and cognitive function outcomes, there is only a limited body of evidence suggesting that CPAP treatment reverses spindle abnormalities (368, 369). Accordingly, RCTs investigating the effect of CPAP treatment and withdrawal on spindle abnormalities would help identify the significance of CPAP in reversing spindle abnormalities.

The MAILES Study cohort consists exclusively of male participants, and associations between OSA and sleep macro and microarchitecture parameters and cognitive function in community-dwelling women could not be investigated. Currently, limited evidence from smaller community-based and case-controlled studies supports associations between sleep-disordered breathing (27, 423), sleep microarchitecture (43), and cognitive dysfunction and decline in older women. The limited literature highlights the need for further community-based cohort studies in considerably larger samples of middle-aged and older community-dwelling women to determine if the observed associations presented in this thesis may be generalisable to the broader population of women.

Endotypic traits associated with OSA could potentially contribute to cognitive function decline. For example, respiratory control (loop gain) abnormalities, decreased muscle tone, and anatomical abnormalities could increase the degree of intermittent hypoxemia, hypoxia (tissue-related oxygen deficiency), and sleep fragmentation, leading to cognitive function decline (439). However, there do not appear to be any studies that have directly investigated potential associations between the endotypic traits of OSA and cognitive function decline, which requires investigation.

Cognitive reserve (CR), which refers to inter-individual variability in intelligence, personal and life experiences, and educational and occupational attainments and other factors that can influence maintenance of cognitive health and increase or decreased susceptibility age-related cortical changes, cognitive decline and AD pathology (440, 441) was unable to be investigated in this thesis. Low CR has been reported as a risk factor for poor cognitive function or cognitive decline among cognitively unimpaired older adults with low socio-economic status (442). Importantly, a growing literature suggests that higher CR may reduce the impact of disrupted or fragmented sleep architecture on cognitive function, especially in individuals with OSA (443) and the effect of OSA on cognitive function may vary significantly due to inter-individual differences in brain structure and functional plasticity (444). Additional community-based cohort studies remain warranted to investigate the associations between CR and cognitive dysfunction or decline.

9.24 Concluding remarks

In conclusion, this thesis supports that sleep macro and microarchitecture parameters are cross-sectionally associated with cognitive function among community-dwelling men. Specifically, lighter, more fragmented sleep is cross-sectionally associated with worse visual attention and processing speed among older (≥65 years) community-dwelling men, whereas lower relative power in slower-frequency EEG bands and higher power in faster-frequency EEG bands during NREM and REM sleep is cross-sectionally associated with worse visual attention, processing speed, and executive function among men ≥65 years. Sleep spindle metrics, including occurrence, density, frequency, and amplitude, were also cross-sectionally associated with visual processing speed, visual attention, and executive function, with OSA severity playing a significant moderating role. However, reverse causation could also be occurring as poor cognitive performance could be associated with OSA parameters and altered sleep macro and microarchitecture.

The findings in this thesis support that there is promise in examining the rich electrophysiological (quantitative EEG) data from overnight PSG. Therefore, future studies could be conducted in large clinical and community-based cohorts to better define how specific qEEG markers, including faster EEG activity during NREM sleep and EEG slowing during REM sleep, which are commonly seen in patients with OSA,

can be targeted through CPAP treatment or SWA enhancement to potentially improve daytime cognitive function in this population. Further studies of this nature would be useful to improve precision care of patients with OSA and better define heterogeneity in qEEG markers.

Importantly, cross-sectional analyses prevent conclusions regarding causal inference. The absence of longitudinal associations between baseline sleep microarchitecture and future cognitive function indicates that qEEG might have limited prognostic value as an early brain-specific marker. Therefore, the clinical and public health importance of the results presented in this thesis should be interpreted with caution, and additional large prospective studies with longer follow-up durations between the baseline PSG and future cognitive assessments in community-dwelling men and women remain warranted to further clarify the prognostic value of qEEG as a brain-specific cognitive function marker.

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