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.