Factors Associated with Cognitive Impairment in Obstructive Sleep Apnoea

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

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Declaration

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any other academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research program; any editorial work, paid or unpaid, carried out by a third party is acknowledged; and, ethics procedures and guidelines have been followed.

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List of Abbreviations

AASM	American Academy of Sleep Medicine
ABPM	Ambulatory blood pressure monitor
AHI	Apnoea–Hypopnea Index
AM	Austin maze
AMI	Autobiographical Memory Interview
ANOVA	Analysis of variance
ANS	Autonomic nervous system
AUC	Area under the curve
BMI	Body Mass Index
BP	Blood pressure
BQ	Berlin questionnaire
CPAP	Continuous positive airway pressure
DASS	Depression Anxiety Stress Scale
DBP	Diastolic blood pressure
ECG	Electrocardiography
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
EMG	Electromyography
EOG	Electrooculography
ESS	Epworth Sleepiness Scale
fMRI	Functional magnetic resonance imaging
FDR	False discovery rate
HF	High frequency

HIF1α	Hypoxia-inducible factor-1α
HPA	Hypothalamic-pituitary-adrenal
HRV	Heart rate variability
IGT	Impaired glucose tolerance
IH	Intermittent hypoxia
LF	Low frequency
MRI	Magnetic resonance imaging
MSLT	Multiple sleep latency test
NADPH	Nicotinamide adenine dinucleotide phosphate
NF-kB	Nuclear factor-kB
NF2L2	Nuclear factor erythroid 2-like 2
NLR	Negative likelihood ratio
NO	Nitric oxide
NOS	Nitric oxide synthase
NPV	Negative predictive value
NREM	Non-rapid eye movement
ODI	Oxygen Desaturation Index
OHS	Obesity hypoventilation syndrome
OSA	Obstructive sleep apnoea
OSAHS	Obstructive sleep apnoea–hypopnea syndrome
POMS	Profile of mood states
PLR	Positive likelihood ratio
PNS	Parasympathetic nervous system
PPG	Photoplethysmography
PPV	Positive predictive value

PSG	Polysomnography
PTT	Pulse transit time
PVT	Psychomotor vigilance test
PWA	Pulse wave amplitude
RDI	Respiratory Disturbance Index
REM	Rapid eye movement
RERA	Respiratory effort-related arousal
RG	Retroglossal region
ROC	Receiver operating characteristic
ROS	Reactive oxygen species
RP	Retropalatal
RT	Reaction time
SBP	Systolic blood pressure
SBQ	STOP-Bang questionnaire
SD	Standard deviation
SDB	Sleep-disordered breathing
SNS	Sympathetic nervous system
SOD	Superoxide dismutase
SPSS	Statistical Package for the Social Sciences
SQ	STOP questionnaire
SWS	Slow-wave sleep
T2D	Type 2 diabetes
US	United States
VIF	Variance inflation factor
WASO	Wake time after sleep onset

WSQ	Wisconsin sleep questionnaire

Preface

This thesis includes four interrelated research projects (Chapters 2–5), which have been prepared as draft publications (each with an abstract, introduction, methods, results and discussion). This structure has necessitated a degree of duplication in the methods sections of these chapters. The candidate formulated and wrote all thesis chapters, obtained ethics approval, performed the entire study, analysed all data and interpreted the results for chapters 2-5. Chapter 3 has been published in *Sleep*, chapter 4 has been published in *Scientific Reports Journal – Nature*, and Chapter 5 is under review in *Hypertension Journal*, for Chapter 2 it is prepared for the submission (See appendix 2). Chapter 1 provides an introduction and literature review for the research projects, while Chapter 6 provides a general discussion of the main outcomes and findings of the research projects.

Abstract

Obstructive sleep apnoea (OSA) is a sleep disorder characterised by repetitive episodes of airway obstruction, which lead to transient hypoxia and sleep fragmentation. Persons with OSA can suffer from excessive daytime sleepiness (EDS) and mood swings and are twice as likely as healthy peers to have difficulty concentrating, performing repetitive tasks and acquiring new knowledge. Sleep fragmentation and intermittent hypoxia (IH) are only able to account for 30–40% of the cognitive impairment, so additional factors must be involved. One possibility is depressive symptoms, as these are common in OSA. People with depressive symptoms but no other comorbid condition exhibit cognitive deficits that can include memory loss, ambiguity in decision making, a decline in judgment and problem-solving skills and an inability to pay attention during routine activities. Another potential factor is increased nocturnal activity of the sympathetic nervous system (SNS), which can lead to changes in heartbeat and spikes in nocturnal blood pressure (BP). In the general population, high BP in midlife has been strongly linked to impairments in visuospatial ability, motor speed and attention. Since little is known about the contributions of depressive symptoms and SNS over-activation to the cognitive impairments in OSA, the present study has examined whether these factors are associated with cognitive impairments in OSA patients, after controlling for the confounding effects of age, smoking, IH and sleep fragmentation.

The first aim of this study was to characterise the participants. They were drawn from patients who had been referred to a Saudi Arabian sleep laboratory to undergo a sleep study using polysomnography (PSG). It was hypothesised that participants should show no differences in OSA characteristics or risk factors compared with participants in previous studies in Western countries. Of the 100 patients who presented consecutively to the Sleep Medicine and Research Centre, 90 met the study inclusion criteria. This study measured OSA via overnight PSG and

the participants were asked to complete the Arabic version of the *STOP-Bang questionnaire* (SBQ). Of the participants, 62 (69%) were male; mean participant age was 42.0 ± 12.7 years; and mean Body Mass Index (BMI) was 33.4 ± 9.4 kg/m^2. PSG showed that 14 of the 90 participants did not have OSA, 30 had mild OSA, 23 had moderate OSA and 23 had severe OSA. Eight of the 90 participants did not answer the SBQ completely; therefore, the SBQ data are from 82 participants. Multiple regression analysis revealed that age and BMI ($p < .05$) but not smoking status ($p > .05$) were significant predictors of OSA severity. The prevalence of depressive symptoms and EDS was 74% and 50%, respectively. In addition, 60% of participants with OSA had impaired glucose tolerance (IGT) or type 2 diabetes (T2D). These proportions are similar to reports from other countries, making it likely that the research findings from this Saudi cohort have global relevance.

Data from this cohort demonstrated a significant correlation ($p < .05$) between the SBQ score and the Apnoea–Hypopnea Index (AHI), confirming the utility of the SBQ as a predictor of OSA severity. Receiver operating characteristic curve analysis revealed that a total SBQ score >2 predicted an AHI > 5 with high sensitivity (90%) but low specificity (54%), and an AHI of >15 with a sensitivity of 98% and a specificity of 32%. The loud snoring item provided superior prediction of mild OSA (AHI >5), while the observed apnoeas item predicted an AHI >15 with a sensitivity of 87% and specificity of 76%.

The second aim was to determine the extent to which IH, sleep fragmentation and depression are independently associated with cognitive impairment. Hypoxia was measured as time spent with a blood oxygen concentration of <90% during sleep, and sleep fragmentation was measured using the Arousal Index. Depressive symptoms were determined by the depression subscale of the *Depression–Anxiety Stress Scale* (DASS-21). Cognitive function was evaluated using the 10-trial Austin maze (visuospatial ability), the 10-minute psychomotor vigilance test

(sustained attention and reaction time [RT]) and the Autobiographical Memory Interview (semantic and episodic memories). IH was independently associated with impairments in sustained attention and RT ($p < .05$). Sleep fragmentation was independently related to impairments in visuospatial ability ($p < .05$). Depressive symptoms were independently associated with impairments in the domains of sustained attention, RT, visuospatial ability and semantic and episodic memories ($p < .05$).

The third aim was to investigate the contributions of SNS over-activity to cognitive impairment. It was hypothesised that SNS over-activity might be a significant contributor to cognitive impairment in OSA patients. SNS activity was measured using heart rate variability (HRV; high-to-low frequency ratio), pulse wave amplitude (PWA) drops and stress response biomarkers (first-morning sample of urinary and blood cortisol, and blood glucose). PWA, HRV and morning blood glucose ($p < .005$), but not morning urine and blood cortisol, were associated with OSA severity. Moreover, the PWA index, PWA time duration and HRV ratio were associated with impaired visuospatial ability ($p < .005$). However, impairments in sustained attention, RT and autobiographical memory were not significantly associated with any of the SNS indices.

The fourth aim was to investigate whether nocturnal peaks in BP are associated with cognitive dysfunction in patients with clinically verified OSA. It was hypothesised that as high BP is known to damage the cerebral cortex through micro-strokes, peaks of nocturnal BP might be associated with impaired cognitive function. Nocturnal peaks in BP were measured continuously (beat-to-beat) using the pulse transit time method. Results showed that nocturnal peaks in systolic blood pressure (SBP) were associated with OSA severity ($p < .005$), whereas diastolic BP peaks were not. Moreover, patients with the most severe OSA had the largest differences between resting and nocturnal SBP ($p < .005$). Additionally, peaks in nocturnal

SBP and the mean value of the differences between resting and nocturnal SBP were associated with impaired visuospatial ability ($p < .005$). Impairments in sustained attention and RT, and autobiographical memory were not significantly associated with nocturnal BP.

This study has shown that IH, sleep fragmentation and depressive symptoms independently contribute to cognitive impairment in OSA. Further, PWA, HRV and nocturnal peaks in SBP correlate with impairments in visuospatial function. The present study has extended understanding of the factors that contribute to cognitive impairment in OSA by revealing that two additional factors, depressive symptoms and SNS over-activation, appear to account for some of the cognitive impairment, independently of age, smoking, nocturnal hypoxia and arousals from sleep. These novel findings have implications for both the measurement of OSA in overnight sleep studies and for the treatment of cognitive impairment in patients with OSA.

Chapter 1: Literature Review

1.1 Obstructive Sleep Apnoea

Obstructive sleep apnoea (OSA) is the most frequently diagnosed sleep-related breathing disorder (Epstein et al., 2009). OSA is defined by repeated episodes of cessation of breathing during sleep, with episodes lasting for 10 seconds or more (Memon & Manganaro, 2020). Breathing cessation alternates with regular breathing and can involve a partial or complete obstruction of the upper airway (hypopnoea or apnoea, respectively) (Bradley & Phillipson, 1985; Shochat & Pillar, 2003). Typical symptoms of OSA include loud snoring, gasping for air upon waking, dry mouth, headaches in the morning, insomnia (difficulty staying asleep), waking in the night while choking, excessive daytime sleepiness (EDS), unrefreshing sleep and fatigue (American Academy of Sleep Medicine [AASM], 2014; Kapur et al., 2017).

The three key predictive risk factors for OSA are being male, being overweight and being middle-aged. Estimates of the prevalence of OSA have increased over time (Franklin & Lindberg, 2015) in parallel with rising obesity rates (Peppard et al., 2013). In developed societies, up to 20% of middle-aged males and approximately 17% of middle-aged females may experience OSA (Gislason & Sunnergren, 2014). The rates of OSA are even higher in old age. A systematic review by Franklin and Lindberg (2015) suggested a mean worldwide OSA prevalence of 22% for males (range 9–37%) and 17% for females (range 4–50%). A narrative literature review by Benjafield et al. (2019) estimated that globally, 936 million people aged 30–69 years have mild-to-severe OSA while 425 million in this age range have moderate-to-severe OSA (Benjafield et al., 2019). While perhaps surprising that almost a billion people worldwide may suffer from OSA, the true number might be even higher due to the rapidly increasing rates of obesity in most countries. The wide variability and uncertainty in estimates of the prevalence of OSA result from variation among countries in how it is defined, different

diagnostic standards, incomplete clinical records and variable levels of clinical awareness of OSA (Arnardottir, Bjornsdottir, Olafsdottir, Benediktsdottir, & Gislason et al., 2016; Greenber, Lakticova, & Scharf, 2017; Ravesloot, Maanen, Hilgevoord, Wagensveld, & Vries, 2012). These factors are discussed in more detail in subsequent sections.

The first reported observation of breathing failure in sleep was made by Silas Weir Mitchell in the 1850s (P. Lavie, 2008). However, it was not until 1918 that the Canadian physician, Sir William Osler, used the term 'Pickwickian syndrome' (after a character in a 1837 novel by Charles Dickens) to describe patients who presented with a combination of obesity and EDS (Bickelmann, Burwell, Robin, & Whaley, 1956; P. Lavie, 2008, p. 27). Early research into Pickwickian syndrome concentrated on obesity rather than disordered breathing during sleep (Hansford, 2011, p. 1). Pickwickian syndrome was eventually delineated from OSA because it is primarily characterised by 'obesity hypoventilation' and, was later termed 'obesity hypoventilation syndrome' (OHS) (Olson & Zwillich, 2005, p. 948). More recent research has concluded that OHS and OSA are very similar in clinical presentation as they share pathogenesis and pathophysiology, making it difficult to differentiate between the two (Liu, Chen, & Yu, 2017). However, patients with OHS demonstrate daytime hypercapnia (abnormally high concentrations of carbon dioxide in the blood) and nocturnal oxygen desaturation without airflow obstruction (Sateia, 2014).

In the mid-1960s, sleep apnoea was first identified through the use of an electroencephalogram (EEG) in a pioneering study that explored the neurophysiology of abnormal night-time sleep in patients with OHS (Jung & Kuhlo, 1965). As a result of this study, polysomnography (PSG) became the standard tool for diagnosing sleep apnoea (Medical Advisory Secretariat, 2006), and by the late 1970s, the first cases of OSA had been clinically diagnosed (Guilleminault, Tilkian, & Dement, 1976; P. Lavie, 2008). Today, an OSA diagnosis involves the use of

screening measures (e.g. the *STOP-Bang questionnaire* [SBQ]) followed by PSG (Kapur et al., 2017). The following section describes the consequences of OSA, the main tools used to diagnose and assess its severity, current treatments, risk factors, physiological and neurocognitive correlates, main complaints of sufferers and potential bases of the cognitive dysfunction seen in OSA.

1.2 Physiological Consequences of Obstructive Sleep Apnoea

Upper airway obstruction during sleep results in intermittent breathing, triggering intermittent hypoxia (IH), which is a deficiency in blood oxygen levels (desaturation followed by resaturation) (Kyotani, Takasawa, & Yoshizumi, 2019). OSA is also accompanied by intermittent hypercapnia, which is an abnormal elevation of carbon dioxide levels in the blood (Sforza & Roche, 2016). In OSA, the muscles of the tongue and throat relax during sleep and intermittently block the airway, as illustrated in Figure 1.1 (Mayo Clinic, 2020). Obstructive events (apnoeas/hypopneas) can be detected with pulse oximetry that measures fluctuations in arterial oxygen saturation (Terrill, 2020). A respiratory event in an adult is classified as an apnoea when there has been ≥90% reduction of airflow relative to baseline lasting ≥10 seconds; a hypopnea corresponds to a 30–90% reduction in airflow relative to baseline for ≥10 seconds, accompanied by a blood oxygen desaturation of >3% and/or an arousal lasting ≥10 seconds (Berry, Budhiraja, et al., 2012).

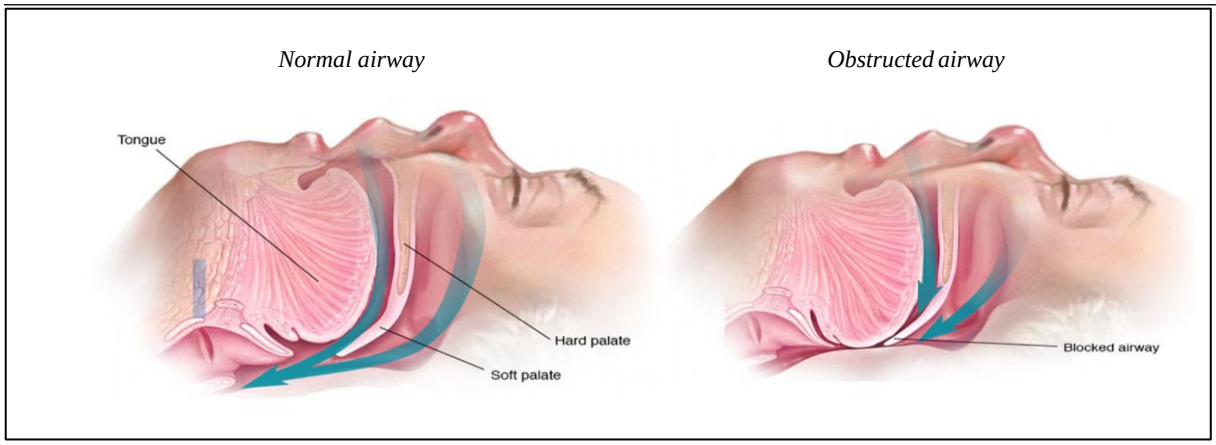

Figure 1.1 Normal *v.* obstructed airway during sleep.In the normal airway, blue shading indicates the route of airflow to the lungs, whereas in the obstructed airway the blue shading shows how the airflow becomes blocked by the tongue during an apnoea (Mayo Clinic, 2020).

In terms of pathophysiology, anatomical and neuromuscular factors modulate upper airway obstruction, and affect diagnosis rates for OSA (Pham & Schwartz, 2015). As illustrated in Figure 1.2A, patients with OSA have restricted upper airways compared with those without OSA, even during wakefulness (Dempsey, Veasey, Morgan, & O'Donnell, 2010). OSA is associated with structural and anatomical alterations of the airway, including tonsillar hypertrophy, retrognathia and malformations in craniofacial structures (Cakirer et al., 2001; Lyberg, Krogstad, & Djupesland, 1989; Moser & Rajagopal, 1987; Watanabe, Isono, Tanaka, Tanzawa, & Nishino, 2002). OSA is more common in people with a large neck circumference (Ibrahim et al., 2007; Martinez-Rivera, Abad, Fiz, Rios, & Morera, 2008) and an upper airway that is constricted by nasal abnormalities or enlargements of the tonsils, tongue or uvula (Schellenberg, Maislin, & Schwab, 2000). One of the main anatomical changes during the rapid eye movement (REM) stage of sleep is the relaxation of skeletal muscles, including the genioglossus of the tongue (Dempsey et al., 2010). In OSA, the relaxed genioglossus slides backwards to occlude the pharynx (Figure 1.2B) (White, 2006). Therefore, episodes of non-breathing in OSA are not caused by a lack of inspiratory effort; on the contrary, the patient struggles to breathe against their occluded pharynx until they can suck in air, but this effort can

arouse them from sleep and place stress on the cardiovascular system through stimulation of the sympathetic nervous system (Tietjens et al., 2019).

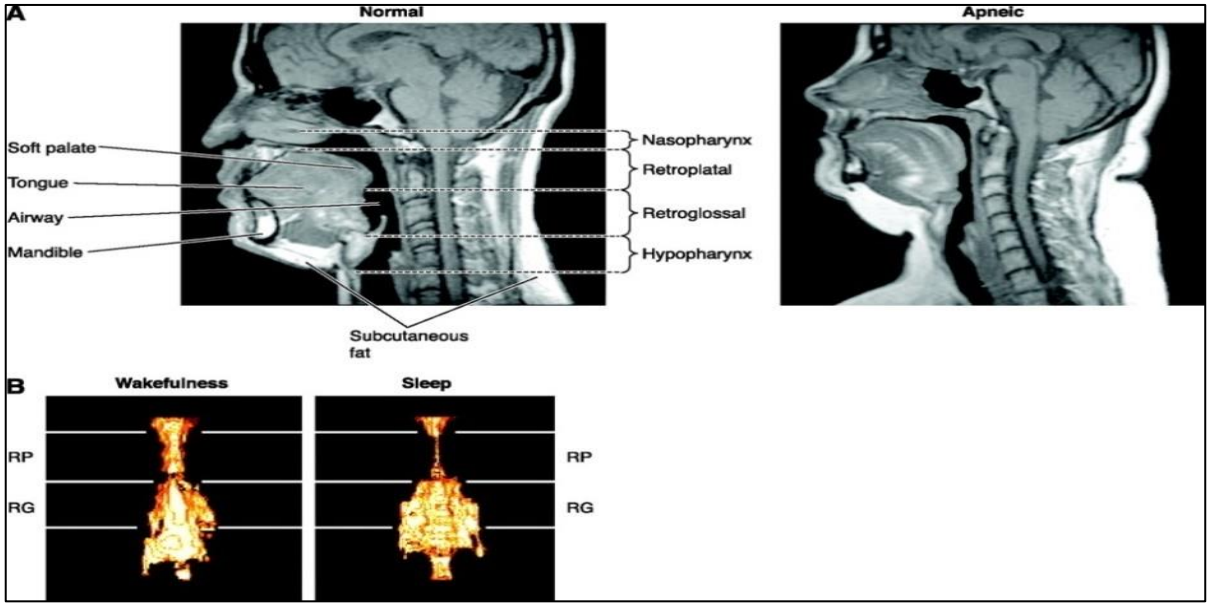

Figure 1.2 A: Magnetic resonance images showing the restriction of the airway by the tongue in an awake apnoeic person (right panel), compared with a person without OSA (left panel). B: 3-D reconstruction of the upper airway during wakefulness and sleep (Dempsey et al., 2010). RP: retropalatal; RG: retroglossal region.

1.2.1 Hypoxia and Oxidative Stress

Hypoxia can be caused by the interrupted breathing associated with OSA. According to (Samuel & Franklin, 2008), it is essential to differentiate between hypoxia, which refers to low oxygen in tissues, and hypoxemia, which is a consequence of low partial oxygen pressure in arterial blood. Hypoxemia may exist without hypoxia if patients compensate for low oxygen in tissues by increasing their cardiac output, which increases oxygen delivery to tissues. Ordinarily, hypoxemia involves IH and may be involved in OSA-related comorbidities, such as discontinuous blood gas abnormalities, and an increased risk of hypertension, cardiovascular complications and cerebrovascular diseases (Dewan, Nieto, & Somers, 2015).

The effects of repeated IH at the molecular, cellular and physiological levels have been well documented (Nam, Haque, Shin, Park, & Rhee, 2020) and are suggested to result in a pro-inflammatory response, endothelial dysfunction, atherosclerosis, an increase in cardiovascular and cerebrovascular morbidity, cognitive decline and neurocognitive disease (Lévy et al., 2015; Ridgway & McFarland, 2006). In animal models, IH results in cell and tissue injury as a result of the activation of reactive oxygen species (ROS) and pro-inflammatory pathways within the body (L. Lavie, 2019). Ultimately, the formation of ROS and induction of pro-inflammatory pathways induces inflammation, endothelial dysfunction, activation of the immune system (innate and adaptive) and transcriptional reprogramming, which contributes to a vast array of morbidities, especially cardiovascular events, and leads to increased mortality (Eltzschig & Eckle, 2011; L. Lavie, 2019).

IH creates oxidative stress by inducing mitochondrial dysfunction and increasing the activities of nicotinamide adenine dinucleotide phosphate oxidase and xanthine oxidase while promoting the uncoupling of nitric oxide synthase (NOS). In an oxidative state, superoxide and nitric oxide (NO) accumulate if they are not rapidly cleared, and they react with neighbouring molecules to create ROS such as hydroxyl, hypochlorite and peroxynitrite. These ROS are highly reactive and can damage major organs such as the heart, brain, eyes and kidneys (Rogier van der Velde, Meijers, & de Boer, 2015; J. Zhang & Veasey, 2012).

Interaction between NO and ROS further perpetuates oxidative stress while limiting the bioavailability of NO for other processes in the body (Lévy et al., 2015). The low-grade inflammation caused by the oxidative stress leads to chronic activation of the sympathetic nervous system (SNS), thereby increasing angiotensin II and endothelin I levels, and contributing to the development of systemic hypertension (Oyarce & Iturriaga, 2018). ROS also upregulate the production of redox-sensitive transcription factors such as nuclear factor-

kB (NF-kB), hypoxia-inducible factor-1α (HIF1α) and nuclear factor erythroid 2-like 2 (NF2L2) (Lévy et al., 2015). Both HIFIα and NF2L2 are suggested to provide some protection against ROS damage, whereas NF-kB is suggested to increase the inflammatory response. ROS also play a key role in comorbidities such as obesity, hyperlipidaemia and diabetes mellitus. Therefore, these conditions are exacerbated by the oxidative stress characteristic of OSA (Lévy et al., 2015).

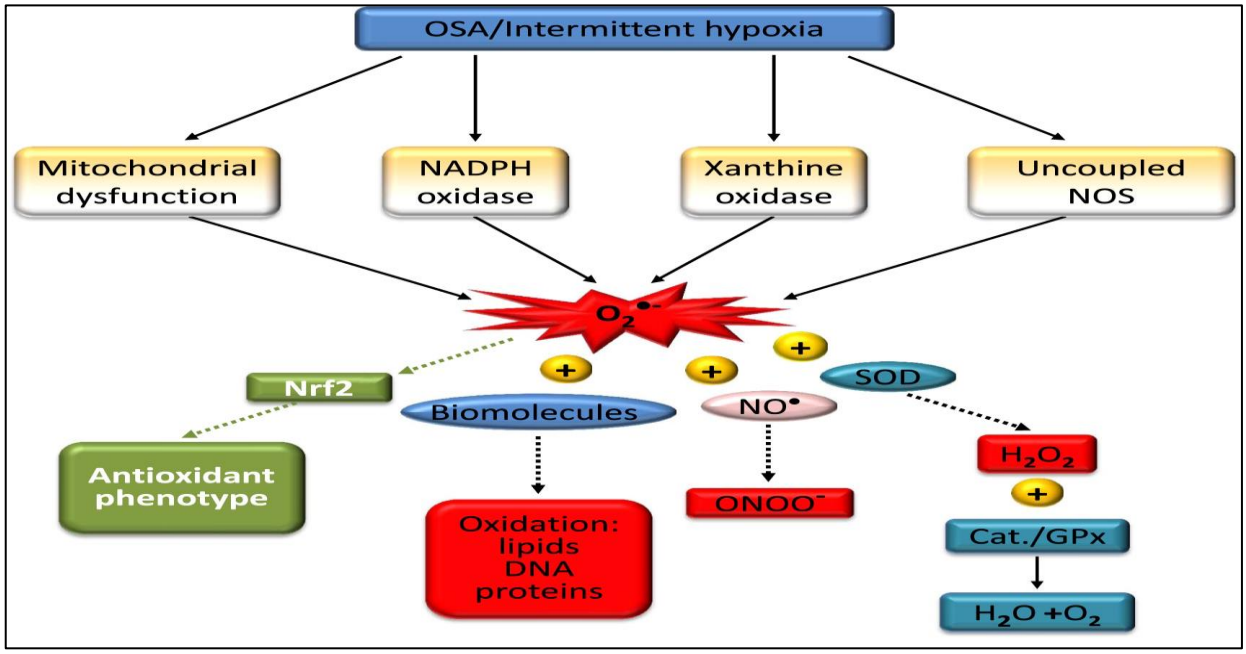

Figure 1.3. Schematic diagram summarising the major biochemical pathways that lead to the production of free radicals and oxidative stress following hypoxic episodes (Lavie, 2015). OSA: Obstructive sleep apnoea; NADPH: nicotinamide adenine dinucleotide phosphate; NOS: nitric oxide synthase; O2.: superoxide anion; SOD: superoxide dismutase; NO: nitric oxide; $ONOO^-$: peroxynitrite; H_2O_2: hydrogen peroxide; Nrf2: nuclear factor (erythroid-derived 2-like 2); Cat.: catalase; GPx: glutathione peroxidase; DNA: deoxyribonucleic acid.

1.2.2 Sleep Fragmentation

Another consequence of OSA is sleep fragmentation, which can be broadly defined as the occurrence of numerous brief interruptive arousals during a sleep cycle following termination of an apnoea or hypopnea (Noda et al., 2019). It is important to understand that sleep has two distinct stages: REM sleep and non-rapid eye movement (NREM) sleep. REM sleep is

characterised by quick simultaneous ('saccadic') eye movements, high levels of cortical activity, low muscle tone and a propensity for vivid, emotionally charged narrative dreams (Dempsey et al., 2010). NREM sleep is known for its dreamless sleep stages and jerky eye movements (Hong et al., 2018). Brain waves consist of different dominant EEG frequencies "(Delta: up to 4 Hz, Theta: 4-8 Hz, Alpha: 8 -15 Hz, Beta: 15-32 Hz, and Gamma: ≥ 32 Hz), depending on the NREM sleep stages and REM sleep stage.

According to the sleep scoring rules established by the AASM (Berry, Brooks, et al., 2012) there are three stages of NREM sleep and one stage of REM sleep. It is important to note that earlier guidelines referred to four stages of NREM sleep (Hori et al., 2001), but the scoring system was changed in 2012. In NREM sleep 1, the dominant frequency is 4–7 Hz (theta waves), and this stage is characterised by drowsiness with slow rolling eye movements. NREM 2 sleep is deeper sleep and is characterised by the appearance of 'spindles' and 'K-complexes', which are spikes of 11–16 Hz; the eyes stop moving in this stage. In NREM sleep 3, the dominant frequency decreases to 0.5–3 Hz (delta waves). Stage 3 of NREM sleep is also known as slow-wave sleep (SWS) and is the stage when human growth hormone is released (boosting restorative biological processes), breathing and metabolic functions slow, and mentation (thinking) and muscular activity are limited. During REM sleep all skeletal muscles are paralysed (atonic), except for the eye muscles and the muscles involved in breathing. In this stage the EEG pattern resembles the frequency ranges seen during wakefulness. Atonia of the tongue and throat muscles in REM sleep increases the probability of apnoeic events occurring during this stage (Carley & Farabi, 2016).

In a given sleep period, the stages alternate cyclically, progressing through NREM sleep stages 1–3 and then into REM sleep (Dijk, 2009). A typical overnight sleep consists of several sleep cycles, where the initial sleep cycle has a duration of 70–100 minutes and later cycles last 90–

120 minutes (Carskadon, Dement, Kryger, Roth, & Roehrs, 2005). Typical sleep architecture encompasses the following: 2–5% of the total sleep time is spent in NREM sleep stage 1, 45–55% in NREM sleep 2, 10–20% in NREM sleep 3, and 20–25% in REM sleep (Carskadon & Dement, 2005). However, in OSA, the duration of the sleep stages noticeably increases for NREM sleep 1 and 2 and decreases for NREM sleep 3 and REM sleep, as a result of sleep fragmentation (Basunia et al., 2016).

Patients whose sleep is regularly disrupted suffer numerous health consequences. Sleep fragmentation induces a stress response that is characterised by an increase in sympathetic nervous system (SNS) activity (Ekstedt, Akerstedt, & Söderström, 2004; Meerlo, Sgoifo, & Suchecki, 2008; Tiemeier, Pelzer, Jönck, Möller, & Rao, 2002), which causes transient hemodynamic, vasoconstrictive and prothrombotic processes (Irwin, Thompson, Miller, Gillin, & Ziegler, 1999). There is strong evidence for a link between the short sleep duration associated with sleep fragmentation, and cardiovascular disease (Nagai, Hoshide, & Kario, 2010). Moreover, stress hormones induced by sleep fragmentation may directly affect functionality during wakefulness, including impaired cognition and mood (Medic, Wille, & Hemels, 2017).

Sleep fragmentation can be measured by an Arousal Index that is calculated by dividing the total number of arousals by the total hours of sleep (Younes, 2017) and/or wake time after sleep onset (WASO). The WASO refers to the cumulative amount of time for which an individual stays awake after their first arousal from sleep—in other words, the amount of time the patient stays awake in the middle of the night after having initially fallen asleep and before being able to go back to sleep (Shrivastava, Jung, Saadat, Sirohi, & Crewson, 2014).

1.3 Obstructive Sleep Apnoea Diagnostic Tool—Polysomnography

PSG is the ‘gold standard’ for diagnosing OSA, but it is not feasible in all situations, such as in underdeveloped countries or smaller hospitals that lack the requisite equipment (Joosten, 2017). During sleep, PSG concurrently records multiple physiological signals, including heart rate, breathing and brain activity, all of which are used to diagnose OSA. PSG tests involve measurements of airflow, breathing patterns, blood oxygen levels and, in some cases, limb movements and snoring intensity (Bloch, 1997). The Apnoea–Hypopnoea Index (AHI) is the most common method used to determine OSA severity (Goyal & Johnson, 2017).

The AHI is based on the number of apnoea + hypopnea episodes per hour of sleep (Goyal & Johnson, 2017). As defined in Section 1.1, a hypopnoea partially obstructs the upper airway, while an apnoea is a complete obstruction (Shochat & Pillar, 2003). As illustrated in Table 1.1, minimal OSA is classified as less than five apnoeas or hypopneas per hour of sleep. Those diagnosed with mild OSA suffer five or more episodes but less than 15 per hour of sleep. Moderate OSA involves 15 or more episodes but less than 30 per hour of sleep, while those with severe OSA experience at least 30 episodes per hour of sleep (Mohamad & Ismail, 2011).

Table 1.1 Classification of OSA severity based on the AHI.

Classification	Events per hour (AHI)
Normal sleep	<5
Mild OSA	5–14
Moderate OSA	15–29
Severe OSA	≥30

OSA: obstructive sleep apnoea; AHI: apnoea–hypopnoea index.

Although the AHI is the most common way to diagnose OSA, other measures exist (Goyal & Johnson, 2017). One such measure is the Respiratory Disturbance Index (RDI) (Kapur et al., 2017), which assesses the number of apnoeas, hypopnoeas and respiratory effort-related

arousals (RERAs) that occur in the total sleep time (Goyal & Johnson, 2017). RERAs involve at least 10 seconds of increased respiratory effort that prompts arousals (arousals from a lower to a higher sleep stage), but they do not meet the criteria for an apnoea and hypopnoea. As illustrated in Table 1.2, normal sleep involves less than five of any of these events per hour of sleep. Minimal apnoea would be characterised by 5–14 episodes per hour. Mild apnoea would be characterised by 15–29 episodes, and moderate-to-severe apnoea would involve at least 30 episodes per hour of sleep (Gottlieb et al., 1999).

Table 1.2 Classification of OSA severity based on the RDI (Gottlieb et al., 1999).

Classification	Events per hour (RDI)
Normal sleep	<5
Minimal OSA	5–14
Mild OSA	15–29
Moderate-to-severe OSA	≥30

OSA: obstructive sleep apnoea; RDI: respiratory disturbance index.

A limitation of the AHI and RDI is that they focus on cessation of breathing or arousal from sleep rather than hypoxia, even though it is known that severe hypoxia in OSA is associated with elevated cardiovascular risk and increased mortality (Temirbekov, Güneş, Yazıcı, & Sayın, 2018, p. 1), metabolic disorders (Sforza & Roche, 2016) and cognitive dysfunction (Champod et al., 2013; Fowler, Taylor, & Porlier, 1987; Nair, Dayyat, et al., 2011; Nair, Ramesh, Li, Schally, & Gozal, 2013; Yaffe et al., 2011).

An index of OSA severity that takes hypoxia into consideration is the Oxygen Desaturation Index (ODI). While oximetry was previously ignored by empirical studies of OSA, recent research suggests that its diagnostic accuracy is similar to that of AHI (Fawzi, Basheer, Patel, & Sharma, 2017). Further, AHI does not provide information about the duration and depth of apnoeic episodes, whereas measures based on oximetry, such as the ODI, can provide detailed information about each episode (Temirbekov et al., 2018). ODI indicates ‘the number of times

per hour that oxygen desaturates by a certain percentage' (Rashid et al., 2020, p. 2). Therefore, the number does not account for the length of time an individual is desaturated; rather it shows the frequency of events that involve a particular level of desaturation. As illustrated in Table 1.3, ODI can be used to diagnose OSA severity (Rashid et al., 2020).

Table 1.3 Classification of OSA severity based on an ODI of 4% blood oxygen desaturation.

Classification	Events per hour (4% ODI)
Normal sleep	<10
Potential OSA	≥10
OSA	≥15

OSA: obstructive sleep apnoea; ODI: oxygen desaturation index.

Researchers have not compared all three diagnostic measures (AHI, RDI and ODI). Instead, the literature largely focusses on comparing the sensitivity of one of these variables to PSG or comparing the relative effectiveness of two of the measures. A systematic literature review (Rashid et al., 2020) found eight studies comparing AHI with ODI findings. All eight used PSG as a reference test (Álvarez, Hornero, García, del Campo, & Zamarrón, 2007; Chiner et al., 1999; Golpe, Jiménez, Carpizo, & Cifrian, 1999; Gyulay et al., 1993; Hang et al., 2015; Lin, Yeh, Yen, Hsu, & Hang, 2009; Series, 1993; Takeda et al., 2006), rather than comparing AHI and ODI directly, because of variation in 'hypopnea scoring, different oxygen desaturation categories, and different criteria for grading OSA severity' (Rashid et al., 2020, p. 1). The review concluded that 4% ODI of ≥15 events/hour can reliably diagnose adult OSA, whereas 4% ODI ≥10 events/hour requires additional assessment. Additional studies are required to directly compare the three diagnostic measures of OSA to ascertain their relative benefits and advantages. However, since the AHI is considered the most accurate measure for OSA severity, it has been used in the following studies.

1.4 Screening Tools for Obstructive Sleep Apnoea Severity

The increasing prevalence of OSA has created a need for rapid and effective methods of diagnosis. While PSG is the gold standard, it is very costly and time consuming because it must be conducted by trained personnel in sleep clinics (Joosten, 2017). Researchers have developed a number of questionnaires that can screen for probable OSA and facilitate diagnosis. OSA screening tools that are commonly used in sleep clinics include the Berlin questionnaire (BQ) (Netzer, Stoohs, Netzer, Clark, & Strohl, 1999), STOP questionnaire (SQ) (Chung et al., 2008), SBQ (Chung, Subramanyam, Liao, Sasaki, Shapiro, & Sun, 2012), Epworth sleepiness scale (ESS) (Johns, 1991), OSA50 (Chai-Coetzer et al., 2011) and Wisconsin sleep questionnaire (WSQ) (Young et al., 2002).

A review of 10 studies that examined OSA screening questionnaires indicated the SBQ was the most frequently used (Abrishami, Khajehdehi, & Chung, 2010). The SBQ predicts the likely severity of OSA, and its name is derived from the eight items in the questionnaire: snoring, tiredness, observed apnoea (pausing in breathing during sleep), blood pressure (BP), Body Mass Index (BMI), age, neck size and gender (Chung et al., 2008). Given that the SBQ is widely used in sleep clinics around the world, it has been translated into a number of other languages including Arabic (BaHammam et al., 2015).

A meta-analysis comparing the diagnostic accuracy of the BQ, the SBQ, the SQ and the ESS found significant variation in the four questionnaires' sensitivity and specificity (Chiu et al., 2017) (see Table 1.4). The SBQ and SQ are most sensitive for predicting mild and moderate OSA, while the SBQ, SQ and BQ have high sensitivity for severe OSA. The SBQ, SQ and BQ have low specificity (28–58%), and even the ESS has a specificity of only 60–65%. According to Chiu et al., 'sensitivity refers to the proportion of subjects with OSA who have a positive

questionnaire' and specificity 'refers to the proportion of subjects without OSA who have a negative questionnaire' (Chiu et al., 2017, p. 178).

Table 1.4 Sensitivity and specificity of the BQ, SBQ, SQ and ESS (table derived from Chiu et al., 2017).

OSA severity (events/hour)	Variables	BQ	SBQ	SQ	ESS
AHI ≥5 (Mild)					
	Sensitivity (%)	76	88	87	54
	Specificity (%)	59	42	42	65
AHI ≥15 (Moderate)					
	Sensitivity (%)	77	90	89	47
	Specificity (%)	44	36	32	62
AHI ≥30 (Severe)					
	Sensitivity (%)	84	93	90	58
	Specificity (%)	38	35	28	60

OSA: obstructive sleep apnoea; AHI: Apnoea–hypopnoea index; BQ: Berlin questionnaire; SBQ: STOP-Bang questionnaire; SQ: STOP questionnaire; ESS: Epworth sleepiness scale.

Another study that compared the capacity of the BQ, SBQ and OSA50 to predict moderate-to-severe OSA found that the questionnaires' sensitivity levels were 82%, 94% and 94%, respectively, and their specificity levels were 39%, 32% and 31%, respectively (Hamilton & Chai-Coetzer, 2019). A study that examined the WSQ determined that its sensitivity and specificity were 95% and 64% respectively for OSA with an AHI of 5 or higher, and 93% and 43% for OSA with an AHI of 15 or higher (Abrishami et al., 2010). In summary, the literature suggests that all of the current OSA screening questionnaires (BQ, SBQ, STOP, ESS, OSA50, WSQ) have high sensitivity for OSA, but their specificity is relatively low. When referrals for an overnight PSG are based purely on the results of these screening questionnaires, 40–70% of individuals will be found not to have OSA, representing an inefficient use of scarce clinical resources.

1.5 Risk Factors for Obstructive Sleep Apnoea

Factors associated with increased susceptibility to OSA include increased age, elevated BMI, male sex, ethnicity, smoking and comorbidities such as coronary artery disease, end-stage renal

disease, systemic hypertension and type 2 diabetes (T2D) (Pinto, Ribeiro, Cavallini, Duarte, & Freitas, 2016). In the following sections these risk factors are discussed in more detail.

1.5.1 Age

Several studies have suggested a positive relationship between age and OSA (Franklin & Lindberg, 2015). The prevalence of OSA among middle-aged males in Western societies has been estimated to be around 20%. The severity of OSA increases steadily with age, especially over the age of 60 years (Young et al., 2002). According to a systematic review of 24 studies by Senaratna et al. (2017), the severity of OSA increases with age for both males and females. Based on an AHI of 5 or higher, the prevalence of OSA has been estimated as 88% among males aged 65–69 years and 90% for males aged 60–85 years. For females in the same age groups, the prevalence of OSA has been estimated as 66% and 78%, respectively.

1.5.2 Body Mass Index

Obesity is generally measured by BMI, which is the ratio of weight in kilograms to height in metres squared. BMI reflects a person's degree of obesity: overweight individuals are defined as those with a BMI higher than 25 kg/m^2 and obesity is defined as a BMI over 30 kg/m^2 (Nuttall, 2015). BMI correlates strongly with the severity and prevalence of OSA within the general population. Approximately 45% of individuals who suffer from obesity have OSA (Romero-Corral, CaplesLopez-Jimenez, & Somers, 2010). Among adults with a BMI above 30 kg/m^2, the prevalence of severe OSA is 25% (Resta et al., 2001), while 40–90% of adults with morbid obesity (BMI >40 kg/m^2) are likely to have severe OSA (Rajala et al., 1991; van Kralingen et al., 1999). Evidence indicates that a 10% increase in body weight is sufficient to increase the AHI by 30% (Peppard, Young, Palta, Dempsey, & Skatrud, 2000).

One study exploring the global obesity epidemic suggested that individuals in certain countries are much more likely to be overweight or obese than those in others (Chooi, Ding, & Magkos, 2019). Further, all regions in that study (the Americas, Europe, the Eastern Mediterranean, Africa, Southeast Asia, the Western Pacific) have seen an increase in the prevalence of both overweight and obese individuals within their populations. Based on the link between OSA and obesity, this also suggests a worldwide increase in the prevalence of OSA (Chooi et al., 2019).

Some studies have identified sex-based relationships between BMI and OSA severity (Huang et al., 2014). An Egyptian study of 60 males and 37 females found that, although the females had higher BMIs than their male counterparts, the males in the study had higher AHIs (Assal & Kamal, 2016). Zammit, Liddicoat, Moonsie and Makker (2010) pointed to sex differences in regional fat accumulation, which might explain the higher severity of OSA among males. This is discussed in greater detail in the following section.

1.5.3 Sex and Geography

Table 1.5 shows the prevalence of OSA by sex according to nine studies from across the world. Despite some variation in the findings, most studies found that OSA is more common in males than in females. The lowest rate reported for females was 0.9%, in Denmark (Jennum & SjØL, 1992), while the highest rate for females was 15%, in Spain (Durân, Esnaola, Rubio, & Iztueta, 2001). For males, the lowest reported rate was 1.3%, in Denmark (Jennum & SjØL, 1992) and the highest, 19%, in Spain (Durân et al., 2001).

Table 1.5 Estimated prevalence of obstructive sleep apnoea stratified by sex, age and country.

Location	Prevalence	Age (years)	Authors
Hong Kong	4.1% males 2.1% females	30–60	Ip et al. (2004)
United States	7.2% males 2.2% females	20–100	Bixler et al. (2001)
Australia	8.5% males 4.7% female	40–65	Bearpark et al. (1993)
Denmark	1.3%–1.9% males 0.9% females	30–60	Jennum and SjØL (1992)
India	7.5% males 4.5% females	35–65	Udwadia, Doshi, Lonkar, & Singh (2004)
Saudi Arabia	4.0% males 1.8% females	30–60	Wali, Abalkhail, & Krayem (2017)
Spain	19% males 15% females	30–70	Durân et al. (2001)
South Korea	4.5% males 3.2% females	30–70	Kim et al. (2004)

In a literature review on the prevalence of diagnosed OSA across multiple ethnicities (White, Indian, Chinese and Korean), Punjabi (2008) found an estimated prevalence of 3.1–4.5% in males aged 20–100, and 1.2–2.3% in females of the same age. Recent studies report similar results. For example, a study of Saudi school employees aged 30–60 years found that 4.0% of the males and 1.8% of the females had been diagnosed with OSA (Wali et al., 2017). The higher prevalence and severity of OSA in males than females (Wimms, Woehrle, Ketheeswaran, Ramanan, & Armitstead, 2016) can be partly attributed to sex differences in weight distribution. Although females are more likely to be overweight or obese than their male counterparts (James, 2004; Kapse, Patel, Mhaisekar, & Kulkarni, 2019), females tend to accumulate body fat around the waist and hips. In contrast, males tend to have greater deposits of adipose tissue around the stomach and neck region, making them more likely to experience airway obstruction and suffer from OSA (Whittle et al., 1999). Moreover, studies showed that post-menopausal females indicated higher OSA severity, and the prevalence of OSA in females

rises markedly after menopause from 47% to 67% (Jehan et al., 2015). OSA severity may increase in post-menopausal females due to weight gain after menopause (Jehan et al., 2016). However, previous findings indicated that although females are more symptomatic, they show lower apnoea–hypopnoea index scores in contrast to males. Furthermore, females show more prolonged partial upper airway obstruction and more frequently report severe insomnia as an OSA symptom (Bonsignore et al., 2019). Additionally, progesterone and oestrogen are known to enhance genioglossus contractility, counteracting the upper airway collapsibility during sleep (Hou et al., 2010; Popovic and White, 1998). However, after menopause, progesterone and oestrogen levels decrease, increasing the risk of OSA severity (Saaresranta et al., 2015).

In females, pregnancy increases the likelihood of OSA. There are two types of OSA severity in pregnancy. Women with pre-existing OSA can experience a worsening of the condition during pregnancy, while others develop OSA for the first time during their pregnancy. It was recently estimated that new-onset OSA in pregnancy affected 20% of 120 women tested, but most cases of new-onset OSA in the pregnant women were mild (Facco, Ouyang, Zee, & Grobman, 2014). Moreover, in a large general population cohort, OSA was notably linked with pregnancy hypertension, even after adjusting for pre-existing hypertension, age, obesity and smoking status (Bin, Cistulli, & Ford, 2016). Further studies confirm that CPAP treatment improves BP levels in pregnant females (Edwards, Blyton, Kirjavainen, Kesby, & Sullivan, 2000; Poyares et al., 2007). Louis et al. (2018) identified several factors that predict the likelihood of OSA during pregnancy, such as age, BMI and snoring. Additionally, Pien et al. (2014) conducted PSG studies of 105 pregnant females in their first and third trimesters. In the first trimester, 10.5% of participants had an AHI score above 5. By the third trimester, however, the percentage of participants with OSA had risen to 26.7%. This effect remained pronounced even after correcting for BMI: 8.4% of participants still had an AHI above 5 in the first trimester, and 19.7% had an AHI over 5 in the third trimester. Another potential cause of OSA

during pregnancy is the fluid accumulation in tissues as a result of hormones released from the adrenal glands, particularly if a woman develops pre-eclampsia (Chapman et al., 1998). When that fluid moves from the limbs to the neck, it can contribute to pharyngeal obstruction, which increases OSA severity (Redolfi et al., 2009).

1.5.4 Smoking

Smoking is reportedly more common among patients with OSA than in the general population (Kashyap, Hock, & Bowman, 2001). Smoking causes inflammatory oedema in the pharyngeal and bronchial walls, as well as increased mucus production, leading to a reduction in the diameter of the airways (Krishnan, Dixon-Williams, & Thornton, 2014). Research has yielded mixed findings on the association between smoking and OSA. Many Saudis smoke water pipes (shisha) or tobacco (Al Moamary et al., 2012); both are thought to be risk factors for OSA (Al Moamary et al., 2012). The overall prevalence of cigarette smoking in Saudi Arabia is 21.4%, but the rate is higher (32.5%) among males aged 25–45 years (Algabbani, Almubark, Althumiri, Alqahtani, & BinDhim, 2018). As a result of the increased burden of OSA in this population, treatment guidelines are being proposed in an attempt to mitigate the untoward effects of disease progression (Al-Hamdan, Saeed, Kutbi, Choudhry, & Nooh, 2010; Saeed et al., 2011).

Some scholars have suggested that smoking is associated with more severe OSA, and studies in Saudi Arabia have found a strong relationship between smoking and OSA severity (Alharthi, Masoodi, Alomairi, Almuntashiri, & Alfaifi, 2018; Bielicki, Trojnar, & Sobieraj, 2018). In addition, Wetter, Young, Bidwell, Badr and Palta (1994) found that patients who currently smoked were more likely to have OSA than non-smokers or former smokers. In contrast, after controlling for sex effects, a study of 3,509 OSA patients with OSA reported that, although heavy smokers had higher AHI scores than non-smokers, there was no significant relationship

between cigarette smoking and OSA (Hoffstein 2002). Since males are more likely to have higher smoking rates (Gowing et al., 2015) and a greater OSA severity than females (Kim & Taranto-Montemurro, 2019), a possible explanation for these inconsistent findings is that the relationship between smoking and OSA severity is confounded by sex.

1.5.5 Comorbid Conditions that Affect the Prevalence and Severity of Obstructive Sleep Apnoea

Certain genetic abnormalities, ethnic physiological characteristics and pre-existing conditions or diseases may increase the likelihood that an individual will develop OSA. For example, Down syndrome, a condition caused by the duplication of chromosome 21, is best known for causing intellectual disability, yet OSA is prevalent in approximately 40% of adults with Down syndrome (Hill, 2016). The high prevalence of OSA in this population may be attributed to physical features associated with the syndrome, such as reduced muscle tone, a flattened face and large tongue, all of which increase the risk of OSA. A similar explanation has been offered for ethnicity-related differences in the prevalence of OSA. For instance, several studies have indicated higher OSA severity among Asians than among Caucasians even after subjects were matched for BMI (Li, Kushida, Powell, Riley, & Guilleminault, 2000; Ong & Clerk, 1998), which may point to the role of craniofacial features. Lee et al. (2010) proposed that the flatter craniofacial profile of Chinese individuals increases their susceptibility to airway restriction. In another study, Lee, Chan, Grunstein and Cistulli (2009) found that even among Caucasian populations, independent of BMI, individuals with OSA are more likely to have a group-indicated shorter and retracted jaw, and a wider and flatter mid- and lower face compared with those without OSA.

Research suggests an increase in mortality rates for patients suffering from coronary artery disease (heart disease), end-stage renal disease, obesity, hypertension and/or T2D, particularly

when these conditions co-occur each other and with OSA (da Silva, Kasai, Coelho, Zatz, & Elias, 2018; Marrone, Lo Bue, Salvaggio, Dardanoni, & Insalaco, 2013). For instance, fluid retention in tissues, a common condition in patients with chronic kidney or heart disease, is also associated with the development of OSA. Patients with end-stage renal disease are more likely to suffer from OSA because renal failure increases fluid accumulation in all tissues, including those surrounding the pharynx (Abuyassin, Sharma, Ayas, & Laher, 2015). A study conducted in the 1980s found that 12 out of 29 men (41%) who underwent haemodialysis for kidney disease also reported symptoms of OSA. Eight patients on haemodialysis were randomly selected to undergo PSG; of those, six (75%) met the diagnostic criteria for OSA (Millman, Kimmel, Shore, & Wasserstein, 1985). Other studies support the link between cardiovascular disease and OSA via fluid retention (da Silva et al., 2018; Kasai, Floras, & Bradley, 2012). During the day, while the patient is standing or sitting, gravity causes excess fluid to accumulate in the legs. Once the patient is supine, this fluid redistributes throughout the body, including the upper airway, increasing the risk of OSA (White & Bradley, 2013).

Since males, daytime sleepiness and drowsiness are associated with hypertension, research points to a bidirectional relationship between OSA and hypertension that is modulated by sex, age and excessive sleep or drowsiness (Torres, Sánchez-de-la-Torre, & Barbé, 2015). As many as 35–80% of patients diagnosed with OSA may also suffer from systemic hypertension (Parati et al., 2013). However, among patients with resistant hypertension, 80% or more may also suffer from OSA (Logan et al., 2001). Recent research has confirmed a link between OSA and resistant hypertension (Walia et al., 2014). Hou et al. (2018) presented a systematic review and meta-analysis that confirmed the association between OSA and systemic and/or essential hypertension.

A major contributor to the increasing prevalence of OSA may be the increased prevalence of metabolic syndrome (Gaines, Vgontzas, Fernandez-Mendoza, & Bixler, 2018). Metabolic syndrome is characterised by obesity, insulin resistance, hypertension and dyslipidaemia (Tasali & Ip, 2008), all of which increase the risk of OSA (Gaines et al., 2018). The simultaneous occurrence of OSA and metabolic syndrome is called Syndrome Z (Hassan, 2018; Wilcox, McNamara, Collins, Grunstein, & Sullivan, 1998). In an investigation of the relationship between metabolic syndrome and OSA, McArdle, Hillman, Beilin and Watts (2007) reported that males with OSA displayed higher insulin resistance. Insulin resistance, or impaired glucose tolerance (IGT), is a precursor to type 2 diabetes (T2D). The transition from IGT to T2D may take several years, with 70% of pre-diabetic individuals eventually developing T2D (Nathan et al. 2007). Further, Brooks et al. (1994) found a 70% prevalence of OSA in a sample of overweight diabetic patients. A study exploring the empirical evidence for Syndrome Z (Nock, Li, Larkin, Patel, & Redline, 2009) suggested that the most important determining factor for the development of OSA was obesity, followed by sleep disturbance, insulin resistance, hypertension and dyslipidaemia.

1.6 Obstructive Sleep Apnoea Treatment: Continuous Positive Airway Pressure

The first-line treatment for OSA is continuous positive airway pressure (CPAP). It is usually recommended for patients who have been diagnosed with OSA, especially moderate or severe OSA (Epstein et al., 2009). The CPAP device was developed in the 1980 by Professor Colin Sullivan at the Royal Prince Alfred Hospital in Sydney. It uses an air pump connected by a hose to a face mask to pneumatically splint the airway during sleep. Pneumatic splinting prevents the throat from collapsing and the soft palate, uvula and tongue from shifting into the airway (Sullivan, Issa, Berthon-Jones, & Eves, 1981).

CPAP treatment has improved significantly since its introduction. By 1985 more than 100 patients in Sydney used CPAP at home, with machines that had been manufactured in the Hospital's workshop. The first mobile CPAP machine consisted of a bulky mask that required adhesives to be used (Sullivan et al., 1981). In 1985 Respironics (USA) began the commercial production of CPAP machines. Many patients complained of a sore throat and general dryness after CPAP use. Since then, one of the most significant advances has been the addition of a humidifier (Massie, Hart, Peralez, & Richards, 1999). Scientists have also developed an automated smart (autoset) CPAP machine that calibrates positive airway pressure based on the pressure required to overcome airway resistance (Teschler et al., 1996). Although current modern CPAP machines are digitally controlled, efficient and quiet, patients are often non-compliant for a number of reasons, including mask-related issues (60%), patient factors (25%) and/or machine-based issues (15%) (Singhal, Joshi, Singh, & Kulkarni, 2016). Many patients are not able to use the device for the recommended minimum of four hours per night (required to achieve normal levels of sleepiness and daily functionality) because of discomfort and/or because they simply forget to use the device (Singhal et al., 2016).

Patients are required to use CPAP as a long-term treatment to prevent OSA symptoms and to improve sleep quality, with effectiveness increasing with regular use. However, CPAP therapy only relieves the symptoms of OSA; it does not treat the underlying condition, and symptoms return if use is discontinued. Long-term CPAP use may reduce the sympathetic hyperactivity, hypertension, EDS, fatigue and motor vehicle accidents associated with OSA (Chotinaiwattarakul, O'Brien, Fan, & Chervin, 2009; George, 2001; Marshall et al., 2006; McArdle et al., 1999; Park & Kang, 2018).

1.7 Physiological and Neurocognitive Correlates of Obstructive Sleep Apnoea

OSA involves low blood oxygen levels and sleep disturbances, with several consequences that occur nocturnally (e.g. increased SNS activity) and diurnally (e.g. EDS, depressive symptoms, and cognitive impairment). Section 1.8.1 describes the effects of OSA on nocturnal SNS activity, while EDS, depressive symptoms and cognitive impairments are described in Section 1.9.

1.7.1 Sympathetic Nervous System

Moderate-to-severe OSA involves frequent respiratory arrests and arousals from sleep. The body physically responds to this highly stressful situation by activating the SNS (part of the autonomic nervous system [ANS]) to prepare the body for fight or flight, as illustrated in Figure 1.4 (McCorry, 2007). This self-preservation reflex, facilitated by a surge of adrenaline, has physiological consequences such as increased heart rate, elevated BP, increased muscle tone and release of energy from glycogen stores. Simultaneously, less urgent physiological processes, such as digestion, are slowed down.

The SNS originates in the spinal cord and consists of two sets of neurons. First, the preganglionic neurons are situated between the first thoracic (T1) and the third lumbar (L3) spinal segments. Pre-ganglionic neurons project to another group of neurons called post-ganglionic neurons, which are located in a series of autonomic ganglia. These neurons connect to a respective target organ, muscles and/or glands. Pre-ganglionic neurons release a neurotransmitter called acetylcholine, which binds to specific receptors on post-ganglionic neurons that, when activated, release noradrenaline onto their local targets. Some pre-ganglionic neurons synapse directly with the adrenal medulla, which acts as a modified version

of post-ganglionic neurons (McCorry, 2007). The adrenal medulla can successfully mimic neural tissue since it shares the same embryonic origin. In response to stimulation by pre-ganglionic neurons the adrenal medulla releases adrenaline, which is transported by the blood to target tissues and organs; adrenaline and noradrenaline bind to receptors on cells in their target organs, prompting physiological effects such as pupil dilation, increased heart rate, elevated BP and increased muscle tone (McCorry, 2007). Cortisol, also known as the stress hormone, is released by the adrenal glands upon stimulation by the SNS (D. Y. Lee, Kim, & Choi, 2015). It increases the concentration of glucose in the blood, which is an important source of energy for muscles and the brain (McCorry, 2007).

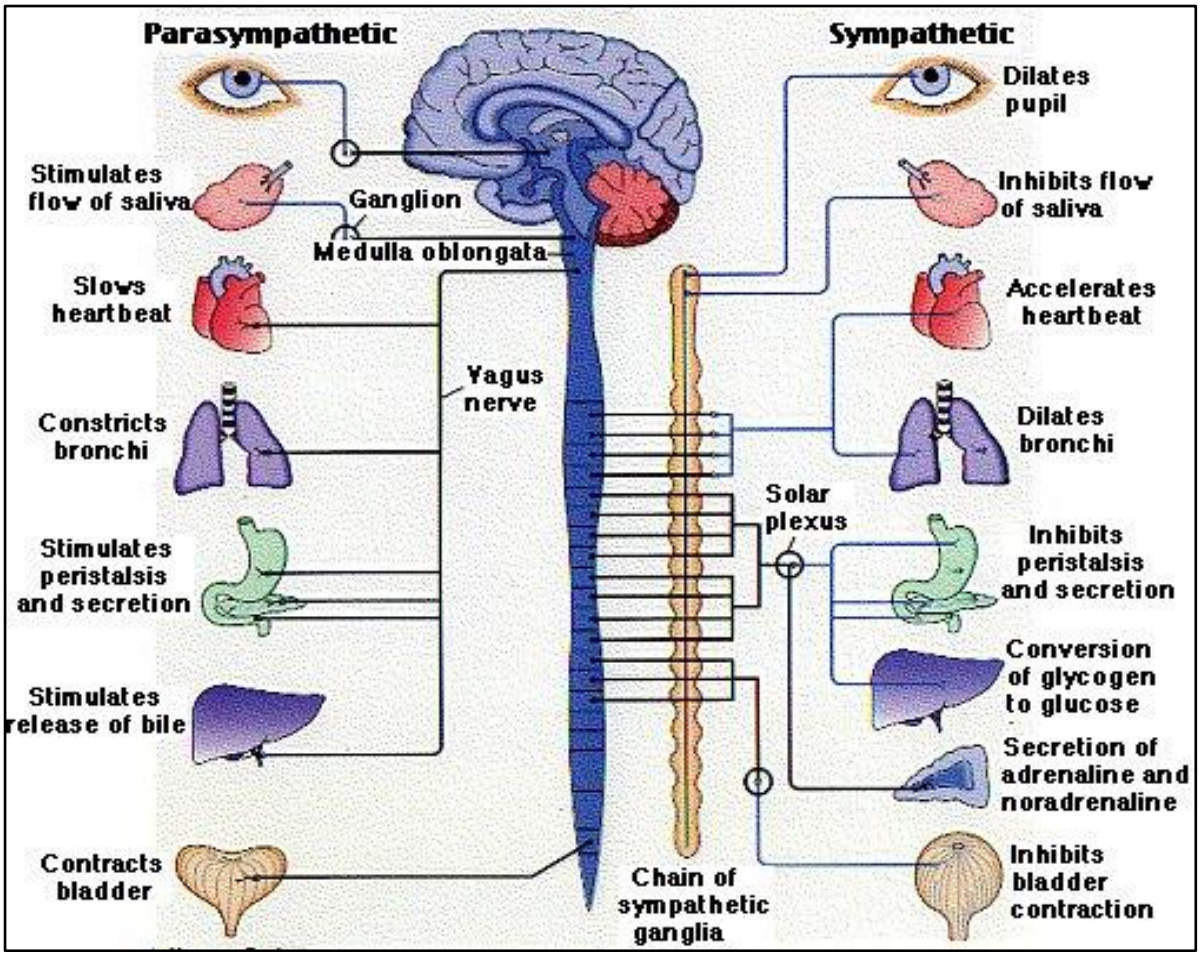

Figure 1.4 Schematic diagram of the autonomic nervous system showing how the parasympathetic and sympathetic nervous systems provide complementary innervation to the same organs (Petkar et al., 2010).

Increased SNS activity during apnoeic events is known to elevate BP (Dopp, Reichmuth, & Morgan, 2007; Lombardi, Pengo, & Parati, 2019). OSA has been documented to cause nocturnal peaks in BP as well as daytime hypertension (Wolf, Hering, & Narkiewicz, 2010). Based on the circadian rhythm, BP in normal healthy individuals is reduced by 10–20% at night compared with daytime, in a process known as 'dipping BP' (Kario, 2018). Studies have shown that OSA blunts the magnitude of this dip and increases the probability of BP not dipping (Cuspidi et al., 2019). In a study of 42 OSA patients, nocturnal BP was found to be elevated during apnoeic events (Sasaki et al., 2018), while a study of 58 patients with mild-to-severe OSA found that severe OSA is associated with increased variability in nocturnal BP (Martynowicz, Porębska, Poręba, Mazur, & Brzecka, 2016). Brief surges of SNS activity that occur during sleep in OSA are associated with nocturnal BP peaks (Crinion, Ryan, & McNicholas, 2017). IH and sleep fragmentation independently contribute to increased SNS activity and high BP (Chouchou et al., 2013; Weiss, Tamisier, & Liu, 2015).

Many methods can be used to measure SNS activity. A common method in research and clinical studies is heart rate variability (HRV). HRV represents the physiological phenomenon of heartbeat periodicity variation, as illustrated in Figure 1.5. The duration between successive heartbeats fluctuates when a person is relaxed, but as they become stressed their heartbeat becomes more regular (K. Li, Rüdiger, & Ziemssen, 2019). Spectral analysis of HRV is a non-invasive and easy-to-perform method for evaluating cardiac autonomic activity (Draghici & Taylor, 2016). The amount of variability in the duration between heartbeats can be used to estimate the relative activities of the SNS and parasympathetic nervous system (PNS), with this variability being measured on two time scales: 2.5–6.7 seconds (high frequency [HF] variability) and 6.7–25 seconds (low frequency [LF] variability). By convention, these time scales are referred to as HF power (0.15–0.40 Hz), reflecting modulation of vagal tone (part of the PNS), and low frequency (LF) power (0.04–0.15 Hz), reflecting sympathetic activity (Burr,

2007). However, LF HRV can also be influenced by PNS activity (Goldstein, Bentho, Park, & Sharabi, 2011; Sassi et al., 2015), and HF HRV can be influenced by individual differences such as patterns of breathing and sleeping posture (Akselrod, 1995; Hirsch & Bishop, 1981; Malpas, 2002; Taylor, Carr, Myers, & Eckberg, 1998). Pagani et al. (1984) suggested that the LF/HF ratio may provide a useful index of sympatho-vagal balance, and this ratio has been widely adopted since, despite some authors questioning its reliability (e.g. Shaffer & Ginsberg, 2017).

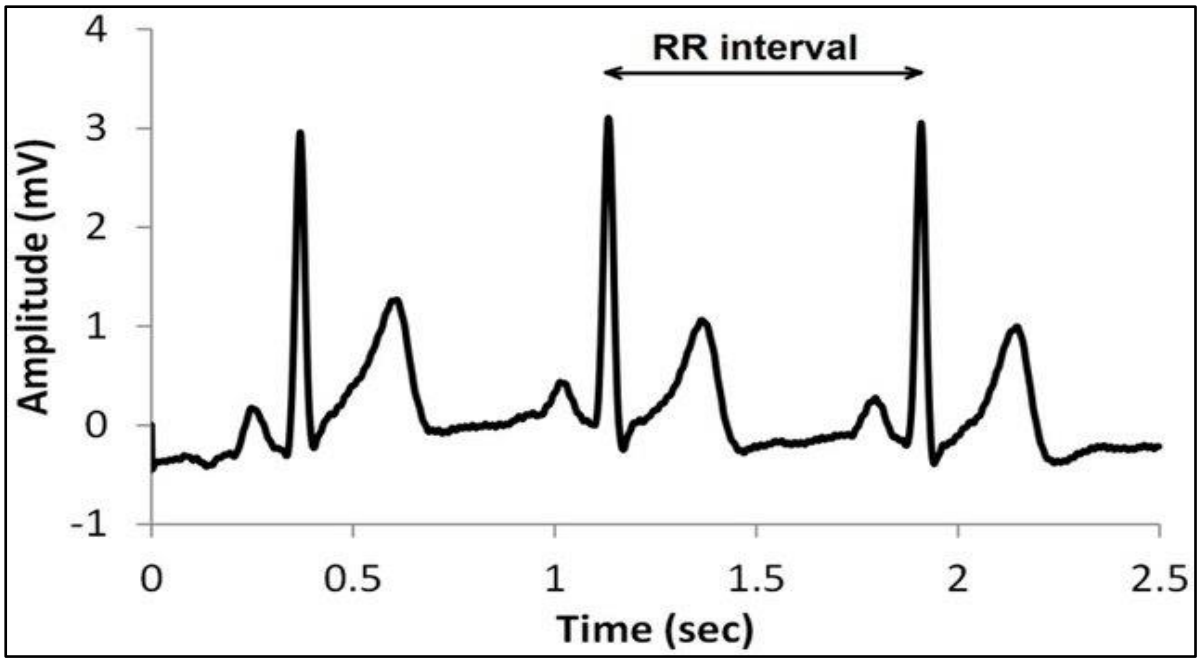

Figure 1.5 Heart rate variability: variation in the duration between heartbeats (Cornforth, Tarvainen, & Jelinek, 2014). RR interval: R wave to R wave interval; Sec: second.

HRV analysis has shown that patients with moderate-to-severe OSA have a heightened cardiac sympathetic modulation relative to those with mild OSA and control subjects, as indicated by an elevated LF/HF ratio during the day and during sleep (Sequeira, Bandeira, & Azevedo, 2019). Treatment of OSA with CPAP has been found to reduce the sympathetic modulation of the heartbeat (Bonsignore et al., 2006), while the use of CPAP over a longer period (e.g. >2 years of treatment) augments the coupling between parasympathetic modulation and N3 sleep (Jurysta et al., 2013).

The measurement of HRV during sleep in OSA patients is complicated by various factors that can add biological noise to the signals (Wang et al., 2008). For example, up to 63% of OSA patients have periodic leg movements that are likely to elevate the HRV (Budhiraja et al., 2020; Sasai, Matsuura, & Inoue, 2013). It is also evident that OSA influences the regular pattern of breathing, which in turn, can influence rhythmic oscillations in HRV. However, Malliani (2006) indicated that the HRV LF/HF ratio is the best measure of sympathy-vagal balance. This point will be discussed in detail in the relevant chapters below.

Pulse wave amplitude (PWA) is a signal waveform obtained from infrared finger plethysmography. PWA is a measure of blood flow through the finger at any given moment (Burch, 1954), and the signal consists of a series of spikes, each corresponding to a single heartbeat. The magnitude of the signal (i.e. from minimal to maximal flow at each heartbeat) is influenced by the moment-to-moment activity of the SNS. Increased sympathetic tone causes vasoconstriction in the small vessels of the finger (Catcheside et al., 2002) and this is observed as a reduction in the amplitude of the PWA signal (Figure 1.6).

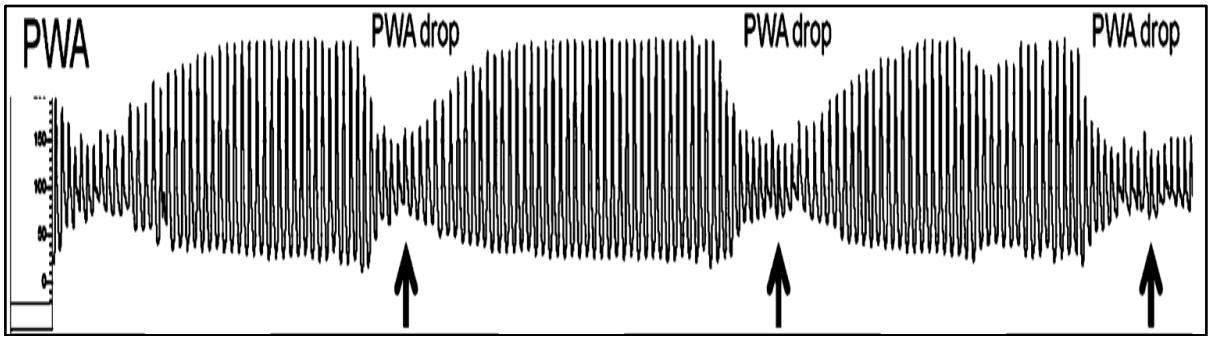

Figure 1.6 Pulse wave amplitude (PWA) trace obtained from finger plethysmography illustrating three temporary reductions in blood flow due to activation of the SNS (Vat et al., 2015). Note: each spike corresponds to a heartbeat.

Variation in PWA appears to be directly linked to the sympathetic outflow to the vessels of the finger and can be enhanced by the administration of norepinephrine and prevented by the administration of sympathetic nerve blockers such as bupivacaine (Hirotsu et al., 2020). During

sleep, cortical arousals induced by apnoeas and hypopneas are accompanied by PWA drops, indicating that these events are associated with increased activation of the SNS (Adler et al., 2013). During sleep, there is a normal fluctuation in the amplitude of the PWA signal. It was originally proposed that a PWA drop of 20% represents SNS activation (Delessert et al., 2010), but it is now accepted that an average 30% reduction is a more reliable indicator (Bosi et al., 2018; Haba-Rubio et al., 2005; Hirotsu et al., 2020; Vat et al., 2015).

Since activation of the SNS leads to constriction of peripheral arteries, elevation in BP can indicate elevation in SNS activity. Nocturnal BP monitoring through the use of a 24-hour ambulatory blood pressure monitor (ABPM) has been used in some studies of OSA, but it is uncomfortable and disturbs the normal sleep pattern, artificially inflating BP levels (Agarwal & Light, 2010). Another problem is that ABPM measures BP intermittently at predefined intervals (approximately every 15–30 minutes) which can lead to BP overpass recording. Since BP peaks induced by OSA events can occur at any time and can be quite brief, limiting measurement of BP to once every 15–30 minutes will miss most events.

A few recent studies have used a non-invasive and cuff-less method, referred to as pulse transit time (PTT), which compares signals from finger photoplethysmography (PPG) and electrocardiography (ECG) to estimate BP without disturbing the patient's sleep (Gesche, Grosskurth, Küchler, & Patzak, 2012). PTT is the time elapsed between the EEG R-peak recorded above the heart and the corresponding peak recorded in the finger during a single cardiac cycle, the duration of which varies systematically as a function of BP (see Figure 1.7) (Ding, Yan, Karlen, Zhang, & Tsang, 2020). PTT, as a new method for measuring BP non-invasively, has been criticised on the basis of some study findings. For example, Krisai et al. (2019) reported a significant difference between 24-hour BP measured via cuff-based BP and PTT. Specifically, PTT indicated a higher average (+5.0 mmHg) systolic blood pressure (SBP)

and diastolic blood pressure (DBP) than cuff-based BP. Another study reported that while BP as measured by PTT (SOMNOtouch non-invasive BP) was an average of 4 mmHg higher than that measured by cuff-based BP, the measures were highly correlated throughout the 24-hour period (Zachwieja et al., 2020). Other studies have found good agreement between the two methods. For instance, measurements obtained through nocturnal BP recording via the PTT method were strongly correlated with BP measured directly via the cuff-based BP device (Gesche et al., 2012; Hennig et al., 2012; Wong, Poon, & Zhang, 2009), supporting the accuracy of PTT as a continuous measure of BP. Until now it has not been practicable to continuously measure BP during sleep (Almeneessier et al., 2020; Gehring, Gesche, Drewniok, Küchler, & Patzak, 2018). By making it possible to record continuous BP throughout a PSG study, the PTT method can improve our knowledge about fluctuations in nocturnal BP in OSA patients and demonstrate whether transient spikes in BP are associated with OSA severity.

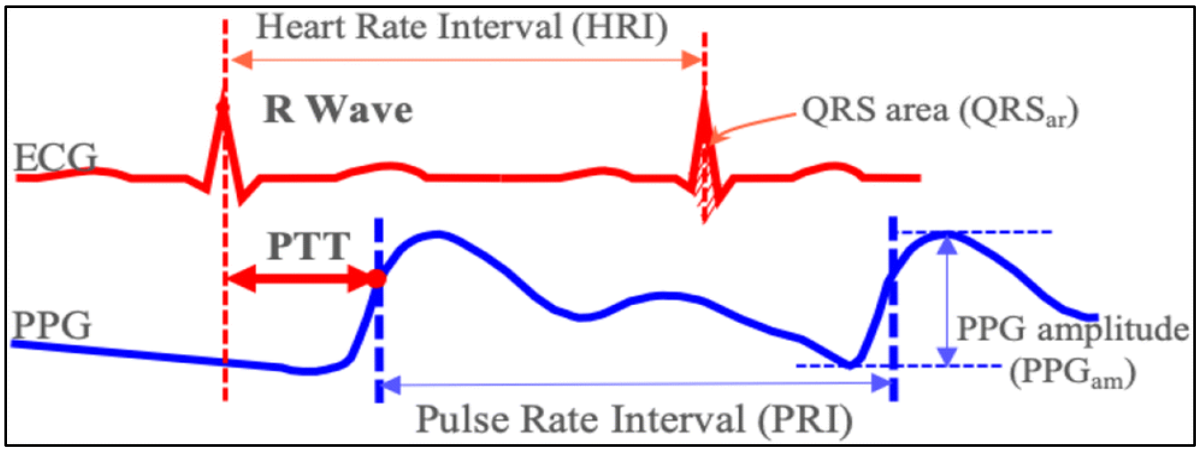

Figure 1.7 Pulse transit time (PTT) is the time elapsed between the EEG R-peak recorded above the heart and the corresponding peak recorded in the finger during a single cardiac cycle (Ding et al., 2020). PPG: photoplethysmography; ECG: electrocardiogram.

1.8 Daytime Dysfunction in Obstructive Sleep Apnoea

OSA patients frequently display EDS, mood disturbance (depressive symptoms) and cognitive impairment. The following sections discuss these symptoms.

1.8.1 Excessive Daytime Sleepiness in Obstructive Sleep Apnoea

EDS is characterized by a difficulty in staying awake and a lack of energy during waking hours, even after prolonged sleep. EDS in OSA patients leads to decreased alertness and vigilance and is a common cause of traffic and workplace accidents (Garbarino et al., 2018; Y. Li et al., 2017). However, not all people with OSA have EDS, even among those with severe OSA (Durân et al., 2001). A study of more than 6,000 participants (⩾5 AHI) recruited from 17 European countries and Israel (Saaresranta et al., 2016) compared OSA patients with comorbid EDS and/or insomnia (defined as difficulty initiating or maintaining sleep). The study found that 44.4% of the cohort suffered from EDS and these individuals were more likely to have severe OSA, yet those with comorbid insomnia were more likely to have psychiatric comorbidities. According to a recent review conducted by Garbarino et al. (2018), there is no consensus regarding whether people with EDS represent a distinct sub-group. In contrast to this conclusion, a Chinese study (Shao et al., 2019) reported that OSA patients with EDS show increased levels of AHI, Arousal Index, oxygen desaturation <90%, obesity and comorbidity. Similarly, Bixler et al. (2005) claimed that several factors are independently linked to EDS in OSA: BMI, age, typical sleep duration, diabetes, smoking history, depression and AHI. Mediano et al. (2007) found that OSA patients with EDS have a shorter sleep latency, increased sleep deficiency and lower nocturnal oxygenation than those without EDS.

EDS has become a primary criterion in the initial diagnosis of OSA (Ramos et al., 2017) and is also used as an indicator of patient compliance with CPAP. According to the meta-analysis of Patel, White, Malhotra, Stanchina and Ayas (2003), CPAP treatment significantly decreases the mean of ESS scores, with the largest differences being observed in patients with moderate and severe OSA compared with those with mild OSA. Additionally, Saaresranta et al. (2016) concluded that after adjusting for age, sex, BMI and sleep apnoea severity, EDS improved with

longer CPAP adherence. A substantial enhancement of ESS scores was found after one month of CPAP use by patients with moderate and severe OSA (Goel, Talwar, & Jain, 2015). Tomfohr, Ancoli-Israel, Loredo and Dimsdale (2011) pointed out that CPAP use did not generally improve ESS scores in patients who did not have EDS to begin with, whereas patients with EDS showed great improvement in ESS scores after CPAP use. However, Antic et al. (2011) stated that because of the coexistence of other factors in OSA, such as depression and sedating medication, even optimum CPAP adherence may not improve EDS. Another important finding is that OSA patients with EDS appear to benefit from CPAP use via decreases in their risk of cardiovascular disease, insulin resistance, hypertension and endothelial dysfunction, whereas such benefits are not as evident for OSA patients without EDS (Garbarino et al., 2018). When viewed together, the preceding observations indicate that EDS has important implications for patient health and clinical assessment.

1.8.2 Depressive Symptoms

Depressive symptoms are common in breathing-related disorders. An estimated 46% of breathing-related sleep-disordered patients show comorbidity for depressive symptoms (Rezaeitalab, Moharrari, Saberi, Asadpour, & Rezaeetalab, 2014). It is notable that while OSA patients are usually screened for depressive symptoms, patients with depressive symptoms are rarely screened for OSA. Given this high comorbidity rate, it has been recommended that when a person is diagnosed with either OSA or a clinical mood disturbance, the other condition should be investigated, since there may be an underlying pathological relationship uniting the two conditions (Ejaz, Khawaja, Bhatia, & Hurwitz, 2011).

Studies have indicated an association between depressive symptoms and OSA severity (Aloia et al., 2005; Edwards et al., 2015). OSA patients with serious depressive symptoms may have more severe OSA (Harris, Glozier, Ratnavadivel, & Grunstein, 2009). Patients with severe

OSA experience a decrease in their quality of life, which is significantly correlated with symptoms of depression (Akashiba et al., 2002). Research also showed links between depressive symptoms and EDS in OSA patients (Ishman, Cavey, Mettel, & Gourin, 2010). Therefore, depressive symptoms should be investigated more systematically in patients with OSA because they are likely to have far-reaching consequences in terms of treatment compliance, and emotional and cognitive functioning.

The overlap of symptoms between depression and OSA have been well studied. Research has shown that insomnia, fatigue, sleep disturbance and psychomotor retardation are shared by depression and OSA (Bucks et al., 2018; Jehan et al., 2017). Both of these conditions can disguise each other due to the significant symptom similarity (Harris et al., 2009). Nevertheless, Nanthakumar et al. (2016) suggested that to reduce the likelihood of overestimating the prevalence of depression in OSA, depression questionnaires should have a low level of symptom overlap between OSA and depression and a higher proportion of anhedonia symptoms.

CPAP treatment can mitigate some of the mood disturbances that arise secondarily to OSA (B. -H Yu, Ancoli-Israel, & Dimsdale, 1999). Sleep disturbance in OSA promotes dysfunctional mood states that can be reversed once sleep quality is improved (Derderian, Bridenbaugh, & Rajagopal, 1988). Anger and vigour, as measured by the Profile of Mood States (Biehl & Landauer, 1975), have been found to be related to sleep variables in sleep apnoea patients (Bardwell, Berry, Ancoli-Israel, & Dimsdale, 1999). A meta-analysis of 20 randomised trials, including 4,255 participants, confirmed a limited benefit of CPAP in reducing depression symptoms in OSA patients with cardiovascular disease, independently of improvements in sleepiness (Zheng et al., 2019). Depressive symptoms frequently persist after CPAP treatment (Harris et al., 2009). Studies have indicated that Modafinil (a common wake-promoting

pharmaceutical agent) is effective in ameliorating residual sleepiness in CPAP-treated OSA (Bittencourt et al., 2008; Chapman et al., 2014), and simultaneously improves the depressive symptoms (Konuk, Atasoy, Atik, & Akay, 2006). Bucks et al. (2018) compared the effects of CPAP treatment on overlapping depressive symptoms (such as insomnia, lethargy, impaired concentration and psychomotor retardation) and non-overlapping depressive symptoms (such as negative affect, anhedonia and depressive cognition). The study concluded that even though both overlapping and non-overlapping depressive symptoms improved with CPAP treatment, greater and faster reduction was observed in overlapping depressive symptoms. Thus, non-overlapping depressive symptoms might be behind the persistence of depression after CPAP treatment, as some studies have observed.

1.8.3 Cognitive Dysfunction in Obstructive Sleep Apnoea

OSA has been linked to deficits in a variety of cognitive domains. Since the present study examined three cognitive domains (sustained attention and reaction time [RT]; visuospatial ability; and autobiographical memory), the following sections are limited to a discussion of these domains.

1.8.3.1 Visuospatial Function

'Visuospatial function' refers to the capacity to 'generate, retain, retrieve, and transform or manipulate mental models of a visual and spatial nature' (Lohman, 1979, p. 126). Visuospatial ability influences several cognitive functions, including spatial ability, spatial cognition, spatial perception, visual object processing and visual acuity (Chapman, Hagen, & Gallagher, 2016). Using these functions, people can estimate the distance between two objects, which is essential for daily functions such as driving or parking a car. Additionally, visuospatial skills are vital for imagining a place described by someone else. Researchers have also indicated that visuospatial functions play an important role in mathematics skills (Sella, Sader, Lolliot, &

Cohen Kadosh, 2016). Hence, these functions might be negatively affected by OSA through visuospatial dysfunction. Although few studies have examined the visuospatial function of OSA patients, the limited evidence indicates that visuospatial function is compromised. For example, a meta-analysis found strong evidence for a significant role of OSA in visuospatial memory deficits (Wallace & Bucks, 2013). Moreover, after adjusting for age, sex and education, OSA patients revealed impaired visuospatial ability compared with non-OSA patients (D'Rozario et al., 2018). Studies have reported notable improvements in visuospatial performance among OSA patients after CPAP treatment. For instance, one study found that OSA patients had poor visuospatial learning, but after CPAP treatment for 15 days, their performance had improved to normal levels (Ferini-Strambi et al., 2003). Similarly, after 3 months of CPAP compliance, OSA patients in one study showed a significant improvement in visuospatial memory (Aloia et al., 2003). A recent meta-analysis concluded that similar visuospatial deficits are not found in patients with chronic obstructive pulmonary disease or insomnia, and the reason for the unique impairment of visuospatial ability in OSA is unknown (Olaithe, Bucks, Hillman, & Eastwood, 2018).

The present study measured visuospatial function using the Austin maze (AM) (Milner, 1965). Early studies reported the AM to measure frontal lobe function and working memory (Darby & Walsh, 2005; Milner, 1965), but more recent studies have shown it to be insensitive to deficits in executive function and working memory. Instead, the AM is now considered to be a test of visuospatial function, which is affected by damage to the right medial temporal lobe (Hocking et al., 2013), a site known to be involved in visuospatial function (Milner, Johnsrude, & Crane, 1997). Early studies suggested that the first few trials on the AM are reliant on spatial ability in respect of orientation to the task, whereas last trials are based on visuospatial learning to consolidate memory for path details (Crowe et al., 1999). These authors tested a large cohort of healthy controls using a battery of neuropsychological tests to assess which cognitive

abilities were being measured by the AM. They reported a strong relationship between AM performance, visuospatial ability and visuospatial memory but did not find an association between AM performance and executive function or working memory tests, leading them to question the utility of the task for identifying frontal lobe dysfunction Crowe et al. (1999). Later, Stolwyk, Lee, McKay and Ponsford (2013) used a battery of cognitive tests to demonstrate that the AM is mainly linked to visuospatial ability and visuospatial memory and that no executive measures such as planning, working memory or error utilisation, contribute prominently to performance on the AM. Thus, the AM is now regarded as a test of visuospatial function.

1.8.3.2 Sustained Attention/Reaction Time

Deficits in attention and vigilance are a feature of OSA (Beebe, Groesz, Wells, Nichols, & McGee, 2003; Bucks, Olaithe, & Eastwood, 2013; Canessa et al., 2011; D'Rozario et al., 2018; Gagnon et al., 2014; Luz et al., 2016; Simões, Padilla, Bezerra, & Schmidt, 2018; Tanno et al., 2017). Research has indicated that individuals suffering from OSA have greater difficulty in sustaining attention than do their healthy counterparts (Luz et al., 2016), as evidenced by their slower RT (Ayalon, Ancolie-Israel & Drummond, et al., 2009; Luz et al., 2016) and rate of inaccuracy in cognitive testing (Mazza et al., 2005; Sforza, 2012). Additionally, the effects of OSA on attention have been reported to differ, depending on the type of attentional subdomain and performance (e.g. accuracy *v*. speed) being measured (Luz et al., 2016; Mazza et al., 2005; Sforza, 2012).

The present study used the psychomotor vigilance test (PVT), which examines sustained attention and RT (Basner & Dinges, 2011; Basner, Mollicone, & Dinges, 2011). Patients with moderate-to-severe OSA have been found to make more errors and have longer RTs on the PVT than healthy controls (Basner et al., 2011; Kim, Dinges, & Young, 2007). This is

consistent with reports that poor PVT performance is most evident in severe OSA (AHI ⩾30) (Arnardottir et al., 2016; Ye, Pien, Ratcliffe, & Weaver, 2009). Slow RTs have been linked to sleep deprivation and short sleep duration (Pack et al., 2006), while other studies have reported that nocturnal hypoxaemia is associated with poor PVT performance (Bedard, Montplaisir, Richer, & Malo, 1991; Tanno et al., 2017). A recent study of 743 OSA patients by Kainulainen et al. (2020) concluded that hypoxaemia, but not OSA severity (AHI) or sleep fragmentation, is significantly linked to an increased risk of impaired PVT performance. In terms of CPAP treatment, several studies have observed notable improvements in the vigilance measured by the PVT following 3 months of CPAP use (Bakker, Campbell, & Neill, 2010; Ye et al., 2009).

1.8.3.3 Autobiographical Memory (Episodic and Semantic Memories)

Autobiographical memory is described as memory for specific events in a person's life (Gregory, 2011) and is generally divided into two categories: personal semantic information and personal episodic information. Personal semantic information can be described as a sense of knowing or familiarity with one's self, including facts about birth, family or one's past. Personal episodic information includes specific events a person has experienced throughout their past and includes greater detail and specific experiences (Holland & Kensinger, 2010). Both categories of autobiographical memory significantly affect a person's sense of identity (Wilson & Ross, 2003). Typically, individuals with poor autobiographical memory describe their recollections in very general terms without providing specific details (e.g. dates, names, places). This is referred to as 'over-general' memory.

The literature on the association between OSA and autobiographical memory is relatively limited. However, several studies have found that OSA involves deficits in autobiographical memory. In one of the first studies, Mackinger and Svaldi (2004) proposed that autobiographical memory is sensitive to the cognitive dimensions of depression in OSA. In

support of Mackinger and Svaldi's findings, V. V. Lee et al. (2016) compared 21 patients with OSA and comorbid depression with 17 OSA patients without depression and 20 healthy controls. The study concluded that the patients with OSA had higher level of over-general recall compared with the control group, but depressive symptoms were not found to affect autobiographical memory. In a later study by the same group (Delhikar et al., 2019), 44 OSA patients were compared with 44 age-matched controls in terms of semantic and episodic memories; 44 OSA patients were also compared with 37 controls in terms of over-general memory recall. The study reported that OSA patients showed weak semantic recall of early adult life and more over-general autobiographical memories. In contrast to their earlier study, poor semantic recall was found to be strongly associated with depressive symptoms.

The neurological bases for these deficits in autobiographical memory are unclear. However, it seems relevant that the volume of the hippocampus is reduced in moderate-to-severe OSA compared with in healthy controls (Bucks et al., 2013; Lal, Strange, & Bachman, 2012; Owen, BenediktsdÓttir, Gislason, & Robinson, 2019). Since this region of the brain is involved in the consolidation and retrieval of memories, the reduced hippocampal volume in OSA might contribute to the impairments observed in autobiographical memory.

1.9 Potential Mechanisms of Cognitive Dysfunction in Obstructive Sleep Apnoea

Many studies have shown that OSA is associated with significant cognitive impairment and have speculated on the possible mechanisms contributing to the dysfunction. The two main factors that are believed to play a role are IH and sleep fragmentation; however other factors, such as depression and nocturnal SNS over-activation may also play a role. The following sections discuss the evidence implicating these factors.

1.9.1 Intermittent Hypoxia

It has been known for many decades that IH is an important contributor to the cognitive impairments observed in OSA (for a review, see Caporale et al., 2020). For example, Findley et al. (1986) reported that sleep apnoea with chronic hypoxia might involve more severe cognitive impairment than sleep apnoea without hypoxia. Naëgelé et al. (1995) found that IH is associated with deficits in psychomotor performance in OSA, while Bedard, Montplaisir, Malo, Richer and Rouleau (1993) showed that planning abilities and manual dexterity (psychomotor performance) are strongly associated with the severity of nocturnal hypoxia. In support of these findings, Hoth, Zimmerman, Meschede, Arnedt and Aloia (2013) highlighted that memory recall was poorer in a high hypoxia group than in a low hypoxia group. Moreover, a functional magnetic resonance imaging (fMRI) study Macey et al. (2008) indicated that IH in OSA causes brain structural changes that are linked to the limbic system, pons, frontal, temporal and parietal cortices. These structural changes are presumed to underpin cognitive impairment. However, Olaithe et al. (2015) found no relationship between IH using mean and lowest SpO2 and attention, long- and short-term memory or executive functions. These contrasting findings might be explained by the studies' different IH measures. Chapter 3 will extensively discuss and confirm the role of IH in cognitive dysfunction.

Some studies have independently examined the effects of continuous hypoxia on cognitive function among people who live at high altitude. For instance, de Aquino Lemos et al. (2012) confirmed that hypoxia was associated with deficits in attention, the visual component of working memory and processing speed among highlander people. However, since people who live at high altitude are more likely to experience sleep fragmentation and increased AHI (Latshang et al., 2013), the findings of de Aquino Lemos et al. (2012) may be confounded by sleep fragmentation, which can also induce cognitive impairment.

1.9.2 Sleep Fragmentation

Sleep fragmentation is thought to cause cognitive impairment in OSA patients through disruption of the sleep/wake cycle (Martin, Engleman, Deary, & Douglas, 1996; Otero, Figueredo, Riveros-Rivera, & Hidalgo, 2019). Experimental studies in healthy individuals have found that sleep fragmentation results in cognitive impairment. For instance, a group that was exposed to a high amount of sleep fragmentation showed poorer cognitive function compared with a group that did not experience sleep fragmentation (Ferri et al., 2010). In addition, in research using an animal model, M. Lee et al. (2016) noted memory deficits and attributed these to an impaired ability to cycle through all phases of sleep required for the memory consolidation process. In their review, Rauchs, Desgranges, Foret and Eustache (2005) confirmed that episodic and semantic memories are strengthened by deep sleep stages; OSA patients can reduce the duration of deep sleep, leading to deficits in autobiographical memory. One night of sleep fragmentation in healthy participants can impair sustained attention during the daytime (Martin et al., 1996). An fMRI study (Ayalon, Ancole-Israel, Aka, et al. 2009) found that OSA patients performing the go/no-go task had decreased brain activation relative to control participants, particularly in the prefrontal and parietal regions involved in attention. The study showed that a loss in attentive function in OSA patients was caused by sleepiness resulting from sleep fragmentation. These results indicate an independent role for sleep fragmentation in cognitive impairment in OSA, even when total sleep time is not reduced.

There is a solid body of evidence indicating that hypoxia and sleep fragmentation can induce cognitive impairment in OSA patients (Bucks et al., 2013; Canessa et al., 2011; Tamilarasan et al., 2019; Verstraeten, 2007). However, hypoxia and sleep fragmentation do not fully account for the cognitive impairment observed in OSA patients, suggesting that additional

factors may contribute to this impairment. Limited evidence, reviewed in the following sections, suggests that two other factors may also contribute to cognitive impairment in OSA.

1.9.3 Depressive Symptoms

As discussed in Section 1.9.2, depressive symptoms are very common in people with OSA. While it is likely that the nightly interruption to sleep and IH contribute to this depression, the severity of depressive symptoms is not closely linked to the severity of OSA (Bjorvatn, Rajakulendren, Lehmann, & Pallesen, 2018), and such symptoms only improve marginally following CPAP treatment (Zheng et al., 2019). Thus, it is possible that a component of the depressive symptoms is attributable to other factors.

Diminished concentration, increased indecisiveness and visuospatial dysfunction are prevalent among depressive patients without OSA (McIntyre et al., 2013). There is also a connection between memory and depression, with a lower specificity of autobiographical memory being associated with depression (Kleim & Ehlers, 2008). Although there have been few studies on OSA in regard to depressive symptoms and cognitive dysfunction, the literature suggests an association between autobiographical memory and depression (Mackinger & Svaldi, 2004). As noted above, Delhikar et al. (2019) found that autobiographical memory impairment in OSA patients is related to depressive symptoms. R. L. Cross et al. (2008) pointed out that OSA patients with depressive symptoms showed more neural injuries in several brain regions including, frontal cortices, temporal cortex, amygdala, and hippocampus than OSA patients without depressive symptoms. These observations suggest that depression may intensify the brain damage induced by OSA, as well as causing injury in different regions known to be associated with depression.

The findings reviewed above indicate a need for further investigations into the possibility that depressive symptoms contribute to cognitive dysfunction in OSA, independently of hypoxia and sleep fragmentation.

1.9.4 Nocturnal Sympathetic Nervous System Over-activity

Another factor that may contribute to cognitive dysfunction in OSA is over-activation of the SNS, which may also be related to hypoxia resulting from apnoea events (Sforza & Roche, 2016). SNS over-activity leads to increased BP, elevated stress hormone levels (cortisol) and elevated blood glucose levels. These factors can directly lead to brain injury and cognitive impairment. SNS over-activity has detrimental impacts on attention, memory and visuospatial processes, and is sometimes used as an indicator of probable cognitive impairment (Knight, Giuliano, Shank, Clarke, & Almeida, 2020). SNS over-activity, as measured by HRV, has been associated with white matter lesions in patients with cognitive impairment (Galluzzi et al., 2009). Poor visuospatial performance has been linked to HRV, after adjustment of demographic, clinical and behavioural confounding variables (Frewen et al., 2013). Acute hyperglycaemia (increased blood sugar level) is another outcome of SNS over-activity that has been associated with mild cognitive dysfunction (Cox et al., 2005), while clinical studies have found that elevated blood cortisol is associated with poorer overall cognitive functioning, as well as poorer episodic memory, spatial memory and processing speed (Ouanes & Popp, 2019). Only one study has investigated the association between nocturnal SNS overactivity and cognitive performance in OSA (Idiaquez et al., 2014). The study was conducted on 58 males, and SNS activity was measured by LF/HF ratio. The study did not find any associations between SNS activity and cognitive performance. These negative findings may be attributed to several weaknesses, such as including only male participants, which may lead to biased

results. Additionally, as co-founders, depression, age and smoking status are well known to have direct effects on cognitive performance, which was not controlled for in this study.

High BP is associated with disruption to the structure and functioning of the cerebral blood vessels (Pires, Dams Ramos, Matin, & Dorrance, 2013); the associated microbleeds can damage the brain's white matter, which plays a crucial role in cognitive functioning (Iadecola et al., 2016). Magnetic resonance imaging (MRI) studies have concluded that higher BP predicts more severe ischemic white matter lesions and lower brain tissue volume (Korf, White, Scheltens, & Launer, 2004; Strassburger et al., 1997; Wiseman, Saxby, Burton, Ford, & O'Brien, 2004), with similar effects on brain structure in both humans and animals. In free hypertensive rats, brain tissue volume and cortical thickness were found to be 11–25% lower than in control rats (Tajima et al., 1993). High BP can also lead to brain atrophy and brain structure change through stopping cerebral blood flow and compromising the integrity of blood-cerebrospinal fluid and the blood-brain barrier. These damages may curtail nutrient delivery to brain tissue, resulting in the death of cells (Al-Sarraf & Philip, 2003; Gesztelyi et al., 1993). A higher resting BP is associated with a higher risk of cognitive decline in people without dementia or stroke (Forte et al., 2019).

All of the indices of SNS over-activity have been shown to be associated with cognitive impairment in people without OSA, yet very few studies have investigated the association between nocturnal over-activity of the SNS and cognitive dysfunction in OSA. One study examined the role of nocturnal over-activity of the SNS in cognitive impairment in OSA and found no relationship between the two factors (Idiaquez, Santos, Santin, Del Rio, & Iturriaga, 2014). However, that study included only males and did not control for confounding variables.

SNS over-activity also involves elevated BP. Cognitive impairment associated with OSA may result from overnight spikes in BP and prolonged daytime hypertension. A review Mansukhani,

Kolla and Somers (2019) concluded that systemic hypertension is strongly associated with cognitive dysfunction in OSA patients. Supporting the idea that elevated BP in OSA patients may cause brain pathology, Borges et al. (2013) reported that OSA patients without hypertension show no cognitive decline. However, as there is no direct evidence that abnormal nocturnal BP plays a role in cognitive impairment in OSA, further research on this issue is needed.

1.10 Obstructive Sleep Apnoea in Saudi Arabia

The present study examines a cohort of patients recruited through a sleep laboratory at a hospital in Saudi Arabia. Saudis have an elevated risk of OSA due to high obesity rates. Saudi Arabia has been classified as the world's 'fifteenth most obese country, with an overall obesity rate of 33.7%' (Alqarni, 2016, p. 3). This trend in Saudi Arabia may be the result of economic growth and the adoption of a more Westernised lifestyle (Vats, Mahboub, Al Hariri, Al Zaabi, & Vats, 2016). Increased adoption of Western dietary and lifestyle habits, coupled with weather conditions that encourage a sedentary lifestyle, and increased urbanisation, may facilitate the increasing prevalence of obesity, along with the resulting increase in metabolic syndrome and OSA (Vats et al., 2016).

A cross-sectional study by Alshehri et al. (2019) explored the association between obesity and OSA prevalence in patients referred to a sleep centre in Saudi Arabia. The participants were 803 patients who underwent PSG testing between 2012 and 2017. More were male (56.5%), they had a mean age of 45.9 years and 70.0% were obese. The study found that 74.8% of the participants had OSA; males had significantly higher AHIs and a higher prevalence of OSA than their female counterparts. These findings suggest that obesity exacerbates OSA severity among Saudis.

Wali et al. (2017) conducted a study of 2682 school employees in Saudi Arabia, among 346 individuals selected for PSG studies the study found a significantly higher prevalence of OSA in male (4.0%) than female (1.8%) participants. Further, males aged 50 years and older had a higher prevalence of OSA than their female counterparts. Finally, a BMI ≥30 kg/m^2 (obese) and a history of hypertension were identified as significant risk factors for OSA.

A survey of Saudi medical students' knowledge of OSA revealed that they had little knowledge of this condition, implying that it receives little attention in medical school curricula (Almohaya et al., 2013). Another study found that the general population in Saudi Arabia lacked knowledge of OSA. Participants were surveyed on OSA symptoms, risk factors, associated complications and methods of treatment; 80.7% had a low level of knowledge about OSA (Almutairi, 2019). In terms of OSA characteristics in the Saudi regions, no prominent differences between the studies' findings exist (Wali et al.; Alshehri et al., 2019; Alruwaili et al., 2015; Almutairi, 201). Nonetheless, conducting a systematic review is required to confirm OSA characteristics in the Saudi regions.

1.10.1 Pre-screening Tools for Obstructive Sleep Apnoea in Saudi Arabia

As discussed in Section 1.4, several questionnaires can be used to pre-screen patients for possible OSA (Prasad et al., 2017), including the BQ, SBQ, ESS and WSQ (Chiu et al., 2017; Hamilton & Chai-Coetzer, 2019; Prasad et al., 2017). Systematic reviews and meta-analysis studies have concluded that the SBQ has the highest methodological quality among these pre-screening questionnaires (Amra, Rahmati, Soltaninejad, & Feizi, 2018; Chiu et al., 2017; Nagappa et al., 2015).

As stated earlier, the SBQ is sensitive for detecting mild, moderate and severe OSA (Amra et al., 2018), and is easy to administer (Nagappa et al., 2015). The SBQ has been translated into Arabic; this version was reported to have high sensitivity but low specificity (BaHammam et

al., 2015), consistent with previous studies of other versions of the SBQ. The Arabic SBQ has been used in only one other study (Alharthi et al., 2018), which did not comment on the utility of SBQ for predicting OSA severity (Table 1.6). As further studies use the Arabic SBQ, we may learn more about the utility of this version as a screening tool for OSA.

Table 1.6 Studies that have used OSA screening tools that had been translated into Arabic.

Author and year	Screening questionnaire(s) used
(A. N. Ahmad, McLeod, Al Zahrani, & Al Zahrani, 2019)	BQ and ESS
(Alharthi et al., 2018)	BQ, SBQ and ESS
(Wali et al., 2017)	WSQ
(BaHammam et al., 2015)	SBQ
(Bahammam, Al-Rajeh, Al-Ibrahim, Arafah, & Sharif, 2009)	BQ
(Alotair & Bahammam, 2008)	WSQ and ESS

BQ: Berlin questionnaire; ESS: Epworth sleepiness scale; SBQ: STOP-Bang questionnaire; WSQ: Wisconsin Sleep questionnaire.

1.11 Summary

OSA is typically diagnosed by using a combination of screening tools and confirmed by diagnostic procedures such as PSG. The main risk factors for OSA are age, sex, BMI, smoking and comorbidities (e.g. T2D). OSA is characterised by IH and sleep fragmentation during sleep, and diurnally by EDS, depressive symptoms and cognitive dysfunction. It has been documented that OSA affects autobiographical memory, attention/vigilance and visuospatial ability. Research has focussed on hypoxia and sleep fragmentation as the causes of these cognitive impairments, but it is evident that these two factors cannot fully account for the extent of impairment observed.

Only a very small number of studies have examined the associations between depressive symptoms and cognitive impairment (only autobiographical memory) in OSA patients, and it is not yet known whether depressive symptoms have independent effects on other aspects of

cognitive function. Further, SNS over-activation is another feature of OSA that in healthy people has been linked to cognitive dysfunction, but it is not yet known whether nocturnal SNS over-activation contributes to the cognitive impairment in OSA. There is a need to understand the extent to which hypoxia, sleep fragmentation, depressive symptoms and nocturnal SNS over-activation contribute to cognitive impairment in OSA, either as independent factors or in combination with each other.

1.12 Thesis Aims and Hypotheses

1.12.1 Aims

Noting the above research gaps, this thesis has the following aims:

1. to characterise the study sample and explore the usefulness of the Arabic version of the SBQ as a screening tool for OSA (Chapter 2);
2. to examine the independent effects of hypoxia, sleep fragmentation and depression on cognitive dysfunction in OSA (Chapter 3);
3. to determine whether HRV, PWA and stress response biomarkers are associated with cognitive dysfunction in OSA (Chapter 4);
4. to determine whether nocturnal fluctuations in BP are associated with cognitive dysfunction in OSA (Chapter 5).

Aim 1 was proposed in order to establish the similarity and differences of the study sample to other published samples, so that the findings of the study could be generalised to other populations. Aims (2-4) were proposed in order to investigate the role that these factors play in the cognitive impairments seen in OSA.

These aims, and the research questions investigated in this thesis, are summarised in Figure 1.8.

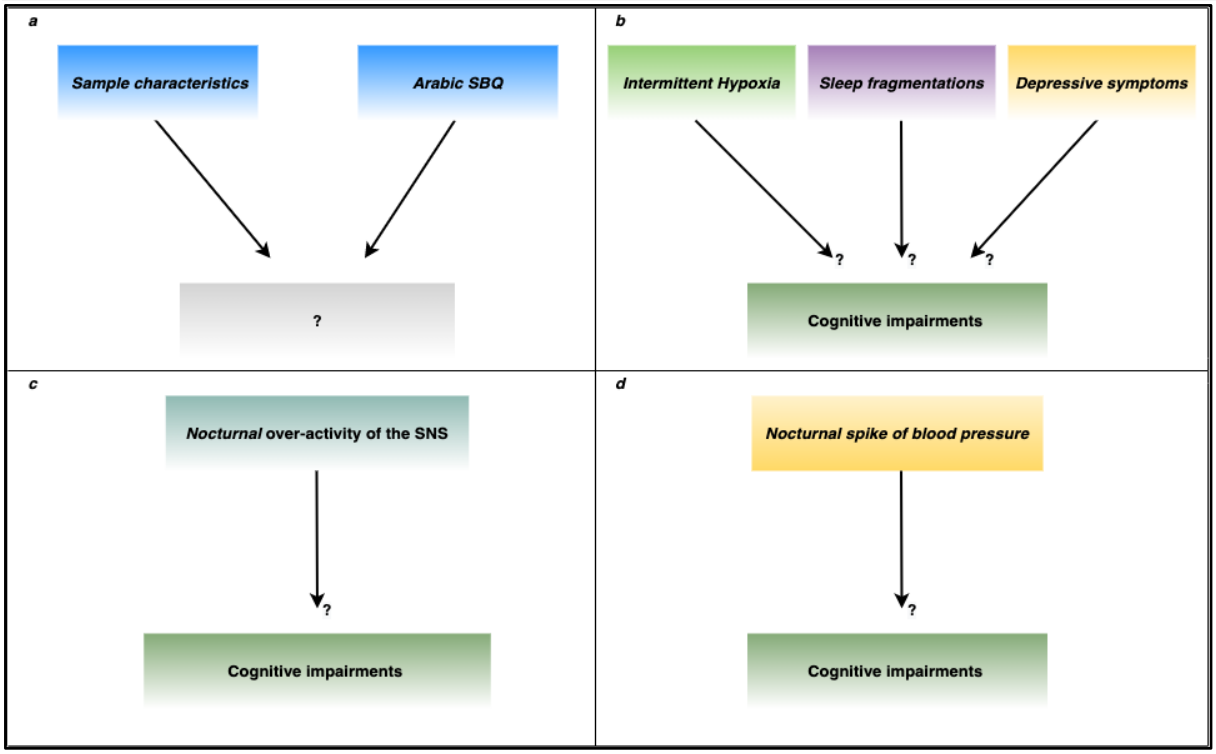

Figure 1.8 Schematic illustration of the research aims of the thesis. Each of the four data chapters (Chapters 2–5) is associated with a different aim (a–d). SBQ: *STOP-Bang questionnaire.*

1.12.2 Thesis Hypotheses

It was hypothesised that patients referred to a sleep laboratory in Saudi Arabia would have the same OSA characteristics and demographic features as reported in previous studies, and that an Arabic version of the SBQ would display similar utility to that reported previously. Further, it hypothesised that depressive symptoms and SNS over-activity would influence cognitive function in OSA independently of IH and sleep fragmentation.

It was anticipated that this research would provide new insights into the factors that lead to cognitive impairment in OSA and would indicate which cognitive functions are likely to be vulnerable to IH, sleep fragmentation, depressive symptoms and SNS over-activity. It is hoped that the findings of the thesis will assist clinicians and researchers in developing more effective interventions for improving cognitive outcomes in patients with OSA.

1.12.3 The Sample Recruitments Summary

A sample size calculation was conducted using G*Power 3 software (Faul et al., 2007). A total of 56 subjects were required to test the null hypothesis for medium effect size (r = 0.30) and 0.80 power (Cohen, 1992). This minimum sample size was increased to provide extra power for multiple comparisons. A total of 112 participants were recruited. However, 22 participants did not meet the inclusion criteria. Thus, the total number of the participants included in the study were 90 particpants. Seventy-six participants were diagnosed with OSA and 14 participants with non-OSA (the main complaint was insomnia). Chapters 2 and 3 included the complete number of the participants (n=90), but Chapter 4 (n= 78) and Chapter 5 (n= 75) included fewer number of the total participants due to incomplete data of the SNS and BP indices (Figure 1.9).

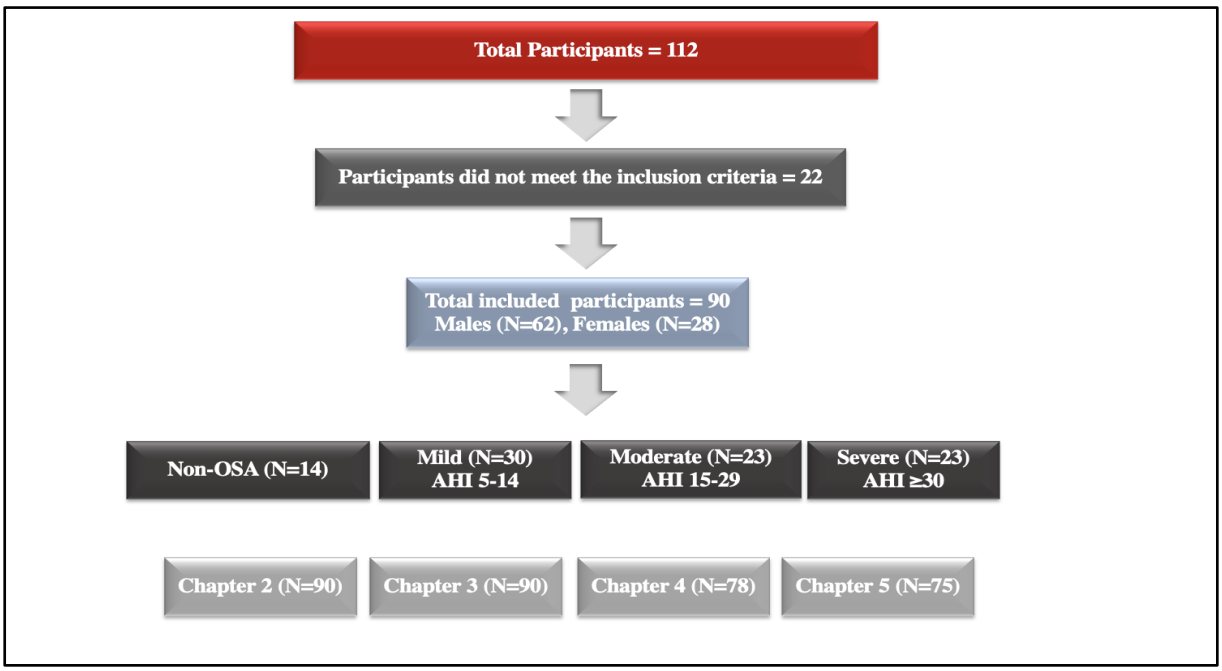

Figure 1.5 Recruitment flow chart for the study sample. OSA: Obstructive Sleep Apnoea; AHI: Apnoea–Hypopnea Index.

Chapter 2: Risk Factors and Characteristics of Obstructive Sleep Apnoea Patients Referred for an Overnight Sleep Study in Saudi Arabia: Utility of the *STOP-Bang Questionnaire* as a Screening Tool

Abstract

OSA is characterised by recurrent episodes of partial or complete cessation of breathing during sleep and increased breathing effort. This study examined a cohort of 90 patients (age18-65 years) who underwent overnight PSG studies at a major sleep laboratory in Saudi Arabia. The study aimed to identify the main characteristics of OSA in this cohort and to assess the utility of the SBQ as a predictor of the severity of this condition. PSG indicated that 14 patients did not have OSA, 30 had mild OSA, 23 had moderate OSA and 23 had severe OSA. Demographic factors associated with increasing severity of OSA were older age (mean age = 42.0 years) and higher BMI (mean BMI = 33.4 kg/m^2). Being a current smoker was not correlated with the severity of OSA. Among patients with OSA, depressive symptoms were present in 74%, EDS was present in 50%, and impaired glucose tolerance (IGT) or T2D in 60%. Multiple linear regressions revealed that EDS and IGT were significantly linked to OSA severity. SBQ scores were strongly associated with the AHI ($R^2 = 0.44$) and predicted the presence of OSA with high sensitivity (90%) and low specificity (54%). Receiver operating characteristic (ROC) curve analysis revealed that the item of loud snoring provided superior detection of mild OSA (AHI >5) while the item of observed apnoeas provided the best specificity for moderate and severe OSA (AHI >15). In conclusion, the risk factors for OSA in this Saudi population are similar to those reported for other populations, and the Arabic version of the SBQ has similar response properties to the English version.

2.1 Introduction

OSA is characterised by recurrent episodes of partial or complete cessation and/or attenuation of breathing during sleep, despite efforts to breathe normally (Epstein et al., 2009). Cessation of breathing usually lasts for at least 10 seconds, is interspersed with regular breathing and involves either partial (hypopnoea) or complete (apnoea) airway obstruction. The AHI classifies the severity of OSA as the average number of apnoea/hypopnoea episodes per hour of sleep. Mild OSA is defined as more than 5 but fewer than 15 episodes per hour of sleep, moderate OSA as more than 15 but fewer than 30 episodes per hour, and severe OSA as 30 or more episodes per hour (McNicholas, 2018). Symptoms of OSA include loud snoring, waking at night with choking, waking in the morning with a dry throat and/or headache, and EDS (Spicuzza, Caruso, & Di Maria, 2015). Risk factors for OSA include sex, age, weight and specific morphological craniofacial features (Punjabi, 2008). OSA is associated with serious health complications, including cerebrovascular and cardiovascular issues, as well as an increased risk of motor vehicle and work-related accidents (Garbarino, Guglielmi, Sanna, Mancardi, & Magnavita, 2016; Mozafari et al., 2014). CPAP therapy is considered the gold standard for the management of OSA (Ballester et al., 1999). This treatment significantly reduces the risk of accidents and injuries related to sleepiness, utilisation of health care services and the negative economic impact of OSA (Knauert, Naik, Gillespie, & Kryger, 2015).

OSA is a common disorder both in the general population and in specific sub-groups with chronic diseases (Franklin & Lindberg, 2015). The reported global prevalence of OSA in middle-aged individuals ranges from 9% to 38% (Senaratna et al., 2017). Obesity, as indicated by a high BMI, is a risk factor for OSA (Schwartz et al., 2008) and OSA is prevalent in developed countries due to rising obesity levels, and in populations where genetic factors

render people more susceptible to significant weight gain (Casale et al., 2009; Woods, Usher, & Maguire, 2015).

Most research on OSA has been conducted in Western countries, particularly the United States (US). There has been very little cross-cultural research. In affluent Middle Eastern countries, there is a high risk of OSA because of increasing obesity rates. For example, 35% of Saudi Arabians are estimated to be obese; thus, the expected risk of OSA is greatly increased in this population (Al-Nozha et al., 2005). However, 80% of Saudis with OSA are not aware of this condition or its effects on their health (Almutairi, 2019). Relatively few studies have been conducted on OSA in Middle Eastern countries, but the limited evidence indicates that risk factors in Middle Eastern countries are similar to those in Western countries. For example, a recent study using PSG identified BMI, age, male sex and hypertension as risk factors for OSA in the Saudi population, with the prevalence of OSA being similar to that observed in Western countries (Wali et al., 2017). Additionally, depression, high blood sugar and EDS are prevalent among OSA patients in Saudi Arabia (Jamal, Eskandrani and Alyahya, 2018). However, a need exists for more studies that confirm the characteristics and risk factors of OSA among Saudi Arabian OSA patients. On the other hand, studies confirmed that although SBQ shows high sensitivity, it has low specificity (Vana, Silva and Goldberg, 2013; Chung et al., 2016; BaHammam et al., 2015), suggesting that some SBQ items might influence the specificity levels.

The present study aimed to extend the literature by further investigating risk factors and the characteristics of patients referred to a sleep laboratory with suspected OSA in Saudi Arabia. The study also makes a methodological contribution by re-examining the sensitivity of and specificity of the Arabic version of the SBQ as a screen for OSA (BaHammam et al., 2015).

2.2 Methods

2.2.1 Study Participants

The study participants were patients aged 18–65 years who had been referred for nocturnal diagnostic PSG studies at the Sleep Medicine and Research Centre, King Abdulaziz University Hospital, Jeddah, Saudi Arabia. The following exclusion criteria were applied: 1) current use of CPAP therapy; 2) a neurodegenerative disease (e.g. Alzheimer's disease, Parkinson's disease); and/or 3) regularly sleeping less than 2 hours per night (the AASM recommends minimum sleep duration of 2 hours) (Epstein et al., 2009).

The study was approved by the Royal Melbourne Institute of Technology University Human Research Ethics Committee (ethics reference number: HREC 21459) and the King Abdulaziz University Hospital Human Research Ethics Committee (ethics reference number: 395-18). Informed consent was obtained from all participants after they had received an explanation of the nature of the study at the Sleep Medicine and Research Centre.

2.2.2 Procedure and Measurements

A nurse measured the height, weight and resting BP (systolic and diastolic) of each participant following admission to the sleep laboratory. Participants then completed a series of questionnaires designed to collect demographic information: likely OSA severity (SBQ), information about daytime sleepiness (ESS) and depressive symptoms (Depression, Anxiety, Stress Scale-21 [DASS-21]). Participants then underwent a nocturnal PSG study and provided first morning urine cortisol and blood serum cortisol samples.

2.2.3 Questionnaires

2.2.3.1 STOP-Bang Questionnaire *(Arabic version) (BaHammam et al., 2015; Chung et al., 2008)*

The SBQ is an eight-item, self-administered questionnaire that requires a 'yes' (1 score) or 'no' (0 score) response to each item. The items are snoring, tiredness, observation of breathing cessation during sleep, diagnosis of high BP, BMI >35 kg/m^2, neck circumference >40 cm, age >50 years and sex. The SBQ is scored by summing the numbers for each item, the minimum score is 0 and maximum is 8. with total scores of 5–8 indicating a high risk of OSA, 3–4 points indicating intermediate risk and 0–2 indicating low risk (Chung, Abdullah, & Liao, 2016).

2.2.3.2 The Epworth Sleepiness Scale *(Arabic version) (Ahmed et al., 2014; Johns, 1991)*

This scale assesses daytime sleepiness and is frequently used with OSA patients. The scale consists of eight items, each rated from 0 to 3, with higher numbers indicating a higher chance of dozing. Scores on these eight items are summed to give an overall score. The minimum score is 0 and maximum is 24, higher scores indicate greater levels of sleepiness; scores of less than 11 indicate little or no daytime sleepiness; scores of 11–14 indicate mild daytime sleepiness; scores of 15–17 moderate daytime sleepiness; and scores greater than 17 indicate severe daytime sleepiness.

2.2.3.3 Depression, Anxiety, Stress Scale-21 (*Arabic version) (Ali et al., 2017; Henry & Crawford, 2005)*

This 21-item questionnaire is designed to measure the magnitude of three negative emotional states, one of which is depression. The DASS depression subscale captures reported low mood, motivation and self-esteem. Scores of 0–9 indicate the presence of normal, mild depressive symptoms is ranged between 10-13, 14–20 indicates moderate depression, more than 21-27

indicates severe depression and scores of 28 or more correspond to extremely serious depression. Research has identified significant correlations between the DASS subscales and Beck depression and anxiety inventories, providing evidence for convergent validity (Lovibond & Lovibond, 1995).

2.2.3.4 Polysomnography Measures

The study utilised overnight PSG (SOMNO Medics Plus) to assess sleep duration, sleep quality, breathing and other sleep-related characteristics. In this study, most of the PSG studies were conducted in the sleep laboratory. However, 15 home PSG studies were also performed, using the same devices and procedures as in the laboratory to ensure consistency across settings. Home studies were usually done because of patient-related issues in attending the laboratory (e.g. distance, transport and mobility issues). A sleep technician applied the PSG sensors 30 minutes before sleep time. PSG consisted of continuous recordings from surface leads for EEG to record sleep stages (NREM sleep 1, NREM sleep 2, NREM sleep 3 and REM sleep) and arousal index, electrooculography (EOG), electromyography (EMG) (from muscles in the submental space and the tibialis anterior muscles bilaterally) and ECG. A thermocouple device measured nasal pressure and oral airflow; chest and abdominal impedance belts measured respiratory muscle effort; a pulse oximeter assessed blood oxygen saturation (SaO_2) and pulse rate; a tracheal microphone measured snoring; and body position sensors measured sleep position.

For technical reasons, there was a loss of some PSG data, and 15 study participants repeated the procedure. There was no difference between this group and the other participants who did not repeat the procedures.

2.2.4 Hypertension

The presence of systemic hypertension was estimated from the resting BP using the standard method (digital sphygmomanometer, OMRON, Kyoto, Japan). Hypertension was defined as SBP >140 mmHg and/or DBP >90 mmHg (Gabb et al., 2016).

2.2.4.1 Impaired Glucose Tolerance and Type 2 Diabetes

IGT and T2D were measured from the first-morning blood glucose sample, taken from a median cubital vein in all patients between 5:00 a.m. and 6:00 a.m. The samples were stored for no longer than 2 hours at 2–8ºC prior to assay. IGT was defined as 5.5–6.9 mmol/dL, and T2D was diagnosed at ≥ 7.0 mmol/dL (Güemes, Rahman, & Hussain, 2016).

2.2.5 Analysis

2.2.5.1 Body Mass Index Calculations

BMI calculations were based on the international standard of dividing weight in kilograms by height in metres squared (Nuttall, 2015).

2.2.5.2 Polysomnography Recordings

PSG recordings were scored manually using a validated protocol, and identification of abnormal breathing events during sleep was based on the recommendations of the AASM (Berry, Brooks, et al., 2012; Berry, Budhiraja, et al., 2012). Breathing abnormalities included a decrease in airflow ≥90% from baseline for ≥10 seconds (apnoea); a reduction in airflow ≥30% of the pre-event baseline using nasal pressure; and a decrease in oxygen saturation ≥3%, followed by either oxygen desaturation or electroencephalographic arousal (hypopnoea) despite the persistent effort of the chest and abdominal muscles to overcome the obstruction. The severity of OSA was estimated from the AHI where non-OSA = 0–4 AHI, mild = 5–14

AHI, moderate = 14–29 AHI, and severe ≥30 AHI. The degree of oxygen desaturation was measured by the ODI, while the degree of sleep fragmentation was based on the number of apnoeic events that resulted in an arousal from sleep (Arousal Index). The measurement of sleep stages included the duration of NREM sleep stages N1, N2 and N3 and the length of the REM sleep stage. Three PSG technicians verified all PSG scores to ensure the consistency of scoring, and randomly selected and scored cases to confirm inter-observer reliability and accuracy.

2.2.5.3 Specimen Analysis

The serum glucose content was analysed using the Dimension Vista® 500 system, and the sample volume was 1.2 µL. The µg/dL units were converted to mmol/L to enhance readability. To increase the reliability of the data, the same biochemist analysed glucose levels in a single laboratory. The biochemist was blind to the OSA severity of the participants.

2.2.5.4 Statistical Analysis

Statistical analysis was conducted with the IBM Statistical Package for the Social Sciences (SPSS, version 26). Data are shown as mean and standard deviation (*SD*) for continuous variables and as frequencies and percentages for categorical variables. Student's t-test analysis determined significant differences between sex groups based on demographic variables and PSG variables. Between-group comparisons of categorical data were made using Pearson's chi-square and Mann–Whitney tests. Linear simple regressions were performed to determine associations between SBQ score and AHI, ODI and Arousal Index. ROC curves were used to assess the predictive power of the SBQ to detect cases of mild, moderate and severe OSA (based on AHI). The area under the curve (AUC) was calculated for each of the three cut-off points and was used to assess the predictive power of the model, with an area of 1.0 indicating perfect agreement and an area of 0.5 indicating no agreement. The calculation of the sensitivity,

specificity, positive predictive values (PPVs), negative predictive values (NPVs), and positive and negative likelihood ratios (LRs) were conducted for the same cut-off values of the AHI. Generally, the absence of disease can be detected when the likelihood ratio is <1, the presence of disease can be demonstrated in a likelihood ratio >1. LRs <0.1 and >10 provides strong evidence to rule out or rule in diagnoses, respectively. A multiple regression analysis was conducted to: 1) identify associations between AHI and the demographic variables; and 2) a binary logistic regressions analysis was used to determine which AHI and demographic variables are associated with depressive symptoms, EDS, IGT and T2D, after controlling for age, BMI and smoking status. The statistical significance is reported for models that had $p < .05$ after the false discovery rate (FDR) (Benjamini & Hochberg, 1995) had been applied to adjust for family-wise error rate (Type 1 error) arising from multiple comparisons. In addition, the only models reported are those that showed no multicollinearity, as assumed with a variance inflation factor (VIF) of <2.0.

2.3 Results

Among 100 patients who presented consecutively to the Sleep Medicine and Research Centre, 90 met the study inclusion criteria. The mean participant age was 42.0 years (*SD* = 12.0 years), mean BMI was 33.4 kg/m^2 (*SD* = 9.4 kg/m^2) and 69% of participants were male. PSG showed that 14 of the 90 participants did not have OSA, 30 had mild OSA, 23 had moderate OSA and 23 had severe OSA. Since 8 of the 90 participants did not answer the SBQ completely, the SBQ data were based on 82 participants (68% male).

Table 2.1 summarises the demographic variables and smoking history, stratified by sex. There was no significant difference in their mean age. Females had a significantly higher BMI and were significantly less likely to smoke than males. OSA (as measured by the AHI) was significantly more severe in males than in females. Correspondingly, the ODI and Arousal

Index were significantly higher in males than in females. There were no significant sex differences in the time durations percentage of sleep stages.

Table 2.2 summarises the prevalence of depressive symptoms, EDS, resting hypertension, T2D and IGT in patients with OSA. DASS-21 data showed that 20 (26%) of the 76 OSA patients did not have depressive symptoms, 8 had mild symptoms (11%), 13 had moderate symptoms (17%) and 35 had severe depressive symptoms (46%). Fifty % reported EDS and 60% had IGT or T2D, yet no participants met the criteria for resting hypertension.

Table 2.1 Comparison of demographic, and sleep-related variables and smoking status between the sexes.

	All participants		**Males**		**Females**			
Variable	***M (SD)***	***n***	***M (SD)***	***n***	***M (SD)***	***n***	***t***	***p-value***
Age, years	42.1 (12.7)	90	40.8 (12.8)	62	44.7 (12.4)	28	-1.35	.10
Body Mass Index	33.3 (9.4)	90	31.6 (8.0)	62	37.0 (11.3)	28	-2.59	**.01**
Apnoea–Hypopnoea Index	21.6 (20.4)	90	25.1 (1.1)	62	13.8 (2.4)	28	2.48	**.01**
ODI/h	20.2 (22.3)	90	23.1 (24.1)	62	12.8 (13.2)	28	-2.183	**.03**
Arousal Index	11.2 (12.8)	90	13.1 (14.4)	62	7.2 (7.1)	28	-2.06	**.04**
N1 sleep time duration (%)	13.7(9.6)	90	14.7 (10.6)	62	11.6 (6.7)	28	-1.37	.17
N2 sleep time duration (%)	51.4 (13.3)	90	51.2 (12.1)	62	20.4 (14.4)	28	-0.26	.79
N3 sleep time duration (%)	20.9 (12.8)	90	21.2 (14.4)	62	20.3 (8.3)	28	-0.28	.76
REM sleep time duration (%)	12.4 (7.7)	90	12.2 (7.3)	62	12.9 (8.6)	28	0.25	.69
Current smoker (%)[a]	22 (24%)	90	21 (34%)	62	1 (6%)	28	-	**.002**

a: Pearson's chi-square test analysis; *SD*: standard deviation; ODI/h: oxygen desaturation index per hour; N1: sleep stage 1; N2: sleep stage 2; N3: sleep stage 3; REM: rapid eye movement sleep stage.

Table 2.2 The prevalence rate of depressive symptoms, daytime sleepiness, hypertension, type 2 diabetes and impaired glucose tolerance among OSA patients (≥ 5 AHI).

Variable	*N*	Diagnostic cut-off point	*Number (%)*
Depressive symptoms	76	>4 scores[a]	57 (74)
Excessive daytime sleepiness	76	>10 scores[b]	38 (50)
Resting hypertension	72	Systolic >140 and diastolic >90 mmHg[c]	0 (0)
Impaired glucose tolerance	76	5.5–6.9 mmol/L[d]	33 (43)
Type 2 diabetes	76	≥7.0 mmol/L[d]	13 (17)

AHI; Apnoea–Hypopnea Index; [a]: (Lovibond & Lovibond, 1995); [b]: (Johns, 1991); c: (Gabb et al., 2016); d: (Pagana et al., 2003).

Table 2.3 shows the results from the multiple linear regression analysis. Accordingly, the results revealed that EDS and IGT were significantly linked to OSA severity.

Table 2.3 Results of the binary logistic regressions analysis for associations between OSA severity (AHI) and depressive symptoms, excessive daytime sleepiness, impaired glucose tolerance and type 2 diabetes after controlling for age, Body Mass Index and smoking status, and applying the FDR multiple comparison adjustment.

Dependent variable	Predictor	*B*	*SE*	*p-value*
Depressive symptoms				
	AHI	0.05	0.06	.42
	Age (years)	0.09	0.09	.33
	Body Mass Index	0.02	0.13	.87
	Current smoker	3.73	2.48	.14
Excessive daytime sleepiness				
	AHI	0.11	0.03	**<.01**
	Age (years)	0.09	0.05	.07
	Body Mass Index	0.01	0.07	.87
	Current smoker	1.69	1.46	.25
Impaired glucose tolerance				
	AHI	0.00	0.00	**.01**
	Age (years)	0.00	0.00	.10
	Body Mass Index	0.01	0.00	**.02**
	Current smoker	0.09	0.11	.37
Type 2 diabetes				
	AHI	0.00	0.00	.07
	Age (years)	0.00	0.00	.98
	Body Mass Index	0.00	0.00	.25
	Current smoker	0.12	0.09	.18

AHI: apnoea–hypopnoea index; *B* = unstandardised regression coefficient; *SE* = standard error.

Table 2.4 summarises the results from multiple linear regression analyses that examined associations between demographic variables, smoking history and OSA severity (based on AHI). The results indicated that a significant amount of variation in AHI scores was accounted for by the predictor variables (F (3,90) = 6.26, p = .001). Age and BMI were significantly associated with OSA severity, whereas current smoking was not.

Table 2.4 Results of the multiple regression analysis for associations between OSA severity (AHI) and age, Body Mass Index and smoking status.

Variables	R^2	p_{model}	*SE*	*β*	*sr*	*p-value*
	0.27	**<.01**				
Age (years)			0.17	0.33	0.30	**<.01**
Body Mass Index			0.22	0.27	9.26	**<.01**
Current smoker			4.81	0.09	0.07	.20

R^2 = models' multiple correlations; *SE* = standard error; *β* = standardised regression coefficient; *sr* = semi-partial correlation.

The second aim of this study was to determine the extent to which responses to the Arabic version of the SBQ predicted the severity of OSA. Based on the AHI, only 14 (15.6%) of the participants were classified as having no OSA. The remaining 33.3%, 25.6% and 25.6% had mild, moderate and severe apnoea, respectively. Table 2.5 shows that, based on the SBQ score, 14 (17.1%) patients were classified as having a low risk of OSA while the remaining 45.1% and 37.8% were at intermediate and high risk of OSA, respectively.

Table 2.5 Descriptive statistics for the categorical results obtained from the Apnoea–Hypopnoea Index and *STOP-Bang questionnaire*.

Category	*N (%)*
AHI category:	90
No OSA	14 (15.6%)
Mild OSA	30 (33.3%)
Moderate OSA	23 (25.6%)
Severe OSA	23 (25.6%)
SBQ category:	82
Low	14 (17.1%)
Intermediate	37 (45.1%)
High	31 (37.8%)

AHI: apnoea–hypopnoea index; OSA: obstructive sleep apnoea; SBQ: STOP-Bang questionnaire.

A SBQ score of 0–2 predicts a low risk of OSA, a score of 3–4 predicts a moderate risk, and a score of ≥5 predicts a high risk (Chung et al., 2016). Each participant's score on the SBQ was

compared with their PSG results (AHI, ODI and Arousal Index) to assess the predictive value of the SBQ (Figure 2.1). Linear regression analysis showed that SBQ scores were correlated with AHI scores (R^2 = 0.44; Figure 2.1a), ODI scores (R^2 = 0.42; Figure 2.1b) and Arousal Index (R^2 = 0.37; Figure 2.1c).

ROC curve analysis using an AHI cut-off value of 5 indicated that the SBQ has excellent sensitivity (90%), and PPVs and NPVs of 91% and 50%, respectively. The cut-off value of 15 for AHI revealed outstanding sensitivity (98%), and PPVs and NPVs of 59% and 93%, respectively. Validation against a cut-off value of 30 revealed outstanding sensitivity of 100% and PPVs and NPVs of 31% and 100%, respectively (Table 2.6, Figure 2.2). Despite the high sensitivity of the SBQ, the specificity was very low, and the resultant AUC ranged from 61.5% (equating to poor discrimination) and 71.9% (equating to acceptable discrimination) (Mandrekar, 2010) (Table 2.6, Figure 2.2).

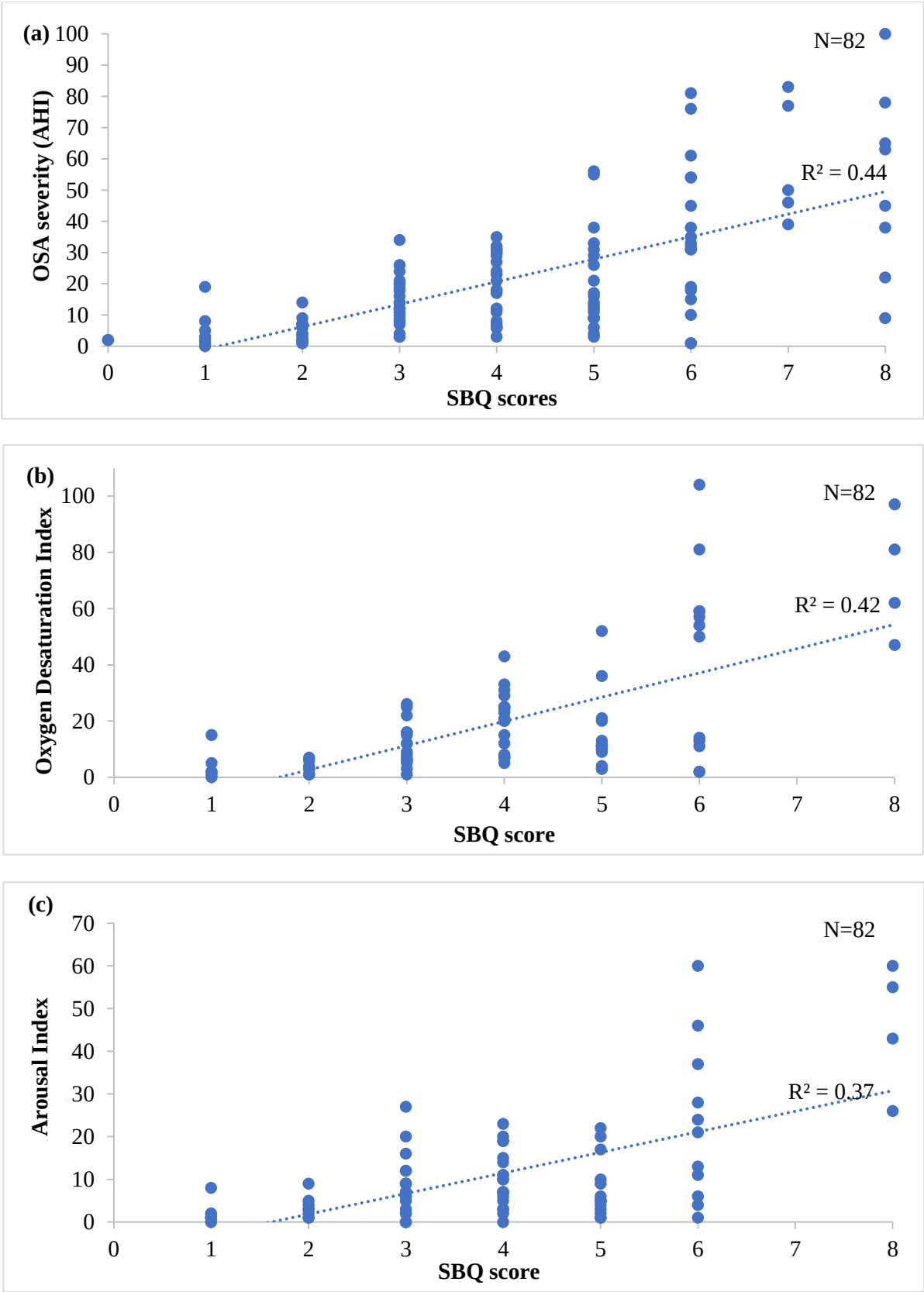

Figure 2.1 The relationship between SBQ scores and OSA severity (AHI) (a), Oxygen Desaturation Index (b), and Arousal Index (c). SBQ: STOP-Bang questionnaire; AHI: apnoea–hypopnoea index.

Table 2.6 Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio for the *STOP-Bang questionnaire* score (< 3 *v.* ≥ 3).

AHI	AUC	Sensitivity	Specificity	PPV	NPV	PLR	NLR
≥5	71.9%	90%	54%	91%	50%	1.95	0.19
≥15	64.6%	98%	32%	59%	93%	1.43	0.08
≥30	61.5%	100%	23%	31%	100%	1.30	0.00

AHI: apnoea–hypopnoea index; AUC: area under the curve; PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio.

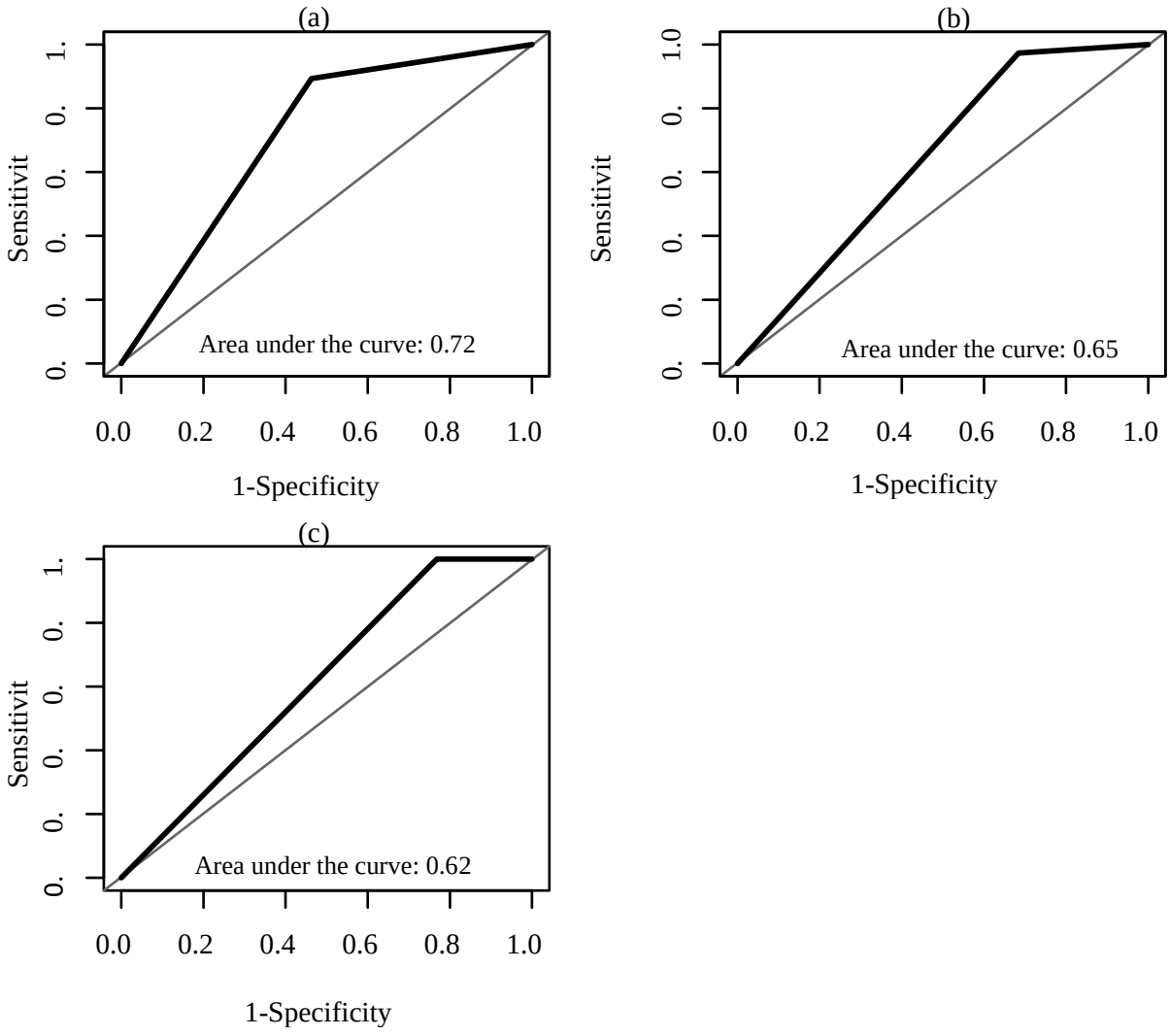

Figure 2.2 Receiver operating characteristic (ROC) curves based on cut-off values for AHI of 5 (a), 15 (b) and 30 (c) for SBQ scores of ≥3, showing the corresponding area under the curve.

ROC curve analysis was also conducted to determine which SBQ items are the best predictors of OSA severity (Table 2.7). The results revealed that loud snoring provided excellent sensitivity and specificity for mild OSA (AHI ≥5 and <15) while observed apnoeic events provided acceptable–excellent sensitivity and specificity for moderate and severe OSA (AHI ≥15). For both items the AUC was superior (>75%) to that obtained for the entire SBQ.

Table 2.7 Diagnostic accuracy for the individual SBQ items for different cut-off values of AHI.

	AHI ≥5		AHI ≥15		AHI ≥30	
SBQ Item	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**	**Sensitivity**	**Specificity**
Loud snoring	**0.86**	0.**79**	0.80	0.45	0.95	0.42
Tiredness, fatigue and sleepiness	0.84	0.31	0.90	0.27	0.95	0.23
Observed apnoeic events	0.49	0.77	**0.87**	**0.76**	**0.81**	**0.78**
High blood pressure	0.28	0.85	0.32	0.80	0.43	0.80
Body Mass Index >35 kg/m^2	0.56	0.55	0.56	0.47	0.64	0.49
Age >50 years	0.43	0.85	0.52	0.76	0.45	0.64
Large neck circumference	0.31	0.70	0.34	0.74	0.37	0.72
Male sex	0.72	0.50	0.78	0.41	0.86	0.37

Note: AHI cut-offs (AHI ≥5; AHI ≥15 and AHI ≥30); SBQ cut-off used SBQ ≥ 3. AHI: apnoea–hypopnoea index; SBQ: STOP-Bang questionnaire.

Participants were divided into four groups based on their AHI scores, to determine which of the eight questions in the SBQ are the best predictors of OSA severity (Table 2.8). The proportion of participants in each OSA severity group who answered ‘yes’ to each question was expressed as a percentage of the total number of participants in that group. An analysis of variance (ANOVA) determined if there was a significant between-group difference for each item in the SBQ. The items showed a significant upward trend as the severity of OSA increased, with loud snoring and observed apnoea events being the most significant predictors.

Table 2.8 Frequency of 'yes' responses to the eight SBQ items stratified by OSA severity.

SBQ item	All groups n = 82	No OSA n = 13	Mild OSA n = 28	Moderate OSA n = 20	Severe OSA n = 21	
Answered 'yes'	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***n (%)***	***p-value***
Loud snoring	54 (66)	4 (31)[2,4]	18 (64)[1]	12 (60)[4]	20 (95)[1,3]	**<.01**
Tiredness, fatigue and sleepiness	68 (83)	9 (69)[4]	21 (75)	17 (85)	21 (100)[1]	**.02**
Observed apnoeic events	36 (44)	3 (23)[4]	7 (25)[4]	9 (45)[4]	17 (81)[1,2,3]	**<.01**
High blood pressure	21 (26)	2 (15)	6 (21)	4 (20)	9 (43)	.07
Body Mass Index >35 kg/m^2	43 (52)	5 (38)	15 (54)	9 (45)	14 (67)	.22
Aged >50 years	32 (48)	2 (15)[3]	8 (29)[3]	12 (60)[1,2]	10 (48)	**.02**
Large neck circumference	19 (23)	1 (8)	6 (21)	5 (25)	7 (33)	.08
Male sex	56 (68)	7 (50)[4]	19 (68)[4]	16 (80)	20 (95)[1,2]	**.01**

Note: OSA severity cut-off values are non-OSA (AHI 0–4); mild OSA (AHI 5–14); moderate OSA (AHI 14–29); severe OSA (AHI ≥30); significant differences between groups were defined by [1], $p < .05$ *v.* non-OSA; [2], $p < .05$ *v.* mild OSA; [3], $p < .05$ *v.* moderate OSA; and [4], $p < .05$ *v.* severe OSA; OSA: obstructive sleep apnoea; SBQ: *STOP-Bang questionnaire*.

2.4 Discussion

This study examined a group of 90 patients who had presented consecutively for a PSG assessment at a Saudi sleep laboratory. The study found that participants those who were older and with higher BMI had more severe OSA. Current smoking rate and the presence of hypertension were not predictors of OSA severity, suggesting that being overweight is a more influential cause of OSA than other negative lifestyle behaviours. The prevalence of depressive symptoms, EDS and IGT/T2D among the OSA patients was estimated as 74%, 50% and 60%, respectively. The total score on the Arabic version of the SBQ (based on eight items) was found to have high sensitivity but low specificity for the presence of OSA. Two items (loud snoring and observed apnoea events) provided a superior prediction of OSA severity.

The severity of OSA is known to increase with age, and thus the findings of this study are consistent with those of earlier studies. For instance, a study of 878 Saudi patients who were

referred to a sleep laboratory found that age was a strong predictor of OSA severity (Alshehri et al., 2019). A study of 2,095 Saudi patients found that advancing age was positively correlated with an increased likelihood of OSA, with only 19.4% of patients younger than 29 years showing symptoms of OSA and 41% of those older than 60 years showing symptoms (Alruwaili et al., 2015).

The present study found that high BMI is a risk factor for OSA severity. This supports the findings of previous studies. A study in Italy of 161 obese patients examined the prevalence of sleep breathing disorders and found that more than 50% of the patients with a mean BMI higher than 40.0 kg/m^2 had OSA (Resta et al., 2001). An Australian study that analysed data collected as part of a national, cross-sectional survey of general practice found that patients with a BMI >30 kg/m^2 had a significantly higher rate of OSA and snoring than those with a BMI <25 kg/m^2 (S. F. Cross et al., 2016). A study in Chile comparing OSA patients to those without OSA showed that a BMI ≥30 was associated with OSA severity (Wosu et al., 2014). A study of 346 Saudi patients (Wali et al., 2017) found a strong association between BMI and OSA severity. Similarly, a study by Jamal, Eskandrani and Alyahya (2018) of 1,925 Saudi participants reported that obesity was the most common comorbidity associated with OSA.

The present study found no relationship between smoking and OSA severity. Research has yielded mixed findings on the association between smoking and OSA. Hoflstein (2002) studied 3,509 patients with OSA and found that although AHI scores were higher in heavy smokers than in non-smokers, there was no significant relationship between smoking and the presence of OSA. Similarly, A. N. Ahmad et al. (2019) reported that smoking was not a risk factor for OSA in the Saudi population. The findings of these two studies are consistent with those of the present study, which found that current smokers were not more likely to have severe OSA. In contrast, some studies have reported that smoking is related to the severity of OSA. For

example, Wetter et al. (1994) found that current smokers are more likely to have OSA than non-smokers or former smokers. Another study indicated a strong relationship between smoking and severe OSA in Saudi Arabia (Alharthi et al., 2018). The inconsistent findings between studies may relate to how smoking status is classified, given that a binary classification of smoking does not account for differences in the frequency of smoking or differences between lifetime smokers and recent smokers. It is possible that smoking is an indicator of other generally unhealthy behaviours such as overeating and low levels of exercise, which might lead to OSA.

Depressive symptoms were prevalent among OSA patients (74%) in the present study. This supports earlier research that links depression and OSA. For example, Baaisharah et al. (2017) found that 50% of Saudi Arabian patients (N = 75, mean age = 47.5 years) with OSA exhibited depressive symptoms. This percentage was higher among individuals with severe OSA. Dai et al. (2016) found that 47.4% of 1,327 Chinese OSA patients aged between 18 and 82 (median age of 47 years) had depressive symptoms. These proportions are higher than observed in general populations. In their systematic review, J. Wang et al. (2017) stated that up to 27% of the general population had depression or depressive symptoms. However, there are minor inconsistencies in research data regarding the prevalence of depression among OSA patients. This variation could be caused by several factors, including cultural differences. The cultural differences among minority groups can affect the reliability and validity of measurements utilised in mainstream cultures (Mushquash & Bova, 2007). In addition, Silva et al. (2016) considered that certain age groups had difficulty understanding the DASS and differentiating between some symptoms assessed. Thus, age differences can lead to instability for the scales.

In agreement with most previous studies, the present study found that depressive symptoms were not related to the severity of OSA as estimated from the AHI. For instance, Macey, Woo,

Kumar, Cross and Harper (2010) examined 49 untreated OSA patients without comorbidities and found that depressive symptoms (measured using the Beck Depression Inventory) were not associated with OSA severity. Ejaz et al. (2011), in their review, stated that the absence of a correlation between depressive symptoms and OSA severity does not necessarily indicate a lack of association, as the prevalence of depressive symptoms is high in patients with OSA relative to those without OSA. Thus, this relationship could be due to EDS, fragmentation of sleep or repeated episodes of hypoxia. The mechanism behind depressive symptoms is extensively investigated in Chapter 3.

Research has found that up to 29% of the general population experience EDS (Hayley et al., 2014; Ohayon, Dauvilliers, & Reynolds, 2012; Tsuno et al., 2007), but within clinical populations, OSA patients have a higher prevalence of EDS. In the present study, 50% of OSA patients reported EDS. Consistent with the current study, a Norwegian study found that approximately 59% of middle-aged OSA patients reported EDS (Bjorvatn et al., 2015). In addition, in a large US community-based cohort, 70% of middle-aged and older subjects with moderate-to-severe sleep-disordered breathing (AHI ≥15) reported EDS (Kapur, Baldwin, Resnick, Gottlieb, & Nieto, 2005). However, self-reported EDS may underestimate the prevalence of EDS. For example, Fong, Ho and Wing, (2005) proposed that the multiple sleep latency test (MSLT) is more effective in assessing EDS associated with OSA severity. Accordingly, Seneviratne and Puvanendran (2004) used MSLT to assess EDS in 195 OSA patients (mean age = 45.5 years) and found a high prevalence rate (87%). However, in the present study, EDS was associated with OSA severity. Similarly, Oksenberg et al. (2010) compared the severity of OSA between patients with and without EDS and concluded that patients with EDS had more severe OSA than those without EDS.

The present study also examined the prevalence of T2D and IGT among OSA patients. In Saudi Arabia, the prevalence of T2D and IGT among the general population is 9.2% and 27.6%, respectively (Aldossari et al., 2018). The current study found much higher incidences of T2D (17%) and IGT (43%) in OSA patients. This finding is consistent with previous research. For instance, Reichmuth, Austin, Skatrud and Young (2005) confirmed that 15% of patients with moderate-to-severe OSA had T2D. Additionally, Mahmood et al. (2009) found that 30% of sleep laboratory patients (N = 1,008) with an AHI ≥5 had T2D. In the present study OSA severity was independently linked to IGT whereas T2D was not. Kim et al. (2013), also found that OSA severity in non-obese patients is associated with IGT. Additionally, as IGT is directly affected by OSA severity, the transition from IGT to T2D may take several years, as stated by Nathan et al. (2007) who found that 70% of pre-diabetic individuals eventually developed T2D.

The present study examined the utility of the Arabic version of the SBQ to screen patients for the presence of OSA. An unexpected finding was that 19 OSA patients reported hypertension, yet none had resting hypertension when tested (Table 2.2). The reason for this discrepancy is unclear. It is possible that their hypertension was being successfully treated, or perhaps the relevant question in the Arabic version of the SBQ was misunderstood by some of the patients. With ≥5 AHI and SBQ ≥ 3 the SBQ has indicated a high sensitivity (90–100%) but a low specificity (23–54%), which aligns with a validation study of the Arabic version of the SBQ that reported a sensitivity of 98% and a specificity of 24% (BaHammam et al., 2015). Reviews of other populations have consistently reported similar patterns. For instance, Chung et al. (2016) reported that the sensitivity and specificity of the English version of the SBQ is 74% and 53% respectively, while Vana, Silva and Goldberg (2013) reported a sensitivity of 93% and specificity of 33%. Although the high sensitivity of the SBQ ensures that most cases of OSA are detected, its low specificity means that around half of all patients will undergo PSG tests unnecessarily, wasting scarce resources and inconveniencing patients. The present study found

that loud snoring and observed apnoeic events provide superior sensitivity and specificity for OSA compared with the full SBQ. While this finding needs to be confirmed in a larger study, it opens the way for clinicians to use these two items of the SBQ to improve the efficiency of screening patients for probable OSA.

One of the limitations of this study is the fact that all participants had been referred to undertake a sleep study as they were known to suffer from sleep problems. It would be technically challenging to conduct a PSG study on randomly selected members of the broader community. Nonetheless, it should be borne in mind that the present results are representative of the sub-group of patients referred to sleep clinics, not the broader population. A second limitation is that the small number of participants with T2D (and mostly mild cases) may have precluded identification of an association between OSA severity and T2D.

2.5 Conclusions

The findings of this study increase understanding of the risk factors and characteristics of OSA patients referred to sleep clinics in Saudi Arabia. The risk factors included age and BMI, consistent with findings from previous studies of other target populations. Further, current smoking status did not affect the severity of OSA. The prevalence of depressive symptoms, EDS, IGT and T2D were much higher in patients with OSA than in the general population; EDS and IGT were significantly linked to OSA severity, whereas depressive symptoms and T2D were not. Further, the results from this study confirm the Arabic version of the SBQ to be a sensitive screening tool for OSA and show that loud snoring and observed apnoeic events have the best utility for predicting the severity of OSA. Overall, the current study supports previous global research on OSA patients in terms of risk factors, demographics and responses to ESS, DASS and the SBQ.

Chapter 3: Differential Associations of Hypoxia, Sleep Fragmentation and Depressive Symptoms with Cognitive Performance in Obstructive Sleep Apnoea

Abstract

OSA is characterised by recurrent episodes of partial or complete cessation of breathing during sleep and an increased effort to breathe. This study examined patients who underwent overnight PSG studies in a major sleep laboratory in Saudi Arabia. The study aimed to determine the extent to which IH, sleep fragmentation and depressive symptoms are independently associated with cognitive impairments in OSA. In the sample of 90 participants, 14 had no OSA, 30 mild OSA, 23 moderate OSA and 23 severe OSA. The findings revealed that hypoxia and sleep fragmentation were independently associated with impairments in sustained attention and RT ($p < .05$). Sleep fragmentation, but not hypoxia, was independently associated with impairments in visuospatial performance ($p < .05$). Depressive symptoms were independently associated with impairments in sustained attention, RT, visuospatial ability and semantic and episodic autobiographical memory ($p < .05$). Since depressive symptoms are independent of hypoxia and sleep fragmentation, effective reversal of cognitive impairment in OSA may require treatment interventions that target each of these factors.

3.1 Introduction

OSA is a sleep disorder characterised by repetitive episodes of airway obstruction that lead to transient hypoxia and sleep fragmentation (Young et al., 1993). According to recent estimates, the global prevalence of OSA ranges from 9% to 38% in middle-aged individuals (Senaratna et al., 2017). Clinical interventions, particularly CPAP, can reduce OSA severity (Schwarz, Stradling, & Kohler, 2018). People with untreated OSA frequently exhibit impairment on tests

of memory, attention, and visuospatial ability (Ayalon, Ancoli-Israel, Aka, et al., 2009; M. Olaithe et al., 2018; Anna Wallace & Romola S. Bucks, 2013), and are 7.5–20 times more likely to have difficulty with concentration, executing monotonous tasks and learning new tasks (Beebe & Gozal, 2002; Ulfberg, Carter, Talbäck, & Edling, 1996). Due to decreased concentration and sleepiness, individuals with OSA have an increased risk of occupational and motor vehicle accidents (Garbarino et al., 2016; Kales & Czeisler, 2016), which in turn may lead to injury, death and an increased economic burden on society (Howard et al., 2004; Ward et al., 2013). Despite widespread agreement that OSA is associated with an increased risk of cognitive impairment, there is no consensus regarding the probable causes of this impairment.

The three most likely causes are hypoxia, sleep fragmentation and depression. For instance, neuroimaging studies have shown that individuals with OSA have structural changes in the brain that are associated with cognitive impairment, and the extent of these changes increases with higher levels of nocturnal hypoxia, as measured during PSG (Lal et al., 2012). Hypoxia in OSA patients has been linked to impairments in global cognitive function (Yaffe et al. (2011), and long-term memory and attention (Findley et al., 1986). Some OSA studies have found that hypoxemia is associated with grey matter hypertrophy, presumably caused by oedema (Baril et al., 2017).

The arousals associated with apnoea events interrupt sleep (Kimoff, 1996). The restorative processes that occur in the brain during sleep are impaired by sleep fragmentation and this is thought to contribute to biochemical and cellular stress that leads to poorer cognitive performance (Beebe & Gozal, 2002). Ayalon, Ancoli-Israel and Drummond (2009) found that sleep fragmentation, but not hypoxia, in OSA patients is associated with significantly slower RTs during a sustained attention task. Moreover, Thomas et al. (2005) suggested that cognitive dysfunction may not necessarily be caused by hypoxia, but rather by sleep fragmentation. In a

review of the literature, Bucks et al. (2013) pointed out that sleep fragmentation has a more profound effect than hypoxia on attention and memory, and they concluded that sleep fragmentation may contribute to a slowing of cognitive processing. An experimental study that examined the effects of sleep disturbances on cognition confirmed that sleep fragmentation can impair cognitive functioning, even in young healthy subjects (Ferri et al., 2010). Animal studies have also demonstrated that sleep fragmentation can cause hippocampal memory impairments (Nair, Zhang, et al., 2011).

It is well established that individuals with depressive symptoms, but without any other comorbid conditions, exhibit cognitive deficits that can include memory loss, visuospatial deficits and an inability to pay attention during routine activities (Faust, Nelson, Sarapas, & Pliskin, 2017; Kaser, Zaman, & Sahakian, 2017). Depression is frequently observed in patients with moderate-to-severe OSA (Shoib, Malik, & Masoodi, 2017) and some studies have suggested that it may play a role in cognitive dysfunction (Delhikar et al., 2019). A neuroimaging study by R. L. Cross et al. (2008) compared OSA patients with depressive symptoms to OSA patients without depressive symptoms and found that OSA patients with depressive symptoms had more extensive areas of brain injury. Research also indicates a connection between autobiographical memory and depression, with lower specificity of autobiographical memory being associated with depressive symptoms (Mackinger & Svaldi, 2004). However, it is not known whether the depressive symptoms observed in OSA are caused by hypoxia or sleep fragmentation, or whether they have a separate aetiology. Thus, it is possible that depressive symptoms are not an independent contributor to cognitive impairment in OSA.

The primary aim of the present study was to determine the extent to which IH, sleep fragmentation and depressive symptoms are each independently associated with cognitive impairment in OSA.

3.2 Method and Materials

3.2.1 Study Participants

The study participants were patients who had been referred for overnight diagnostic PSG studies at the Sleep Medicine and Research Centre, King Abdulaziz University Hospital, Jeddah, Saudi Arabia. The following exclusion criteria were applied: 1) aged <18 years or >65 years; 2) current use of CPAP therapy; 3) a neurodegenerative disease (e.g. Alzheimer's disease, Parkinson's disease); and/or 4) regularly sleeping less than 2 hours per night based on the AASM criteria, which recommend the minimum duration for PSG as 2 hours (Epstein et al., 2009). Ninety out of a sample of 100 patients who presented sequentially to the Sleep Medicine and Research Centre met the study inclusion criteria.

The study was approved by the Royal Melbourne Institute of Technology University Human Research Ethics Committee (ethics reference number: HREC 21459) and the King Abdulaziz University Hospital Human Research Ethics Committee (ethics reference number: 395-18). Informed consent was obtained from all participants after they had received an explanation of the nature of the study at the Sleep Medicine and Research Centre.

3.2.2 Procedure and Measurements

After consenting to participating in the study and being admitted to the sleep laboratory, the participants' height and weight were measured by a nurse. Participants then completed a series of questionnaires designed to collect demographic data as well as information on daytime sleepiness and mood levels. Cognitive tests were conducted at 5:00 pm. The time to completion

all of the tests ranged from 40 to 45 minutes for all participants. The cognitive tests were administered in the following order: the PVT, Austin Maze and the autobiographical memory interview. Subjects were prepared for the polysomnography at 10:00 pm. This followed by a standard overnight PSG study. The same procedures and time of all tests and evaluations in the sleep laboratory were applied to the home studies.

3.2.3 Questionnaires

3.2.3.1 The Epworth Sleepiness Scale *Arabic version (Ahmed et al., 2014; Johns, 1991)*

This sleepiness scale assesses the general level of daytime sleepiness and is frequently used to assess the impact of sleep disorders. The scale consists of eight items, each rated from 0 to 3, with higher numbers indicating a higher chance of dozing. The scores from the eight items are summed to obtain an overall score. The minimum score is 0 and maximum is 24, higher scores reflect greater levels of sleepiness. Scores of less than 11 represent little or no daytime sleepiness; scores between 11 and 14 indicate mild daytime sleepiness; scores between 15 and 17 reflect moderate daytime sleepiness; and scores over 17 indicate severe daytime sleepiness.

3.2.3.2 Depression, Anxiety, Stress Scale-21 *(Arabic version) (Ali et al., 2017; Henry & Crawford, 2005)*

This 21-item questionnaire is designed to measure the magnitude of three negative emotional states, including depression. The DASS depression subscale focusses on reports of low mood, motivation and self-esteem. Scores of 0–9 indicate the absence of depressive symptoms, 10-13 indicates mild depressive symptoms, 14–20 indicates moderate depression, more than 21-27 indicates severe depression and scores of 28 or more correspond to extremely serious depression. There is convergent validity between the DASS and the Beck depression and anxiety inventories (Lovibond & Lovibond, 1995).

3.2.3.3 Polysomnography Evaluation

Overnight PSG (SOMNO Medics Plus, SOMNOmedics, Randersacker, Germany) was used to assess OSA. While most of the PSG studies were conducted at the Sleep Medicine and Research Centre, 15 studies were performed in patients' homes for reasons mainly related to patient convenience. The same PSG devices and procedures were used in these home studies as in the sleep centre. For all PSG studies, a sleep technician wired up PSG sensors half an hour before the sleep time. PSG employed a 10-channel recording montage (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2) to measure EEG activity. Left and right EOG, ECG and submental EMG, oronasal airflow (using a thermal sensor and nasal pressure transducer), body position, thoracic and abdominal excursion (inductance plethysmograph), oxygen arterial blood saturation (SaO_2) measured with finger pulse oximetry, left and right leg movement (EMG channel) and a sound recorder were used.

3.2.4 Neurobehavioral Evaluation

3.2.4.1 10-Minute Psychomotor Vigilance Test (Dinges & Powell, 1985)

This computerised visual test evaluates the ability to sustain attention and respond with a button press in a timely manner to cues presented on a screen. The reliability and validity of the 10-minute version of the test has been confirmed in previous studies (Dinges & Powell, 1985). The test is sensitive to sleep fragmentation and serves to indicate a sustained attention deficit (Jung, Ronda, Czeisler, Wright, 2011). Three PVT outcome measures were used in the present study: 1) mean RT; 2) mean of the slowest 10% RT; and 3) number of lapses with a RT >500 ms. If RT is >100 ms, it is measured as valid. If RT is ≤100 ms or a response occurs without a stimulus being presented, this is recorded as a false start.

3.2.4.2 10-Trial Austin Maze (Milner, 1965)

This computerised maze measures visuospatial ability and visuospatial memory (Crowe et al., 1999; Stolwyk et al., 2013). Participants plot a course through a chequerboard maze by pushing buttons and identifying the correct order through trial and error. Each time the correct button is pushed, a green light is displayed; when an incorrect button is pushed, a red light is displayed, and a buzzer is sounded. The Austin Maze-errors were defined by the total number of missed blocks, and the Austin Maze-time corresponds to the total time spent in each trail. The current study allowed for a maximum of 10 trials because the literature shows a strong correlation between errors that occur up to the tenth trial of an experiment and errors to criterion (Bowden et al., 1992).

3.2.4.3 The Autobiographical Memory Interview (Kopelman et al., 1989)

This method measures both episodic and semantic memory. Memories were assessed for three stages in a participant's lifespan: childhood (before high school); early adulthood (usually including career, relationships, marriage and children); and recent life (acknowledging present and previous hospital or institution stays over the previous 5 years as well as the most recent holidays or journeys). Scoring was based on the autobiographical memory interview (AMI) guidelines (Kopelman, Wilson, & Baddeley, 1989). Regarding episodic memory, participants scored 3 for full recall that included specifics of time and place; 2 for recall that was personal but general; 1 for an unclear personal memory; and 0 for no answer or a semantic memory. There was a maximum of 9 points for each time period (total score maximum = 27). For semantic memory (e.g. names), responses were weighted according to the level of detail retained (e.g. house number, street name and district) with a maximum of 21 points for each time period (total maximum = 63). The AMI has a high level of accuracy, reliability and validity. The candidate has translated the English language version of the AMI results into

Arabic. Two other Arabic-speaking researchers reviewed the translation and suggested refinements in expression, phrasing and concepts. The AMI interviews were then translated into English by an independent bilingual translator with no knowledge of the topic. After the original and translated interviews were compared, no significant differences in the content were evident.

3.2.5 Analysis

Participant BMI calculations were based on the international standard of dividing weight in kilograms by height in metres squared (Nuttall, 2015). PSG recordings were scored using an algorithm, then checked by manually scoring all records according to the 2012 AASM scoring protocol (Berry, Brooks, et al., 2012). The description of abnormal breathing events during sleep was based on AASM recommendations (Berry, Budhiraja, et al., 2012). Breathing abnormalities were defined as follows: a decrease in airflow of 90% or higher from the baseline for at least 10 seconds (apnoea) and a discernible reduction in airflow of at least 30% of the pre-event baseline using nasal pressure, associated with a reduction in oxygen saturation of at least 3% and followed by either oxygen desaturation or an electroencephalographic arousal (hypopnoea), despite persistent effort of the chest and abdominal muscles to overcome the obstruction. The severity of OSA was estimated from the AHI. The degree of hypoxia was identified by SaO_2 time duration (in seconds) <90%. The degree of sleep fragmentation was assessed by the Arousal Index, calculated by dividing the total number of arousals by the duration of sleep (arousals/h). In addition, the duration of NREM sleep stages N1, N2 and N3, and the duration of the REM sleep stage, were analysed. Three PSG technicians verified all PSG scores to ensure the consistency of the scoring process. The technicians also randomly selected and scored cases to confirm inter-observer reliability and accuracy.

Test data for the PVT and AM were calculated using software algorithms developed for each task. The AMI scores were based on the AMI guidelines and were consecutively scored and revised by the same researcher, who followed the same calculation procedures for all participants. The degree of sleep fragmentation was assessed by the Arousal Index that ended apnoeic events.

Statistical analyses were performed with IBM SPSS version 26 (IBM Corp., Armonk, NY, US). Data for continuous variables were reviewed to determine whether any had extremely skewed distributions. Consequently, log transformation was performed to normalise the distribution of the following variables: PVT mean, PVT slowest 10% RT, AM time, AM errors, AMI childhood semantic memory, AMI adult early life memory and AMI recent life memory. The data were expressed as mean and *SD* for continuous variables, and as frequencies and percentages for categorical variables. ANOVA with Bonferroni post-hoc analysis was applied to identify significant differences between OSA severity groups (independent variables) and demographic variables (age, BMI and smoking), depressive symptoms, daytime sleepiness and PSG parameters (dependent variables). Between-group comparisons of categorical data were made using Pearson's chi-square tests. Simple linear regression was used to identify associations between SaO_2 time <90%, Arousal Index and depressive symptoms. A multiple linear regression was conducted to examine associations between depressive symptoms (dependent variables) and demographic data (independent variables). Pearson bivariate correlations were examined to demonstrate relationships between potential confounders and cognitive tests. Education and intelligence quotient were not included as confounders because they are collinear with age. Multiple linear regressions examined the associations between cognitive dysfunction and the variables of hypoxia, sleep fragmentation and depressive symptoms after adjusting for confounders. All regression models were adjusted for multiple

comparisons using the FDR (Benjamini & Hochberg, 1995), and multicollinearity was demonstrated using a VIF of <2.0. Only significant models are shown in Section 3.3.

3.3 Results

The PSG results showed that 14 of the 90 participants did not have OSA, 30 had mild OSA, 23 had moderate OSA and 23 had severe OSA. The mean patient age was 42.0 years (*SD* = 12.7), and the mean BMI was 33.4 (*SD* = 9.4).

Table 3.1 shows comparisons of the dependent variables, based on participants grouped according to their AHI score (14 no OSA, 30 mild OSA, 23 moderate OSA, 23 severe OSA). Participants in the severe OSA group were older than those in the non-OSA group. However, ESS score and depression did not increase significantly with OSA severity. BMI was not significantly different among the four groups. Significant differences were found between OSA severity groups for sleep parameters including SaO_2, time spent <90% and the Arousal Index. The percentage of the time durations of N1 sleep was significantly higher and REM sleep was significantly lower in severe group compared to the other OSA severity groups, whereas the duration of N2 sleep and N3 sleep did not differ between the groups.

Table 3.1 Comparison of demographic variables, depressive symptoms, daytime sleepiness and polysomnography parameters stratified by OSA severity group.

	No OSA (n = 14)	Mild OSA (n = 30)	Moderate OSA (n = 23)	Severe OSA (n = 23)	
Variable	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***p-value***
Age (years)	33.6 (14.2)[4,3]	38.7 (11.8)	46.8 (11.8)[1]	46.7 (10.3)[1]	**.02**
Body Mass Index	32.3 (12.4)	32.8 (8.3)	31.2 (8.4)	36.7 (9.5)	.22
Current smoker (%)[+]	1 (7)	7 (23)	5 (22)	9 (39)	.16
DASS-21 depression subscale	8.0 (8.1)	13.5 (9.3)	11.6 (11.7)	11.3 (8.9)	.39
ESS	9.5 (5.2)	9.5 (4.3)	11.1 (7.1)	13.0 (7.1)	.13
SaO_2 time <90% (mins)	0 (1)[4]	2 (6)[4]	9 (24)[4]	30 (46)[1,2,3]	**<.01**
Arousal Index	1.3 (1.1)[3,4]	5.5 (4.6)[4]	10.3 (4.9)[1,4]	26.0 (16.8)[1,2,3]	**<.01**
N1 sleep time duration (%)	08 (04)[4]	12 (8)[4]	12 (7)[4]	21 (13)[1,2,3]	**<.01**
N2 sleep time duration (%)	49 (10)	45 (12)	51 (15)	44 (14)	.25
N3 sleep time duration (%)	22 (09)	26 (13)	21 (16)	119 (20)	.53
REM sleep time duration (%)	14 (08)[4]	09 (07)	07 (06)	06 (07)[1]	**.04**

Note: Obstructive sleep apnoea (OSA) severity cut-off values: <5 AHI (normal); 5–14 AHI (mild); 15–29 AHI (moderate); ≥30 AHI (severe); significant differences between groups were defined by [1], p < .05 v. non-OSA; [2], *p* < .05 v. mild OSA; [3], *p* < .05 v. moderate OSA; [4], *p* < .05 v. severe OSA; [+]: Pearson chi-square. DASS-21: depression, anxiety and stress scale-21; ESS: Epworth sleepiness scale; SaO_2: oxygen arterial blood saturation; N1, sleep stage 1; N2, sleep stage 2; N3, sleep stage 3; REM: rapid eye movement sleep stage.

Simple linear regression analysis revealed a moderate significant relationship between SaO_2 time <90% and Arousal Index (R^2 = 0.31). Additionally, depressive symptoms were not correlated with any of the PSG factors (p > .05). However, multiple linear regression analysis (Table 3.2) showed that the amount of variation in depressive symptoms was accounted for by predictors (F (3,87) = 5.37, p = .002; Table 3.2). Age and BMI were not associated with depressive symptoms, which were only linked to daytime sleepiness.

Table 3.2 Multiple linear regression analysis for the association between depressive symptoms and demographic variables, and daytime sleepiness.

Variable	R^2	p_{model}	Predictor	*SE*	*β*	*sr*	*p-value*
Depressive symptoms	0.16	**<.01**					
			Daytime sleepiness	0.16	0.38	0.38	**<.01**
			Age (years)	0.08	0.84	0.10	.40
			Body Mass Index	0.10	0.15	0.08	.15

R^2 = models' multiple correlations; *SE* = standard error; *β* = standardised regression coefficient; *sr* = semi-partial correlation.

To identify potential confounding variables, Pearson bivariate correlation tests were conducted. The results revealed that age was positively associated with performance on all PVT and AM indices, as well as most of the stages of AMI episodic memories (total episodic memory, episodic early adult life memory and episodic recent life memory) but age was not associated with any stage of semantic memory. Smoking was positively associated with AM time and AMI episodic recent life memory. Daytime sleepiness was not associated with performance on any of the cognitive tests.

Multiple linear regression analyses were performed to determine whether hypoxia, depressive symptoms and sleep fragmentation independently influenced performance on the PVT, AM and AMI. The confounding variables (age and smoking status) associated with individual cognitive tests were included in the regression models in addition to the other independent factors.

After FDR adjustment, all models that included the variables of PVT, AM and AMI (total semantic memory, recent life semantic memory, total episodic memory and episodic recent life memory) remained significant ($p < .05$). Additionally, no model showed multilinearity according to VIF <2.0.

Accordingly, the results indicated that performance on all three PVT indices was associated with hypoxia and depressive symptoms, while sleep fragmentation was associated with mean PVT and PVT RT lapses >500 ms but not with PVT slowest 10% RT. Performance on AM time and AM errors was associated with depressive symptoms and sleep fragmentation but not with hypoxia (Table 3.3).

Table 3.3 Multiple linear regression analyses for the key measures on the Psychomotor Vigilance Task and Austin Maze test, showing the strength of association between scores on these tests and measures of hypoxia (SaO_2 time <90%), sleep fragmentation (Arousal Index) and depressive symptoms, after adjusting for confounders.

Cognitive test	R^2	p_{model}	Predictor	*SE*	*β*	*sr*	*p-value*
PVT RT-mean	0.26	**<.01***					
			Hypoxia	0.00	0.35	0.28	**<.01**
			Sleep fragmentation	0.54	0.26	0.21	**.02**
			Depressive symptoms	0.60	0.32	0.30	**<.01**
			Age (years)	0.47	0.24	0.22	**.02**
PVT RT slowest 10%	0.17	**<.01***					
			Hypoxia	0.01	0.37	0.31	**<.01**
			Sleep fragmentation	1.93	0.16	0.13	.18
			Depressive symptoms	2.04	0.24	0.23	**.02**
PVT RT-lapses >500 ms	0.29	**<.01***					
			Hypoxia	0.00	0.42	0.34	**<.01**
			Sleep fragmentation	0.06	0.24	0.18	**.03**
			Depressive symptoms	0.07	0.30	0.29	**<.01**
			Age (years)	0.06	0.20	0.19	**.04**
AM-time	0.40	**<.01***					
			Hypoxia	0.00	0.14	0.12	.19
			Sleep fragmentation	0.14	0.22	0.18	**.04**
			Depressive symptoms	0.18	0.26	0.25	**<.01**
			Age (years)	0.13	0.59	0.56	**<.01**
AM-errors	0.24	**<.01***					
			Hypoxia	0.08	0.07	0.07	.48
			Sleep fragmentation	0.28	0.22	0.22	**.03**
			Depressive symptoms	0.27	0.26	0.26	**.01**
			Age (years)	0.07	0.33	0.30	**<.01**

Cognitive test	R^2	p_{model}	Predictor	*SE*	*β*	*sr*	*p-value*
			Smoking	1.81	0.21	0.02	**.03**

Note: *significant model ($p < .05$) after FDR adjustment; PVT: psychomotor vigilance test; RT: reaction time; ms: milliseconds; AM: Austin maze; R^2 = models' multiple correlations; *SE* = standard error; *β* = standardised regression coefficient; *sr* = semi-partial correlation.

The AMI, which measures episodic and semantic memory within life stages, did not show any relationships with either hypoxia or sleep fragmentation. However, depressive symptoms were positively associated with deficits in most of semantic and episodic total memory life stages. (Table 3.4).

Table 3.4. Multiple linear regression analysis of measures on the Autobiographical Memory Interview, showing the strength of association between scores on this test with measures of hypoxia (SaO_2 time <90%), sleep fragmentation (Arousal Index) and depressive symptoms, after adjusting for confounders.

Cognitive test	R^2	p_{model}	Predictor	*SE*	*β*	*sr*	*p-value*
Total semantic memory	0.15	**<.01***					
			Hypoxia	0.00	-0.02	-0.02	.84
			Sleep fragmentation	0.04	-0.18	-0.15	.15
			Depressive symptoms	0.05	-0.37	-0.37	**<.01**
Childhood semantic memory	0.30	.09					
			Hypoxia	0.00	.13	0.11	.31
			Sleep fragmentation	0.03	0.03	0.2	.84
			Depressive symptoms	0.03	-0.29	-0.29	**<.01**
Early adult life semantic memory	0.09	**.04***					
			Hypoxia	0.00	-0.21	-0.18	.09
			Sleep fragmentation	0.22	0.22	0.18	.08
			Depressive symptoms	0.23	-.21	-0.20	**.04**
Recent life semantic memory	0.12	**.02***					
			Hypoxia	0.00	-0.04	-0.01	.67
			Sleep fragmentation	0.02	-0.11	-0.13	.38
			Depressive symptoms	0.02	-0.27	-0.22	**.01**
			Smoking	0.49	-0.25	-0.24	**.02**

Cognitive test	R^2	p_{model}	Predictor	*SE*	*β*	*sr*	*p-value*
Total episodic memory	0.14	**.01***					
			Hypoxia	0.00	-0.02	-0.02	.87
			Sleep fragmentation	0.06	-0.04	-0.03	.77
			Depressive symptoms	0.06	-0.24	-0.24	**.02**
			Age (years)	0.06	-0.30	-0.29	**<.01**
Episodic childhood memory	0.04	.35					
			Hypoxia	0.00	0.06	0.05	.67
			Sleep fragmentation	0.03	-0.2	-0.17	.87
			Depressive symptoms	0.38	-0.19	-0.19	.07
Episodic early adult life memory	0.10	.06					
			Hypoxia	0.00	-0.10	-0.8	.43
			Sleep fragmentation	0.02	0.07	0.06	.57
			Depressive symptoms	0.03	-0.18	-0.17	.12
			Age (years)	0.02	-0.25	-0.23	**.02**
Episodic recent life memory	0.12	**.03***					
			Hypoxia	0.00	-0.06	-0.46	.65
			Sleep fragmentation	0.02	-0.02	-0.02	.87
			Depressive symptoms	0.03	-0.15	-0.17	.16
			Age (years)	0.20	-0.31	-0.29	**<.01**

Note: * significant model ($p < .05$) after FDR adjustment; R^2 = models' multiple correlations; *SE* = standard error; β = standardised regression coefficient; sr = semi-partial correlation.

3.4 Discussion

Ninety participants who had been sequentially admitted to a sleep clinic for an overnight diagnostic PSG were investigated to determine whether IH, sleep fragmentation and/or depressive symptoms are independently associated with cognitive impairments in OSA. The findings revealed that hypoxia and sleep fragmentation are independently associated with impairments in sustained attention and RT. Moreover, sleep fragmentation is independently associated with impairments in visuospatial ability. Depressive symptoms are independently

associated with impairments in the domains of sustained attention, RT, visuospatial ability and semantic and episodic memories.

3.4.1 Intermittent Hypoxia

IH is one of the prominent features of OSA and it has been extensively studied, since it has been linked to brain injury. After controlling for demographic variables, sleep fragmentation and depressive symptoms, the present study revealed that hypoxia is an independent contributor to impairments on the PVT. These findings are consistent with those of a larger study of 912 participants, which found that, after adjusting for demographic variables, the severity of IH was significantly associated with impaired performance on the PVT (Kainulainen et al., 2020). Similarly, a Japanese study reported that sleep related IH, as measured by the ODI, was significantly associated with deterioration in mean RT and number of lapses on the PVT (Tanno et al., 2017). It has also been shown that when healthy individuals are exposed to experimental hypoxia, they display slower RTs on the PVT task (Fowler et al., 1987). Collectively, these results support the conclusion that the severity of IH in OSA contributes to a slowing of response times and an impairment of sustained attention. It is noteworthy that neonatal hypoxia in rats leads to a reduction in the size of neurons in the amygdala, which in turn contributes to a loss of axons that contain corticotrophin-releasing factor and subserve attentional processes (Carty et al., 2010). Although it is not yet known whether similar neuronal changes occur in OSA, brain imaging studies have reported reductions in the volume of the amygdala in patients with severe OSA (H. Yu et al., 2019). The amygdala has been shown to play an important role in attentional processes (Baxter & Murray, 2002).

3.4.2 Sleep Fragmentation

The present study revealed that sleep fragmentation is independently associated with impairments in sustained attention and RT and visuospatial ability. These findings are in line with earlier studies. For instance, Bonnet and Arand (2003) found that sleep fragmentation is as effective as sleep deprivation at impairing psychomotor vigilance. Similarly, Ayalon, Ancoli-Israel and Drummond (2009) compared 14 patients with OSA with 14 healthy control individuals and reported that a higher Arousal Index is associated with slower mean RT and decreased brain activation. Further, although few studies have considered the mechanism behind the visuospatial deficits in OSA, a recent meta-analysis undertaken by Olaithe et al. (2018) concluded that visuospatial deficits are unique to OSA relative to other sleep disorders such as insomnia, and breathing disorders such as chronic obstructive pulmonary disease, suggesting that the mechanism of the visuospatial deficits in OSA might not be caused by hypoxia, hypocapnia or sleep deprivation. However, the present study found for the first time that sleep fragmentation is independently associated with visuospatial deficits. Thus, the current findings support Olaithe and colleagues' statement that 'insomnia may be a poor exemplar of chronic sleep fragmentation experienced in OSA' (p. 47).

3.4.3 Depressive Symptoms

The present study revealed that depressive symptoms are independently associated with slower response times and impairments in sustained attention, as indicated by poorer performance on the PVT and slower times and errors on the Austin maze. Although previous studies have not examined the influence of depression on sustained attention and RT in OSA patients, the present results are consistent with findings from studies of depressed patients. For example, a recent study of 1,569 depressive patients found that impaired performance on the PVT was associated with depressive symptomatology (Plante, Hagen, Ravelo, & Peppard, 2020).

Similarly, a study of young depressive patients who had not received antidepressant medication revealed that depression is associated with a slower speed of information processing (Tsourtos, Thompson, & Stough, 2002).

The current study also found that depressive symptoms are independently associated with impairments in visuospatial ability, as indicated by the number of errors and time taken on the Austin maze. This finding supports those of several studies of depressed patients. For example, Schock, Schwenzer, Sturm and Mathiak (2011) demonstrated that significantly depressed patients have impaired visuospatial ability. Among depressed patients, there was a strong positive relationship between depressive symptoms and visuospatial deficits (Nelson & Shankman, 2016).

The present study found that depressive symptoms are associated with impairments in semantic memory and to a lesser extent episodic memory, as indicated by poorer performance on the AMI. Interestingly, hypoxia and sleep fragmentation were not independently associated with impairments in autobiographical memory. Previous studies have shown that consolidation of semantic autobiographical memory is dependent on non-REM and REM sleep processes, both of which are attenuated in OSA patients as a result of fragmented sleep architecture (Horton & Malinowski, 2015). The present findings are consistent with those of Delhikar et al. (2019) who reported that depression is strongly associated with impairments in semantic memory in OSA patients. In contrast, V. V. Lee et al. (2016) found that impairments in autobiographical memory are not related to depressive symptoms in OSA. However, that study may have been limited by its small sample size and the fact that only older female patients were included.

The present findings support previous research showing that deficits in autobiographical memory recall are a psychological marker for depression (Kuyken & Dalgleish, 1995), and individuals who are non-depressed, but vulnerable to depression, retrieve less specific

autobiographical information than never-depressed individuals (Williams & Dritschel, 1988). Although Lemogne et al. (2006) used a smaller sample size (n = 21) than the current study, they found that impairments in episodic memory were linked to depression, which is consistent with the present findings. The hippocampus is involved in episodic memory (Bird & Burgess, 2008), whereas semantic memory is supported by a distributed network of regions, including the anterior temporal lobes (Rice, Caswell, Moore, Hoffman, & Lambon Ralph, 2018). Therefore, these two forms of autobiographical memory appear to be associated with different brain regions.

The present study has shown that three factors (IH, sleep fragmentation and depressive symptoms) independently account for the cognitive impairments observed in OSA. In particular, since the depressive symptoms were associated with all cognitive tests included in this study the results indicate a major role for depressive symptoms, a factor that has been largely overlooked until now. The fact that depressive symptoms are an independent and primary contributor to impaired performance in a variety of cognitive domains in OSA raises questions about the cause of these depressive symptoms. In the present study, 16% of the variance in depressive symptoms could be accounted for by daytime sleepiness. This finding agrees with those of Ishman et al. (2010), who conducted a case–control study that controlled for race, sex, age and RDI, and found that higher daytime sleepiness was correlated with higher scores on the *Beck Depression Inventory*. Additionally, Macias et al. (2013) included 345 adult patients with OSA diagnosed by PSG in a cross-sectional study. They found that severity of depressive symptoms correlated directly with the severity of daytime sleepiness.

The present study showed that 85% of the variance in depressive symptoms could not be accounted for by EDS, and therefore must have other causes. Vitamin D deficiency is a possible candidate, since it is strongly linked to depression, and supplementation with vitamin D is

associated with a reduction in depressive symptoms and cognitive impairment (Berk et al., 2007; Soni et al., 2012). Further, several studies have shown that vitamin D deficiency is common in obese individuals (Walsh, Bowles, & Evans, 2017) and in OSA (Bouloukaki et al., 2020). People with OSA often lack energy and are less likely to spend time outdoors involved in physical activity (Hong & Dimsdale, 2003). Given that Saudi Arabia has a high incidence of vitamin D deficiency (Bokhari & Albaik, 2019) because of the indoor lifestyle, it may be fruitful to explore this possibility in a future study.

Although the present study is novel, it has several limitations. First, the sample size of the non-OSA group was smaller than that of the OSA group. Thus, it is possible that the smaller number of participants without OSA decreased the statistical power. Second, even though performance on the three chosen cognitive tests was correlated with OSA severity, these tests do not span all cognitive domains, Thus, the other cognition domains that were not tested in the current study might also be affected by OSA severity. Finally, since the present study did not image the brains of the participants, it was unable to correlate the observed cognitive deficits with structural changes. It would be interesting to conduct further studies to address these limitations.

3.5 Conclusion

This study investigated the independent roles of hypoxia, sleep fragmentation and depressive symptoms in cognitive dysfunction in OSA. The analysis revealed that depressive symptoms are associated with impairments in sustained attention, RT, visuospatial ability, and autobiographical memory. Hypoxia and sleep fragmentation are associated with deficits in sustained attention and RT, while sleep fragmentation but not hypoxia is associated with visuospatial deficits. The current findings suggest that cognitive impairment in OSA has

multiple causes, and the reversal of this cognitive impairment may require interventions that simultaneously address all factors.

Chapter 4: Association Between Nocturnal Activity of the Sympathetic Nervous System and Cognitive Performance in Obstructive Sleep Apnoea

Abstract

OSA is a disorder associated with repetitive obstructions of breathing during sleep. These episodes of hypoxia and associated arousals from sleep induce physiological stress and lead to over-activation of the SNS. Cognitive impairment is common among OSA patients and affects their capacity to perform tasks effectively and efficiently. Previous investigations of cognitive impairment in OSA have focussed on the contributions of IH and disrupted sleep but have not addressed nocturnal over-activation of the SNS. The present study investigated whether nocturnal over-activity of the SNS is associated with cognitive impairments in OSA. The extent of nocturnal SNS activation was estimated from HRV, PWA and stress response biomarkers (urine and blood cortisol, and blood glucose). PSG analysis of 78 participants revealed that 12 did not have OSA, 27 had mild OSA, 17 had moderate OSA and 22 had severe OSA. The findings demonstrated that OSA severity (AHI) is significantly associated with PWA indices ($p < .001$) and HRV ($p = .03$), and both are linked to the Arousal Index. Morning blood glucose levels were significantly ($p = .01$) associated with the amount of time with SaO_2 <90%. PWA and HRV were significantly associated with the time taken to perform a task involving visuospatial function ($p < .05$), but not with impairments in sustained attention, RT or autobiographical memory. Morning blood glucose level was not associated ($p > .05$) with any cognitive impairment. The results suggest that some of the visuospatial dysfunction observed in people with OSA may be due to increased nocturnal SNS activity. Thus, interventions that reduce the nocturnal activation of the SNS may improve visuospatial function in patients with OSA.

4.1 Introduction

OSA is sleep-related breathing disorder that involves repetitive obstruction of breathing during sleep, caused by narrowing and/or complete collapse of the upper airway. These episodes of IH followed by arousal from sleep provoke a stress response, as indicated by increased activation of the SNS. One of the consequences of OSA is impairment in a wide range of cognitive abilities, including memory, attention, psychomotor speed and visuospatial skills (Bilyukov et al., 2018). Studies of OSA patients, including the present thesis (Chapter 3), have shown that hypoxia and sleep fragmentation contribute to this impairment (Bucks et al., 2013; Canessa et al., 2011; Tamilarasan et al., 2019; Verstraeten, 2007). Studies of healthy middle-aged subjects have demonstrated that SNS over-activity can be associated with cognitive impairment (Shah et al., 2011), but it is not known whether nocturnal over-activation of the SNS contributes to cognitive impairment in OSA.

When healthy individuals fall asleep, the level of activation of the SNS decreases, and heart rate and BP reduce accordingly (Somers, Dyken, Mark, & Abboud, 1993). In OSA patients, the activation of the nocturnal SNS is increased as a function of the duration and severity of apnoeic events rather than just by the stages of sleep (Narkiewicz & Somers, 2003). HRV is a measure of small differences in the time interval between individual heartbeats and indicates the relative activity of the sympathetic and parasympathetic systems (Catai et al., 2020). Sequeira et al. (2019) measured HRV in adult OSA patients and confirmed that people with OSA exhibit reduced vagal tone and higher sympathetic sensitivity. Decreases in PWA are another indicator of increased activation of the SNS (Delessert et al., 2010). The PWA signal is measured via plethysmography, which is linked to blood flow in the fingers (Burch, 1954). PWA drops are used to detect vasoconstriction, which reflects autonomic activation (Catcheside et al., 2002; Haba-Rubio et al., 2005). Randerath et al. (2016) found that untreated

OSA patients displayed more drops in PWA during sleep than OSA patients who received treatment with CPAP. Blood and urine levels of cortisol and glucose increase as a result of the stress response during sleep in OSA (Buckley & Schatzberg, 2005; Lee et al., 2015). Adherence to CPAP treatment has been shown to decrease the titres of these stress biomarkers in OSA patients (Hedner, Darpo, Ejnell, Carlson, & Caidahl, 1995).

The present study examined whether nocturnal over-activation of the SNS (measured by HRV, PWA, morning glucose and cortisol levels) is associated with impairments in the domains of sustained attention, RT, autobiographical memory and visuospatial skills, and whether SNS over-activation is correlated with OSA severity.

4.2 Method and Materials

4.2.1 Study Participants

All 78 participants had been referred to the Sleep Medicine and Research Centre, King Abdulaziz University Hospital, Jeddah, Saudi Arabia for overnight PSG studies. Potential participants were excluded if they: 1) used CPAP therapy; 2) had been diagnosed with a neurodegenerative disease, such as Alzheimer's disease or/and Parkinson's disease; 3) usually slept less than 2 hours per night (AASM recommends a minimum sleep duration for a valid PSG is 2 hours per night) (Epstein et al., 2009).

Ethics approval to conduct this study was obtained from the Human Research Ethics Committee of the Royal Melbourne Institute of Technology University (ethics reference number: HREC 21459), and from the King Abdulaziz University Hospital Human Research Ethics Committee (ethics reference number: 395-18). All participants provided written consent to participate in the study after indicating that they understood the nature of the study.

4.2.2 Procedure and Measurements

After participants were admitted to the sleep laboratory, height and weight were measured, and they completed a series of questionnaires designed to collect demographic information, and to assess daytime sleepiness and mood levels. Subsequently, cognitive tests were conducted at 5:00 pm. The time to completion all of the tests ranged from 40 to 45 minutes for all participants. The cognitive tests were administered in the following order: the PVT, Austin Maze and the autobiographical memory interview. Subjects were prepared for the polysomnography at 10:00 pm. After subjects awoke at 6:00 am, blood and urine samples were taken to measure first morning sample urinary and blood cortisol levels and fasting blood glucose levels. The same procedures and time of all tests and evaluations in the sleep laboratory were applied to the home studies.

4.2.3 Questionnaires

4.2.3.1 The Epworth Sleepiness Scale *Arabic version (Ahmed et al., 2014; Johns, 1991)*

This sleepiness scale assesses general level of daytime sleepiness and is frequently used with OSA patients. The questionnaire contains eight items, each scored from 0 to 3; with higher numbers representing higher levels of sleepiness and the eight items summed to give an overall score. The minimum score is 0 and maximum is 24, scores of 0–10 indicate no sleepiness; scores of 11–14 indicate mild sleepiness; 15–17 indicates moderate sleepiness; and scores above 17 indicate severe daytime sleepiness.

4.2.3.2 Depression, Anxiety, Stress Scale-21 (*Arabic version) (Ali et al., 2017; Henry & Crawford, 2005)*

The DASS-21 assesses the level of three emotional states: depression, anxiety and stress. The DASS depression subscale is sensitive to levels of mood, motivation and self-esteem. There is

convergent validity between the DASS depression and anxiety subscales and the Beck depression and anxiety inventories (Lovibond & Lovibond, 1995). Scores of 0–9 indicate an absence of depressive symptoms, 10-13 corresponds to mild depressive symptoms, 14–20 indicates moderate depression, more than 21-27 indicates severe depression and scores of 28 or more correspond to extremely serious depression.

4.2.3.3 Polysomnography Evaluation

Overnight PSG (SOMNO Medics Plus, SOMNOmedics, Randersacker, Germany) was used to evaluate sleep duration and quality, breathing and other sleep-related parameters. Most participants underwent PSG studies in the sleep laboratory, but five participants underwent home sleep studies. Home sleep studies employed the same PSG devices and procedures as used in the sleep laboratory and were performed for reasons related to patient convenience and mobility. For all PSG studies, a sleep technician applied the PSG sensors 30 minutes before sleep time. PSG consisted of continuous recordings from surface leads for EEG, EOG, EMG (from muscles in the submental space and the tibialis anterior muscles bilaterally) and ECG. A thermocouple device was used to measure nasal pressure and oral airflow, chest and abdominal impedance belts were used to measure respiratory muscle effort, a pulse oximeter was used to assess SaO_2 and pulse wave, a tracheal microphone was used to measure snoring, and body position sensors measured the sleep position. PSG studies were repeated for three participants (using the procedures outlined above) because of technical issues and loss of data during the initial studies.

4.2.4 Autonomic Nervous System Measurements

4.2.4.1 Heart Rate Variability

HRV is derived from analysis of the intervals between regular heartbeats (NN intervals) (McCraty & Shaffer, 2015) to measure ANS activity (Sztajzel, 2004). The spectrum of RR intervals was analysed within three frequency bands: very LF: deceleration capacity–0.04 Hz; LF: 0.04–0.15 Hz; and HF: 0.15–0.4 Hz. Earlier studies indicated that HRV HF power mainly indicates the activity of the PNS, while HRV LF power predominately indicates activity of the SNS (Camm et al., 1996; Thayer, Yamamoto, & Brosschot, 2010). However, more recent studies have indicated that HRV LF can be influenced, to some extent, by parasympathetic activity (Goldstein et al., 2011; Sassi et al., 2015). In addition, HRV HF may show unstable results as a measure of PNS activity that may be attributed to individual differences, the nature of breathing and sleeping posture (Akselrod, 1995; Hirsch & Bishop, 1981; Malpas, 2002; Taylor et al., 1998). Malliani (2006) suggested that the HRV LF/HF ratio be considered an index of sympatho-vagal balance.

4.2.4.2 Pulse Wave Amplitude

PWA is a signal obtained from finger plethysmography that is directly and positively associated with blood flow (Burch, 1954). Decreases in PWA can indicate increased sympathetic activation (Grote, Zou, Kraiczi, & Hedner, 2003; Jaryal, Selvaraj, Santhosh, Anand, & Deepak, 2009). A ≥30% drop in the PWA has been recommended as the cut-off for identifying arousals and respiratory events in OSA (Haba-Rubio et al., 2005; Zacharia et al., 2008).

4.2.4.3 Biochemical Markers

The stress response during sleep was assessed from the first-morning sample of urine (urinary cortisol) and serum cortisol and glucose. The urine sample was collected using a sanitised kit and the venous blood sample was taken from a median cubital vein between 5:00 a.m. and 6:00 a.m. The blood sampling was done by a nurse, and urine and blood samples were stored for no longer than 2 hours at 2–8ºC prior to assay.

4.2.5 Neurobehavioral Evaluation

4.2.5.1 10-Minute Psychomotor Vigilance Test (Dinges & Powell, 1985)

This computerised visual test evaluates the ability to sustain attention and respond rapidly with a button press to cues presented on a digital screen. The reliability and validity of the 10-minute version of the test has been confirmed in previous studies (Dinges & Powell, 1985). The test is sensitive to sleep fragmentation and identifies lapses of sustained attention (Jung et al., 2011). Three outcome measures were used: 1) mean RT; 2) mean of the slowest 10% RT; and 3) number of lapses with RT >500 ms. An RT >100 ms is considered valid; a false start is recorded when RT is <100 ms or when a response occurs without stimulus presentation.

4.2.5.2 10-Trial Austin Maze (Milner, 1965)

This computerised maze measures visuospatial ability and visuospatial memory (Crowe et al., 1999; Stolwyk et al., 2013). Participants plot a course through a chequerboard maze by pushing buttons and identifying the correct order through trial and error. Each time the correct button is pushed, a green light is displayed; when an incorrect button is pushed, a red light is displayed and a buzzer sound. The Austin Maze-errors were defined by the total number of missed blocks, and the Austin Maze-time was defined as the total time spent in every trail. The current study allowed for a maximum of 10 trials because the literature shows a strong correlation between

errors that occur up to the tenth trial of an experiment and errors to criterion (Bowden et al., 1992).

4.2.5.3 The Autobiographical Memory Interview (Kopelman et al., 1989)

This method assesses both episodic and semantic memory. For present purposes, memories of three time points in each participant's lifespan were assessed: childhood (before high school); early adulthood (including career, relationships, marriage and children); and recent life (including present and previous hospital or institution stays over the previous 5 years as well as recent holidays or journeys). Scoring was based on published guidelines (Kopelman et al., 1989). In the case of episodic memory, participants received a score of 3 for full recall that included specifics of time and place; 2 for recall that was personal but general; 1 for an unclear personal memory; and 0 for no answer or a semantic memory. The maximum possible score for each time period was 9, and the maximum total score was 27. In the case of semantic memory (e,g. names), responses were weighted for the level of detail retained (e.g. house number, street name and district). The maximum possible score for each time period was 21 points, and the maximum total was 63. The AMI is known to achieve high levels of accuracy, reliability and validity (Kopelman et al., 1989). AMI has been translated from English language version into Arabic; two Arabic-speaking researchers reviewed the translation and suggested refinements in terms of expression, phrasing and concepts. The interviews were then translated into English by an independent bilingual translator with no knowledge of the topic. Comparison of the original and translated interviews revealed no significant differences in content or meaning.

4.2.6 Analysis

BMI was estimated according to the international standard (Nuttall, 2015). The PSG studies were scored manually according to the AASM 2012 scoring protocol (Berry, Brooks, et al.,

2012). The classification of abnormal breathing events was based on AASM recommendations (Berry, Budhiraja, et al., 2012). Apnoeas were defined as greater than 90% reduction in airflow from the baseline for at least 10 seconds, while hypopnoeas were defined as a discernible reduction in airflow of at least 30% of the pre-event baseline using nasal pressure, and an associated reduction in oxygen saturation of at least 3%, followed by either oxygen desaturation or an electroencephalographic arousal, despite the persistent effort of the chest and abdominal muscles to overcome the obstruction. The severity of OSA was estimated from the AHI. The degree of hypoxia was based on the cumulative time (in seconds) spent with SaO_2 below 90%, while the degree of sleep fragmentation was assessed by the Arousal Index calculated by dividing the total number of arousals by the number of hours of sleep. In addition, the duration of NREM sleep stages N1, N2, and N3; and the duration of the REM sleep stage were analysed. Three PSG technicians verified all PSG scores to ensure the quality of the scoring process. The technicians also randomly selected and scored cases to confirm inter-observer reliability and accuracy.

HRV was analysed using Lab Chart-Pro analysis software (AD Instruments, Sydney, Australia). During PSG, the ECG was continuously acquired at 1 kHz. The ECG record for the entire night's sleep was divided into 5-minute segments for analysis. Noise (e.g. from body movement) was manually removed. The remaining normal-to-normal RR intervals were analysed using the Fast Fourier Transform algorithm.

The plethysmography data were extracted at 128 Hz during PSG and artefacts were removed using Lab Chart-Pro analysis software (AD Instruments, Sydney, Australia). Analysis was limited to PWA drops of ≥30% for more than 3 seconds and less than 60 seconds (Hirotsu et al., 2020). Nocturnal SNS activity was estimated via two measures: 1) PWA drop index during sleep, calculated by dividing the number of PWA drops into the number of sleep hours; and 2)

PWA drop time duration index, calculated by dividing the cumulative time spent within PWA drops into the number of sleep hours.

Biochemical markers including urine cortisol, and serum cortisol and glucose were analysed in a single laboratory by the same biochemist. The biochemist was blind to participants' OSA severity. Cortisol samples were analysed using an Atellica IM Cortisol analyser using a sample volume of 20 µL. Serum glucose was analysed using the Dimension Vista® 500 system; the sample volume was 1.2 µL. The µg/dL units were converted to mmol/L for easy readability.

Statistical analysis was conducted using SPSS version 26 (IBM Corp., Armonk, NY, US). Continuous data were checked for normality. Variables found to be non-normally distributed were log-transformed prior to statistical analysis: HRV LF/HF ratio, PVT slowest 10%, AM time, AM errors, AMI childhood semantic memory, AMI adult early life memory and AMI recent life memory. The data were expressed as mean and *SD* for continuous variables and as frequencies and percentages for categorical variables. ANOVA using Bonferroni post-hoc analysis was used to determine significant differences between groups based on OSA levels and demographic variables, depressive symptoms, daytime sleepiness, nocturnal SNS indices and PSG parameters. Between-group comparisons of categorical data were made using Pearson's chi-square tests. As a pre analysis, simple linear regressions were performed to determine the strength of associations between nocturnal SNS indices and OSA severity. Correlation analysis was conducted to identify associations between possible confounders and performance on cognitive tests. Simple linear regression was applied to assess the relationship between OSA severity and SNS indices. Multiple linear regression examined associations between nocturnal SNS indices and cognitive performance. All models were corrected for multiple comparisons with the FDR (Benjamini & Hochberg, 1995), and multicollinearity was demonstrated using a VIF of <2.0. Accordingly, the statistical significance was reported for

models that had $p < .05$ after having been adjusted for multiple comparisons with the FDR and/or models that showed no multicollinearity, as assumed with a VIF of <2.0.

4.3 Results

Seventy-eight participants met the inclusion criteria (51 males and 27 females) (age $M = 41.33$, $SD = 13.0$ years; mean BMI, $M = 33.2$, $SD = 9.2$ kg/m^2). The PSG results revealed that 12 of the 78 participants did not have OSA, 27 had mild OSA, 17 had moderate OSA and 22 had severe OSA.

Table 4.1 compares demographic, daytime sleepiness, nocturnal SNS indices and PSG data between the four OSA severity groups. The severe and moderate OSA groups were significantly older than were those in the non-OSA group. BMI, depression and ESS scores varied little among OSA severity groups. In terms of PSG, both SaO_2 time spent below 90%, and the Arousal Index increased significantly with OSA severity (AHI). The percentage of the time duration for sleep stages, in N1 sleep was higher and REM sleep was lower in OSA severe group compared to the other OSA severity groups. For N2 sleep and N3 sleep time duration percentage, there were no significant variances between the groups found. In terms of nocturnal SNS indices, both the PWA drop index and PWA drop duration index increased significantly as OSA severity increased. In addition, the HRV HF/LF ratio was significantly higher in the severe OSA group than in the non-OSA group. Moreover, blood glucose levels were not markedly high among the OSA severity groups.

Table 4.1 Comparison of demographic variables, depression, daytime sleepiness, PSG parameters and nocturnal SNS indices by OSA severity group.

	Non-OSA (n = 12)	Mild OSA (n = 27)	Moderate OSA (n = 17)	Severe OSA (n = 22)	
Variable	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***p-value***
Age (years)	33.1 (14.8)[3,4]	38.6 (11.1)	44.7 (12.3)[1]	46.4 (10.4)[1]	**.01**
Body Mass Index (kg/m^2)	30.2 (9.7)	32.2 (8.1)	32.5 (8.8)	37.1 (9.7)	.11
Current smoker (%)$^+$	1 (8)	6 (23)	4 (16)	9 (47)	.15
DASS-21 depression subscale	8.3 (8.3)	13.3 (9.7)	10.9 (10.7)	11.6 (9.0)	.49
ESS	9.2 (5.3)	9.6 (4.4)	10.5 (6.9)	13.3 (6.4)	.10
Oxygen Desaturation Index	2.6 (1.8)[4]	9.4 (6.7)[4]	16.3 (13.6)[4]	47.6 (25.4)[1,2,3]	**<.01**
SaO_2 durations <90% (sec)	0 (1)[4]	2 (6)[4]	11 (28)[4]	32 (46)[1,2,3]	**<.01**
Arousal number (index)	1.4 (1.1)[3,4]	5.5 (4.8)[4]	12.2 (4.9)[1,4]	26.3 (16.8)[1,2,3]	**<.01**
N1 sleep time duration (%)	08 (04)[4]	12 (8)[4]	12 (7)[4]	21 (13)[1,2,3]	**<.01**
N2 sleep time duration (%)	49 (10)	45 (12)	51 (15)	44 (14)	.25
N3 sleep time duration (%)	22 (09)	26 (13)	21 (16)	119 (20)	.53
REM sleep time duration (%)	14 (08)[3,4]	09 (07)	07 (06)[1,4]	06 (07)[4]	**.01**
PWA drop number (index)	2.9 (3.3)[4]	3.4 (3.5)[4]	5.9 (5.5)[4]	11.3 (9.0)[1,2,3]	**<.01**
PWA drop time duration (index)	2.1 (2.6)[4]	2.8 (2.8)[4]	4.7 (4.7)[4]	9.3 (7.0)[1,2,3]	**<.01**
HRV LF/HF ratio (log)	0.1 (0.6)[4]	0.04 (0.8)	0.04 (0.7)	0.7 (0.8)[1]	**.03**
Morning urine cortisol (mmol/L)	75.1 (67.5)	91.9 (142.2)	107.9 (174.3)	155.8 (173.2)	.40
Morning blood cortisol (mmol/L)	232.3 (115.1)	247.8 (132.3)	289.9 (137.5)	296.9 (133.1)	.17
Morning blood glucose (mmol/L)	5.2 (0.9)	6.0 (2.3)	5.4 (1.0)	6.2 (2.6)	.41

Note: OSA severity cut-offs were: 5–14 AHI (mild); 15–29 AHI (moderate); ≥30 AHI (severe); significant differences between groups were defined by [1], $p < .05$ v. non-OSA; [2], $p < .05$ v. mild OSA; [3], $p < .05$ v. moderate OSA; [4], $p < .05$ v. severe OSA; log: logarithmic transformation; $^+$: Pearson's chi-square; DASS-21: depression, anxiety and stress scale–21; ESS: Epworth sleepiness scale; SaO_2: arterial blood oxygen saturation; PWA: pulse wave amplitude; HRV: heart rate variability; LF: low frequency; HF: high frequency; N1: sleep stage 1; N2: sleep stage 2; N3: sleep stage 3; REM: rapid eye movement sleep stage.

Morning urine cortisol, morning blood cortisol and blood glucose did not display a significant increase in association with OSA severity.

PWA indices were analysed by linear regression, the results showed that those with more frequent drops in PWA and who spend more time with very low PWA also have the most severe OSA ($R^2 = 0.36$) (Figure 4.1a), and with PWA drop time duration index ($R^2 = 0.39$)

(Figure 41b). Additionally, there was a weak association between AHI and the HRV LF/HF ratio (R^2 = 0.09) (Figure 4.1c).

Simple linear regressions were performed to examine the associations between the nocturnal SNS indices. The results revealed that the HRV LF/HF ratio was associated weakly with both the PWA index (R^2 = 0.12) and PWA time duration index (R^2 = 0.10).

Multiple linear regression analyses were performed to examine the relationships between nocturnal SNS indices (PWA, HRV and blood glucose) and BMI, age and PSG parameters (SaO_2 time <90% and Arousal Index) (Table 4.2). All regression models were significant (p < .05), even after FDR adjustments, and they showed no multicollinearity (VIF < 2.0), with the exception of urine and blood cortisol models. The results showed that nocturnal PWA was significantly associated with the Arousal Index. In addition, the HRV LF/HF ratio was associated with age and the Arousal Index. However, morning blood glucose was only significantly related to SaO_2 time <90%.

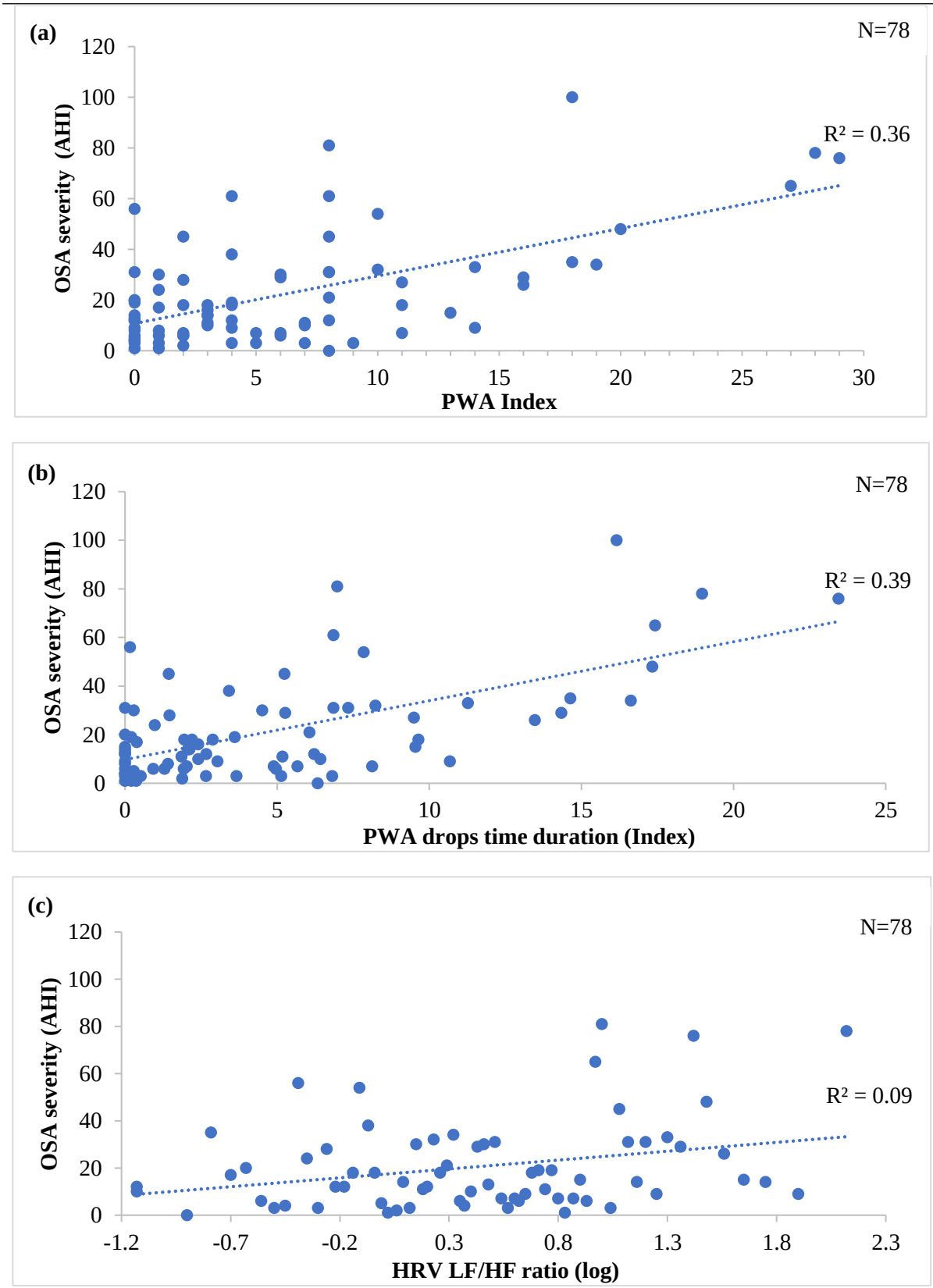

Figure 4.1 The relationship between OSA severity (AHI) and PWA index (a); PWA drop time duration (b); HRV ratio (log) (c). OSA: Obstructive Sleep Apnoea; AHI: Apnoea–Hypopnoea Index; PWA: Pulse Wave Amplitude; HRV: Heart Rate Variability; LF: Low Frequency; HF: High Frequency; log: logarithm transformation.

Table 4.2 Multiple regression analysis including age, SaO_2 time <90%, Arousal Index and Body Mass Index in the model to predict the nocturnal pulse wave amplitude, heart rate variability, and first-morning samples of cortisol and glucose levels, and after applying FDR corrections for multiple comparisons.

Variable	R^2	p_{model}	Predictor	*SE*	*β*	*sr*	*p-value*
PWA drop index	0.40	**<.01***					
			Body Mass Index	0.08	0.13	0.12	.22
			Age (years)	0.06	0.09	0.09	.35
			Arousal number (index)	0.06	0.56	0.46	**<.01**
			SaO_2 time <90%	0.00	0.10	0.81	.38
PWA drop time index	0.37	**<.01***					
			Body Mass Index	0.06	0.09	0.09	.37
			Age (years)	0.04	0.07	0.06	.50
			Arousal number (index)	0.05	0.57	0.38	**<.01**
			SaO_2 time <90%	0.00	0.05	0.43	.65
HRV LF/HF ratio (log)	0.25	**<.01***					
			Body Mass Index	0.00	0.08	0.08	.53
			Age (years)	0.00	0.37	0.35	**<.01**
			Arousal number (index)	0.00	0.37	0.32	**<.01**
			SaO_2 time <90%	0.00	0.20	0.16	.14
Morning blood glucose (mmol/L)	0.26	**<.01***					
			Body Mass Index	0.02	0.08	0.08	.46
			Age (years)	0.02	0.08	0.08	.54
			Arousal number (index)	0.02	0.15	0.13	.22
			SaO_2 time <90%	0.00	0.33	0.32	**.01**

Note: *significant model ($p < .05$) after FDR adjustment; log: logarithmic transformation; R^2 = models' multiple correlations; β = standardised regression coefficient; PWA: pulse wave amplitude; HRV: heart rate variability; LF: low frequency; HF: high frequency; SaO_2: arterial blood oxygen saturation.

Factors that were not related to OSA severity or OSA parameters were excluded from further analysis. To identify confounders that were correlated with cognitive test results, Pearson's correlation tests were applied to reveal variables that were confounders with the cognitive test variables. The results indicated that age was linked to most of the PVT indices and all the AM indices. However, AMI age was only linked to semantic memory stage (total episodic memory,

episodic early adult life memory and episodic recent life memory). Smoking was positively correlated with AM errors and semantic recent life memory, but ESS scores were not correlated with performance in any cognitive tests.

Multiple linear regression analyses were used to determine the effects of the nocturnal SNS indices (PWA indices, HRV LF/HF ratio and morning blood glucose) on the PVT, AM and AMI indices after controlling for hypoxia, sleep fragmentation, depression and the demographic confounding variables (age and smoking status) (Tables 4.3 and 4.4). None of the regression models displayed multicollinearity (VIF < 2.0). After FDR adjustment for multiple comparisons, models that included the PVT, AM and some of the AMI indices (total semantic memory and recent life episodic memory) remained significant ($p < .05$). However, performance on the PVT, AMI and AM errors were not associated with any of the nocturnal SNS indices, whereas performance on the AM time was associated with the PWA index, PWA drop time duration index and HRV LF/HF.

Table 4.3 Multiple linear regression analyses showing the association between the psychomotor vigilance test and Austin Maze and the sympathetic nervous system activity indices.

Cognitive test	R^2	*Predictors*	*SE*	*β*	*sr*	*p-value*
PVT RT-mean						
	0.29	PWA drops (index)*	4.08	0.14	0.11	.32
	0.29	PWA drops time durations (index)*	1.36	0.06	0.04	.68
	0.32	HRV LF/HF ratio (log)*	8.52	0.08	0.07	.54
	0.29	Morning blood glucose (mmol/L)*	3.37	0.04	0.04	.72
PVT slowest 10%						
	0.22	PWA drops (index)*	1.09	0.04	0.03	.77
	0.21	PWA drops time durations (index)*	5.05	0.04	0.04	.77
	0.26	HRV LF/HF ratio (log)*	28.68	0.11	0.09	.37
	0.22	Morning blood glucose (mmol/L)*	12.50	0.14	0.12	.25
PVT RT-10-lapses >500ms						
	0.37	PWA drops (index)*	0.11	0.09	0.07	.42
	0.36	PWA drops time durations (index)*	0.11	0.01	0.01	.90
	0.39	HRV LF/HF ratio (log)*	0.90	0.02	0.07	.87
	0.36	Morning blood glucose (mmol/L)*	0.35	0.04	0.04	.70
AM-time						
	0.43	PWA drops (index)*	0.29	0.29	0.22	**.01**
	0.41	PWA drops time durations (index)*	0.37	0.24	0.19	**.04**
	0.45	HRV LF/HF ratio (log)*	2.76	0.29	0.24	**.01**
	0.39	Morning blood glucose (mmol/L)*	0.92	0.09	0.08	.40
AM-errors						
	0.29	PWA drops (index)*	0.15	0.12	0.09	.35
	0.27	PWA drops time durations (index)*	0.19	0.08	0.01	.88
	0.30	HRV LF/HF ratio (log)*	1.40	0.07	0.06	.60
	0.29	Morning blood glucose (mmol/L)*	0.49	0.14	0.12	.29

Note:*significant model ($p < 0.05$) after false discovery rate adjustment; The model was adjusted for demographic cofounders, hypoxia, sleep fragmentation and depressive symptoms; R^2=the models' multiple correlations; SE=standard error; β=standardized regression coefficient; sr=semi-partial correlation; log=logarithmic transformation; PVT, psychomotor vigilance test; RT, reaction time; AM, Austin Maze; ms, milliseconds; PWA, pulse wave amplitude; HRV, heart rate variability; LF, low frequency; HF, high frequency; mins, minutes.

Table 4.4 Multiple linear regression analyses of the association between autobiographical memory interview indices and sympathetic nervous system activity indices.

Cognitive test	R^2	Predictors	*SE*	*β*	*sr*	*p-value*
Total semantic memory						
	0.12	PWA drops (index)	0.09	0.04	0.03	.76
	0.12	PWA drops time durations (index)	0.06	0.02	0.02	.89
	0.16	HRV LF/HF ratio (log)	0.73	0.01	0.01	.92
	0.14	Morning blood glucose (mmol/L)	0.27	0.01	0.01	.93
Childhood semantic memory						
	0.12	PWA drops (index)	0.05	0.01	0.01	.99
	0.12	PWA drops time durations (index)	0.06	0.02	0.02	.88
	0.20	HRV LF/HF ratio (log)	0.39	0.16	0.15	.19
	0.12	Morning blood glucose (mmol/L)	0.15	0.01	0.01	.91
Early adult life semantic memory						
	0.08	PWA drops (index)	0.05	0.06	0.05	.70
	0.08	PWA drops time durations (index)	0.06	0.03	0.02	.83
	0.13	HRV LF/HF ratio (log)	0.39	0.17	0.16	.18
	0.08	Morning blood glucose (mmol/L)	0.15	0.09	0.08	.47
Recent life semantic memory						
	0.13	PWA drops (index)	0.04	0.05	0.04	.71
	0.13	PWA drops time durations (index)	0.05	0.00	0.00	.95
	0.15	HRV LF/HF ratio (log)	0.36	0.03	0.03	.83
	0.13	Morning blood glucose (mmol/L)	0.14	0.06	0.05	.66
Total episodic memory						
	0.17	PWA drops (index)	0.12	0.06	0.05	.66
	0.14	PWA drops time durations (index)	0.15	0.05	0.04	.71
	0.16	HRV LF/HF ratio (log)	1.01	0.22	0.19	.10
	0.14	Morning blood glucose (mmol/L)	0.36	0.09	0.08	.48
Episodic childhood memory						
	0.01	PWA drops (index)	0.05	0.02	0.02	.88
	0.02	PWA drops time durations (index)	0.06	0.00	0.00	.99
	0.03	HRV LF/HF ratio (log)	0.43	0.12	0.11	.35
	0.02	Morning blood glucose (mmol/L)	0.00	0.05	0.05	.67
Episodic early adult life memory						
	0.17	PWA drops (index)	0.05	0.13	0.10	.36
	0.10	PWA drops time durations (index)	0.06	0.09	0.08	.50

Cognitive test	R^2	Predictors	*SE*	*β*	*sr*	*p-value*
	0.09	HRV LF/HF ratio (log)	0.43	0.16	0.14	.27
	0.09	Morning blood glucose (mmol/L)	0.15	0.03	0.02	.84
Episodic recent life memory						
	0.20	PWA drops (index)*	0.05	0.07	0.06	.59
	0.18	PWA drops time durations (index)*	0.06	0.07	0.05	.62
	0.10	HRV LF/HF ratio (log)*	0.40	0.15	0.13	.26
	0.10	Morning blood glucose (mmol/L)*	0.14	0.12	0.09	.36

Note: *significant model ($p < 0.05$) after false discovery rate adjustment; The model was adjusted for demographic cofounders, hypoxia, sleep fragmentation and depressive symptoms; R^2=the models' multiple correlations; SE=standard error; β=standardized regression coefficient; sr=semi-partial correlation; log=logarithmic transformation.

4.4 Discussion

The present study estimated nocturnal over-activity of the SNS through a variety of measures that included PWA, HRV and stress response biomarkers (first-morning urinary and blood cortisol, and blood glucose samples). The results showed that PWA and HRV are linked to OSA severity, and both are associated with the Arousal Index. In contrast, morning blood glucose levels are associated only with the time spent with an SaO_2 <90%. In terms of cognitive impairment, nocturnal over-activity of the SNS, as measured by PWA and HRV, is linked to visuospatial dysfunction, but not to sustained attention, RT or autobiographical memory. Morning blood glucose is not associated with any cognitive impairment.

The present study confirmed previous reports that nocturnal over-activity of the SNS is associated with OSA severity. A systematic review of Sequeira et al. (2019) confirmed that adults with OSA could have nocturnal reduced vagal tone and higher sympathetic activity. Moreover, Wang, Chen, Cao, Guo and Dong (2006) found that arousal from sleep influences cardiovascular regulation, as measured by HRV. Although the LF/HF ratio is regarded by some as an unreliable marker of SNS activity (Billman, 2013), the current study found a strong association between the LF/HF ratio and the arousals induced by OSA events, indicating that the LF/HF ratio is sensitive to the increased stress caused by apnoeic events. The present study

showed that the LF/HF ratio increases with age, and this finding might help to explain the variable reports on the reliability of the LF/HF ratio in OSA, as age is rarely treated as a confounding factor. Interestingly, a study of awake healthy subjects reported that the LF/HF ratio is unaffected by age in either sex (Agelink, Baumann, Akila, & Ziegler, 2001), which raises the possibility that the effect of age is only evident during sleep.

In contrast to the equivocal views on the utility of HRV, drops in PWA are widely considered a reliable indicator of nocturnal SNS over-activation (Haba-Rubio et al., 2005). Similar to the present results, which showed that PWA indices were predicted by OSA severity and particularly by arousals associated with respiratory events, Delessert et al. (2010) found that the drops in PWA observed in OSA are strongly linked to increased arousals from sleep. In addition, Adler et al. (2013) stated that PWA drops are sensitive indicators of EEG micro-arousals associated with respiratory events. The current study did not find a strong association between PWA and the LF/HF ratio, indicating that they are independent measures. The fact that the present study found that drops in PWA are associated with arousals and with OSA severity lends support to the validity of the LF/HF ratio as a measure of nocturnal SNS activation, since it was also associated with arousals and OSA severity.

The findings of the present study are aligned with those of earlier studies of OSA patients that reported that blood glucose concentrations are associated with the time spent with a SaO_2 <90%. For instance, a retrospective study conducted by Al-Abri, Al-Lawati, Al-Alawi and Al-Manairi (2011) of 116 males and 64 females found that T2D was significantly correlated with time spent with SaO_2 <90%. Further, according to Priou et al. (2012), increased hypoxemia during sleep is independently associated with the levels of glycosylated haemoglobin among non-diabetic OSA patients. Collectively these results indicate that the stress associated with

SaO_2 <90% is sufficient to elevate blood glucose levels for sustained periods of time, such that they remain elevated upon waking.

Despite confirming a relationship between morning blood glucose levels and time spent with SaO_2 <90%, glucose levels were not associated with any cognitive impairments. Previous studies of patients without OSA reported a strong relationship between blood glucose and memory impairments (Weinstein et al., 2015) and visuospatial dysfunction (van Duinkerken & Ryan, 2020). The lack of such a relationship in the present study is probably the result of two factors. First, the cognitive tests were conducted in the evening, by which time the blood glucose levels may have decreased. Second, the morning blood glucose levels were only mildly elevated in the present study, with most values falling within the normal or pre-diabetic range (<7.0 mmol/l), whereas in studies showing a relationship with cognition, patients had much higher glucose levels (i.e. in the diabetic range).

In the current study, HRV and PWA were associated with impairments on a test of visuospatial function, supporting the link between nocturnal over-activity of the SNS and visuospatial dysfunction. A systematic review of HRV and cognitive dysfunction in non-OSA patients by Forte, Favieri, et al. (2019) concluded that lower HRV was associated with poor visuospatial implementation. In contrast, Idiaquez et al. (2014) reported that performance on the Trail Making Test-B, which measures visuospatial skills (Allen, Owens, Fong, & Richards, 2011), and nocturnal over-activation of the SNS, were not related to each other in OSA (Idiaquez et al., 2014). It is unclear why Idiaquez and colleagues did not find a correlation between visuospatial deficits and over-activation of the nocturnal SNS, whereas the present study did. This difference may be due to the larger sample size in the current study, Idiaquez and colleagues' recruitment of a male-only sample, or the different measures of visuospatial function used in the two studies. Additionally, only the current study has controlled for the

cofounders that may have led to the contrasting results between the two studies. Regardless of the reason, the present study revealed a robust relationship between SNS over-activation during sleep in OSA patients, and their performance during wakefulness on the AM. This new finding indicates that nocturnal over-activity of the SNS should be taken into consideration in future studies of cognitive impairment in OSA.

Previous studies of healthy subjects have reported a relationship between sympathetic over-activation and poorer performance on tests of memory (Frewen et al., 2013; Shah et al., 2011) and RT (Mahinrad et al. (2016). The present study did not find such associations. This may be because other studies examined the effects of acute stress on cognitive performance, whereas the present study examined the effect of chronic nocturnal stress on cognitive performance during wakefulness, when stress levels were not elevated. It is pertinent that the levels of cortisol in the blood and urine of the patients in this study were not associated with any measure of OSA severity or cognitive performance. This lack of a relationship indicates that these patients were not physiologically stressed at the time of waking. It follows that the relationship observed between nocturnal over-activity of the SNS and visuospatial dysfunction was not the result of acute stress but some other factor, such as the elevations in nocturnal BP that accompany apnoeic episodes (Gąsecki, Kwarciany, Nyka, & Narkiewicz, 2013), and that are involved in brain injury (Swan, Carmelli, & Larue, 1998). BP as a mechanism for cognitive dysfunction in OSA, will be extensively discussed in the next Chapter.

The present study has limitations that should be considered in future studies. First, the non-OSA group was smaller than the OSA group. Although this difference was negated using correlational analyses that treated OSA severity as a continuous variable rather than a categorical variable, it is possible that the smaller number of participants without OSA decreased the statistical power. Second, blood glucose and cortisol measurements were based

on samples taken upon waking, and it is possible that a more dynamic picture of SNS over-activation could have been obtained by continuously sampling blood throughout the night. Third, the current study did not include any brain imaging, such as MRI, so it was not possible to correlate the observed cognitive deficits with structural changes. It is hoped that future studies will address these limitations.

4.5 Conclusion

This study examined whether there are associations between nocturnal over-activity of the SNS and cognitive impairments in OSA. The study revealed that PWA and the HRV LF/HF ratio are associated with OSA severity, and both are linked to the Arousal Index; whereas morning blood glucose levels are associated with the time spent with an SaO_2 <90%. It was found that SNS over-activity during sleep, as measured by PWA and HRV, is linked to visuospatial dysfunction among OSA patients. Morning blood glucose was not related to impairments on any of the cognitive tests used. These findings suggest that increased SNS activity during sleep contributes to visuospatial dysfunction in OSA. Accordingly, interventions that reduce the nocturnal activation of the SNS may improve visuospatial function in these individuals.

Chapter 5: Association Between Nocturnal Peaks of Blood Pressure and Cognitive Performance in Obstructive Sleep Apnoea

Abstract

OSA is characterised by recurrent episodes of partial or complete cessation of breathing during sleep and an increased effort to breathe. OSA induces repeated spikes of nocturnal BP as a result of increased activity of the SNS during sleep. High resting BP is associated with disruptions in the structure and functioning of the cerebral blood vessels and with cognitive dysfunction. While cognitive impairment is relatively common in OSA, it is not known whether peaks in nocturnal BP are associated with such impairment. In this study, a cohort of patients participated in overnight PSG studies at a major sleep laboratory investigating whether nocturnal elevations in BP are associated with cognitive dysfunction in OSA. Nocturnal BP was continuously measured by PTT. Of the 75 participants, 12 had no OSA, 26 had mild OSA, 18 moderate OSA and 19 severe OSA. The results revealed that SBP peaks were associated with OSA severity, while DBP peaks were not. Peaks of nocturnal SBP were associated with poorer performance on a test of visuospatial function, but not with impairments on tests of sustained attention, RT or autobiographical memory. In conclusion, the present results indicate that nocturnal peaks of SBP that are substantially higher than normal daytime values may contribute to visuospatial dysfunction in OSA.

5.1 Introduction

OSA refers to sleep-disordered breathing characterised by repeated collapse of the upper airway (Epstein et al., 2009). According to recent estimates, the global prevalence of OSA ranges from 9% to 38% in middle-aged individuals (Senaratna et al., 2017). Cognitive

dysfunction is a prominent comorbidity of OSA that negatively affects daytime functioning. People with OSA are twice as likely as healthy peers to have difficulty concentrating, performing repetitive tasks and acquiring new knowledge (Ulfberg et al., 1996). These impairments have been attributed to the detrimental effects of sleep fragmentation and IH (Bucks et al., 2013; Canessa et al., 2011; Tamilarasan et al., 2019; Verstraeten, 2007); however, these factors are only able to account for 30–40% of the variance, so additional factors must be involved. One possible factor is systemic hypertension, which in midlife has been strongly linked to impairments in visuospatial abilities, motor speed and attention (Iadecola & Gottesman, 2019), and elevated SBP has been linked to decreased regional and brain volumes, with further reductions in volume noted over time (Firbank et al., 2007; Leritz et al., 2011). The present study is the first to examine the association between overnight peaks in BP and cognitive dysfunction in OSA.

Patients with OSA often display some degree of hypertension at rest, and the severity of resting hypertension increases with OSA severity (M. Ahmad, Makati, & Akbar, 2017). In addition, studies that have continuously monitored BP during sleep have reported that overnight BP in OSA patients can be considerably higher than resting BP (M. Ahmad et al., 2017); consequently, the resting BP in these patients may not be an accurate indicator of hypertensive risk. As these peaks in nocturnal BP are undetectable during waking, they represent an occult form of hypertension that has potential to cause organ damage during sleep. Indeed, increasing OSA severity is associated with a greater risk of cardiovascular diseases including strokes and cardiac arrhythmias (Mehra et al., 2006; Munoz et al., 2006), and there is strong evidence that nocturnal BP is more closely linked than waking BP to the risk of emerging organ damage and future cardiovascular events (Asayama et al., 2019). As the gold standard treatment for OSA, CPAP significantly reduces nocturnal BP (Dimsdale, Loredo, & Profant, 2000).

People without OSA typically display a 10–15% drop in their BP during sleep, in a pattern known as ‘dipping’ that is determined as the average of the BP value over a nocturnal period. However, nocturnal BP dipping is absent from most OSA patients, and a lack of dipping is associated with a significant increase in the probability of nocturnal peaks in BP (Ahmad et al., 2017). These peaks result from increased activity of the SNS in response to the physiological stress caused by intermittent episodes of hypoxia and arousal from sleep (Bisogni, Pengo, Maiolino, & Rossi, 2016). Nevertheless, Almeneessier et al. (2020) found that increased SBP and DBP are expected following an obstructive event, and their values are higher with increased severity of O2 desaturation.

Until recently, researchers used 24-hour ABPM, which records BP at regular intervals (usually every 15 or 30 minutes). However, ABPM is uncomfortable and can disturb sleep patterns, thereby preventing the BP from dipping (Agarwal & Light, 2010). Further, the temporal resolution provided by ABPM is too coarse to provide an accurate assessment of BP peaks associated with apnoeic events. More recently, researchers have used PTT as a non-invasive measure of beat-to-beat BP (Almeneessier et al., 2020; Gehring et al., 2018; Zhang, Gao, & Mukkamala, 2011). Measures of nocturnal BP obtained with the PTT method are highly correlated with those obtained from the Portapres system that measures BP using a finger cuff (Hennig et al., 2012), indicating the validity of PTT for continuous measurement of BP.

The primary aim of this study was to investigate the association of nocturnal peaks in BP with cognitive dysfunction in patients with clinically verified OSA.

5.2 Method and Materials

5.2.1 Participants

The study participants were patients aged 18–65 years who had been referred for nocturnal diagnostic PSG studies at the Sleep Medicine and Research Centre, King Abdulaziz University Hospital, Jeddah, Saudi Arabia. The following exclusion criteria were applied: 1) current use of CPAP therapy; 2) a neurodegenerative disease (e.g. Alzheimer's disease, Parkinson's disease); and/or 3) regularly sleeping less than 2 hours per night (for a PSG time duration, the AASM recommends a minimum sleep duration of 2 hours per night; Epstein et al., 2009).

The study was approved by the Royal Melbourne Institute of Technology University Human Research Ethics Committee (ethics reference number: HREC 21459) and the King Abdulaziz University Hospital Human Research Ethics Committee (ethics reference number: 395-18). Informed consent was obtained from all participants after they had received an explanation of the nature of the study at the Sleep Medicine and Research Centre.

5.2.2 Procedure and Measurement

After consenting to participate and following admission to the sleep laboratory participants completed a series of questionnaires designed to collect demographic details and information about daytime sleepiness and depressive symptoms. This was followed by a battery of cognitive assessments. Cognitive tests were conducted at 5:00 pm. The time taken to complete all tests ranged from 40 to 45 minutes. The cognitive tests were administered in the same order to all participants. Prior to the sleep study (a standard nocturnal PSG study), participants' height, weight and resting BP (systolic and diastolic) using a sphygmomanometer were recorded. The same procedures and timing of all tests and evaluations in the sleep laboratory applied during all home studies.

5.2.3 Questionnaires

5.2.3.1 The Epworth Sleepiness Scale *Arabic version (Ahmed et al., 2014; Johns, 1991)*

This scale assesses daytime sleepiness and is frequently used with OSA patients. The scale consists of eight items, each rated from 0 to 3, with higher numbers indicating a higher chance of dozing. Scores on these eight items are summed to calculate an overall score. The minimum score is 0 and maximum is 24. In general, a higher score indicates greater levels of sleepiness; scores of less than 11 indicate little or no daytime sleepiness; scores of 11–14 indicate mild daytime sleepiness; scores of 15–17 reflect moderate daytime sleepiness; and scores greater than 17 indicate severe daytime sleepiness.

5.2.3.2 Depression, Anxiety, Stress Scale-21 *(Arabic version) (Ali et al., 2017; Henry & Crawford, 2005)*

This 21-item questionnaire is designed to measure the magnitude of three negative emotional states, including depression. The DASS depression subscale captures reported low mood, motivation and self-esteem. There is convergent validity between the DASS and Beck depression and anxiety inventories (Lovibond & Lovibond, 1995). Scores of 0–9 indicate a lack of depressive symptoms, 10-13 indicate mild depressive symptoms, 14–20 indicate moderate depression, more than 21-27 indicates severe depression and scores of 28 or more correspond to extremely serious depression.

5.2.3.3 Polysomnographic Evaluation

Overnight PSG (SOMNO Medics Plus, SOMNOmedics, Randersacker, Germany) was used to assess sleep duration and quality, as well as breathing and other sleep-related parameters.

Seventy-two of the PSG studies were conducted at the Sleep Medicine and Research Centre; for reasons related mainly to patient convenience, three studies were performed in patients' homes, using the same devices and procedures. In all cases, a sleep technician applied the PSG sensors 30 minutes before sleep time. Using surface leads, the PSG made continuous recordings of EEG, EOG, and ECG data, as well as EEG data from muscles in the submental space and bilaterally from the tibialis anterior muscles. EEG activity was measured using 10-channel recording montage (Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1 and O2) and left/right electrooculography. The nasal pressure was recorded, and nasal and oral airflow were measured by thermocouple device; chest and abdominal impedance belts were used to measure respiratory muscle effort; a pulse oximeter was used to measure SaO2 and pulse wave; a tracheal microphone was used to measure snoring; and body position sensors were used to capture sleep position. The same procedure was repeated in two cases because of technical issues and loss of data at the first attempt.

5.2.3.4 Blood Pressure Measurement

Resting systolic and DBP were measured by standard methods using a digital sphygmomanometer (OMRON, Kyoto, Japan) and PTT using a SOMNOmedics device. Both measurements (resting BPs) were recorded in a sitting position prior to sleep. The first recorded value for the PTT was taken as the resting BP value. The baseline BP was defined as the first recorded value of the PTT at sleep onset. Normal or pre-hypertension is classified as SBP <140 and DBP <90; grade 1 hypertension, SBP 140–159 and DBP 90–99; grade 2 hypertension, SBP 160–179 and DBP 100–109; and grade 3 hypertension, SBP >79 and DBP >109 (Gabb et al., 2016). Beat-to-beat nocturnal BP was analysed automatically using DOMINO software based on a non-linear pulse wave velocity–SBP function in combination with initial BP calibration.

Peaks in nocturnal SBP and nocturnal DBP were taken as the highest value observed during the night.

5.2.3.5 Continuous Blood Pressure Measurement

Continuous nocturnal BP (beat-to-beat) was measured by SOMNOscreen plus, which has been validated in accordance with the European Society of Hypertension protocol (Bilo et al., 2015), using PTT (Gehring et al., 2018). PTT is calculated from the time interval between ECG R-waves and the corresponding pulse wave as detected by pulse oximetry using finger photoplethysmography. Resting SBP and DBP was measured by PTT and by digital sphygmomanometer, while overnight BP was measured continuously with PTT.

The data of PTT were included for 75 subjects for SBP peaks and 61 subjects for DBP peaks. 14 of DBP peaks were excluded due to the artifact and/or missed data. The data of the resting SBP and DBP measured by sphygmomanometer were included for all 75 subjects. However, at the end of the study, we noticed that the resting PTT data from many participants, especially that related to DBP, was distorted by artifacts caused by interference from mobile phone signals. Consequently, resting SBP and DBP measured by PTT included data for only 55 subjects for SBP and only 40 subjects for DBP.

5.2.4 Neurobehavioral Evaluation

5.2.4.1 10-Minute Psychomotor Vigilance Test (Dinges & Powell, 1985)

This computerised visual test evaluates the ability to sustain attention and respond with a button press in a timely manner to cues that are presented on a screen. The reliability and validity of the 10-minute version of the test has been confirmed in previous studies (Dinges & Powell, 1985). The test is sensitive to sleep fragmentation and identifies any sustained attention deficit (Jung et al., 2011). Three outcome measures were used: 1) mean RT; 2) mean of the slowest

10% RT; and 3) number of lapses with RT >500 ms. An RT >100 ms is considered valid; a false start is recorded when RT is <100 ms or when a response occurs without stimulus presentation.

5.2.4.2 10-Trial Austin Maze (Milner, 1965)

This computerised maze measures visuospatial ability and visuospatial memory (Crowe et al., 1999; Stolwyk et al., 2013). Participants plot a course through a chequerboard maze by pushing buttons and identifying the correct order through trial and error. Each time the correct button is pushed, a green light is displayed; when an incorrect button is pushed, a red light is displayed, and a buzzer is sounded. The Austin Maze-errors was defined as the total number of missed blocks and the Austin Maze-time was defined as the total time spent in every trail. The current study allowed for a maximum of 10 trials because the literature shows a strong correlation between errors that occur after the tenth trial of an experiment and errors to criterion (Bowden et al., 1992).

5.2.4.3 The Autobiographical Memory Interview (Kopelman et al., 1989)

This method assesses both episodic and semantic memory. For present purposes, memories of three points in the person's lifespan were assessed: childhood (before high school); early adulthood (usually including career, relationships, marriage and children); and recent life (including present and previous hospital or institution stays over the previous 5 years as well as recent holidays or journeys). Scoring was based on published guidelines (Kopelman et al., 1989). In the case of episodic memory, participants scored 3 for full recall that included specifics of time and place; 2 for recall that was personal but general; 1 for an unclear personal memory; and 0 for no answer or a semantic memory. The maximum possible score for each time period was 9, and the maximum total score was 27. In the case of semantic memory (i.e. names), responses were weighted for level of detail retained (e.g. house number, street name

and district). The maximum possible score for each time period was 21 points, and the maximum total was 63. The AMI is known to achieve high levels of accuracy, reliability and validity. The candidate has translated the English language version into Arabic; two other Arabic-speaking researchers reviewed the translation and suggested refinements in terms of expression, phrasing and concepts. The interviews were then translated into English by an independent bilingual translator with no knowledge of the topic. Comparison of the original and translated interviews revealed no significant differences in content or meaning.

5.3 Analysis

Calculation of participants' BMI was based on the international standard, dividing weight in kilograms by height in metres squared (Nuttall, 2015). PSG recordings were scored using an algorithm and were then checked manually by scoring all records according to the AASM 2012 scoring protocol (Berry, Brooks, et al., 2012). The description of abnormal breathing events during sleep was based on AASM recommendations (Berry, Budhiraja, et al., 2012). Breathing abnormalities were defined as follows: a decrease in airflow of 90% or higher from the baseline for at least 10 seconds (apnoea) and a discernible reduction in airflow of at least 30% of the pre-event baseline using nasal pressure, associated with a reduction in oxygen saturation of at least 3%, followed by either oxygen desaturation or electroencephalographic arousal (hypopnoea) despite persistent efforts to overcome the obstruction using the chest and abdominal muscles. OSA severity was estimated using the AHI. Degree of hypoxia was assessed as SaO_2 duration (in seconds) <90%. The degree of sleep fragmentation was assessed by the Arousal Index, which was calculated by dividing the total number of arousals by the duration of sleep (arousals/h). In addition, duration of NREM sleep stages N1, N2 and N3 and duration of REM sleep was analysed. Three PSG technicians verified all PSG scores to ensure

the quality of the scoring process. The technicians also randomly selected and scored cases to confirm inter-observer reliability and accuracy.

Performance on the PVT and AM was analysed using software algorithms developed for these tasks. AMIs were scored according to the published guidelines and were consecutively scored and revised by the same researcher, using the same calculation procedures for all participants.

Statistical analysis was performed using SPSS version 26 (IBM Corp., Armonk, NY, US). Data from continuous variables were reviewed to determine whether any had extremely skewed distributions. Log transformation was performed to normalise the distribution of the following variables: PVT mean, PVT slowest 10%, AM time, AM errors, AMI childhood semantic memory, AMI adult early life memory, AMI recent life memory. The data were expressed as mean and *SD* for continuous variables and as frequencies and percentages for categorical variables. ANOVA with Bonferroni post-hoc analyses were used to identify significant differences between groups based on OSA levels and demographic variables, depressive symptoms, daytime sleepiness, BP indices and PSG parameters. Between-group comparisons of categorical data were performed using Pearson's chi-square tests.

Simple linear regression was conducted to: 1) examine the relationship between resting BP measured by PTT and sphygmomanometer; and 2) demonstrate the association between OSA severity and BP indices. Multiple linear regression analysis was used to: 1) identify the factors associated with nocturnal peaks of SBP; 2) identify any association between OSA severity and the mean of variances between baseline and peaks of SBP; 3) assess associations between nocturnal peaks of SBP and cognitive tests. Regression models were corrected for multiple comparisons with the FDR (Benjamini & Hochberg, 1995).

Regression models were defined as significant if $p < .05$ and they showed low multicollinearity as indicated by a VIF of <2.0.

5.4 Results

Seventy-five participants (52 males and 23 females) who presented sequentially to the Sleep Medicine and Research Centre met the inclusion criteria for this study. Their mean age was 41.1 (*SD* = 13.0) years, and their mean BMI was 33.2 (*SD* = 9.3). The PSG results indicated that 12 participants did not have OSA, 26 had mild OSA, 18 had moderate OSA and 19 had severe OSA.

Table 5.1 compares the dependent variables based on participant AHI levels. While those in the severe and moderate OSA groups were older than those in the non-OSA group, ESS and depression scores did not increase significantly with OSA severity. BMI did not differ significantly across the four groups, but there were significant differences between the OSA severity groups in terms of sleep parameters, including SaO_2 time <90% and Arousal Index. Sleep stage N1 time duration percentage was significantly higher in the severe groups compared with all other groups. However, REM sleep, N2 sleep and N3 sleep stages time duration percentages were not significantly different between groups. Resting SBP and DBP were significantly higher in the severe OSA group than in the non-OSA group, and nocturnal SBP peaks not DBP peaks was higher in the severe OSA group.

Table 5.1 Comparison of demographic variables, and depressive symptoms, daytime sleepiness, PSG parameters and blood pressure indices, stratified by OSA severity.

	Non-OSA (n = 12)	**Mild OSA (n = 26)**	**Moderate OSA (n = 18)**	**Severe OSA) (n = 19)**	
Variable	***M (SD)***	***M (SD)***	***M (SD)***	***M (SD)***	***p-value***
Age (years)	32.7 (14.8)[3,4]	39.4 (12.1)	45.8 (12.4)[1]	45.7 (11.0)[1]	**.01**
Body Mass Index	30.0 (9.0)	32.1 (8.0)	32.8 (8.6)	37.8 (10.3)	.09
Current smoker (%)[+]	1 (8)	6 (23)	3 (16)	9 (47)	.07
DASS-21 depression subscale	8.1 (8.1)	13.6 (9.7)	11.0 (10.7)	11.5 (9.4)	.55
ESS	9.5 (5.4)	9.2 (4.5)	11.2 (7.1)	13.0 (7.1)	.17
SaO_2 time <90% (mins)	0 (1)[4]	2 (6)[4]	11 (27)[4]	30 (43)[1,2,3]	**<.01**
Arousal Index	1.3 (1.1)[3,4]	5.5 (4.6)[4]	10.3 (4.9)[1,4]	26.0 (16.8)[1,2,3]	**<.01**
N1 sleep time duration (%)	08 (04)[4]	12 (8)[4]	12 (7)[4]	21 (13)[1,2,3]	**<.01**
N2 sleep time duration (%)	49 (10)	45 (12)	51 (15)	44 (14)	.25
N3 sleep time duration (%)	22 (09)	26 (13)	21 (16)	119 (20)	.53
REM sleep time duration (%)	14 (08)[3,4]	09 (07)	07 (06)[4]	06 (07)[4]	**.01**
Resting SBP (mmHg)	124.1 (16.1)[4]	132.3 (15.1)	130.1 (18.2)	140.1 (15.1)[1]	**.04**
Resting DBP (mmHg)	67.1 (9.2)[4]	72.1 (9.2)	70.3 (9.1)	77.1 (7.1)[1]	**.02**
Nocturnal peaks of SBP (mmHg)	146.1 (23.1)[4]	165.1 (25.1)	157.0 (20.1)[4]	180.0 (35.1)[1,3]	**.01**
Nocturnal peaks of DBP (mmHg)[a]	83.3 (8.3)	84.3 (8.6)	84.2 (8.6)	88.0 (8.1)	.46

Note: OSA severity cut-offs are; 5–14 AHI (mild); 15–29 AHI (moderate); ≥30 AHI (severe); significant differences between groups was defined by [1], $p < .05$ *v.* non-OSA; [2], $p < .05$ *v.* mild OSA; [3], $p < .05$ *v.* moderate OSA; [4], $p < .05$ *v.* severe OSA; [a]: total n = 61: non-OSA (n = 8), mild OSA (n = 22), moderate OSA (n = 14), severe OSA (n = 17); DASS-21: *depression, anxiety and stress scale–21*; ESS: *Epworth sleepiness scale; Scale*; SaO_2: oxygen arterial blood saturation; BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; +: Pearson's chi-square, N1: sleep stage 1; N2: sleep stage 2; N3: sleep stage 3; REM: rapid eye movement sleep stage.

Linear regression analysis indicated a strong relationship between the resting BP measured by a sphygmomanometer and estimated by PTT for both SBP ($R^2 = 0.89$) (Figure 5.1a) and DBP ($R^2 = 0.83$) BP (Figure 5.1b) ($p < .001$). Estimates from the PTT method were, on average, higher than sphygmomanometer measurements (+5.0 mmHg [*SD* = 3.4] for DBP and +3.2 mmHg [*SD* = 2.3] for DBP).

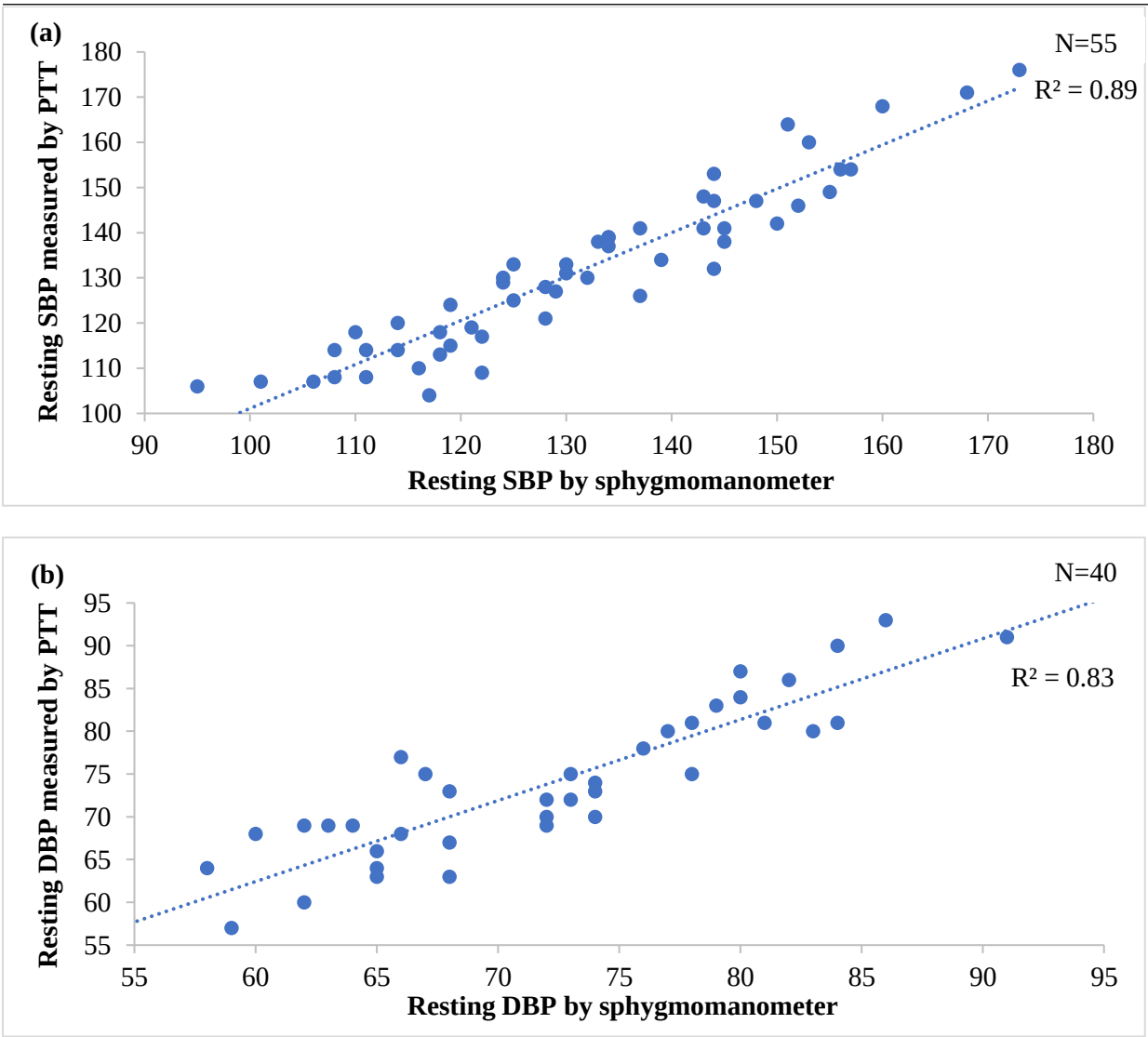

Figure 5.1 Relationship between resting SBP (a) and DBP (b) measured by sphygmomanometer and PTT. SBP: systolic blood pressure; DBP: diastolic blood pressure; PTT: pulse transit time.

Sample linear regression analysis revealed that SBP baseline and peaks were significantly correlated (R^2 = 0.54) (Figure 5.2a), as are DBP baseline and peaks (R^2 = 0.55) (Figure 5.2b).

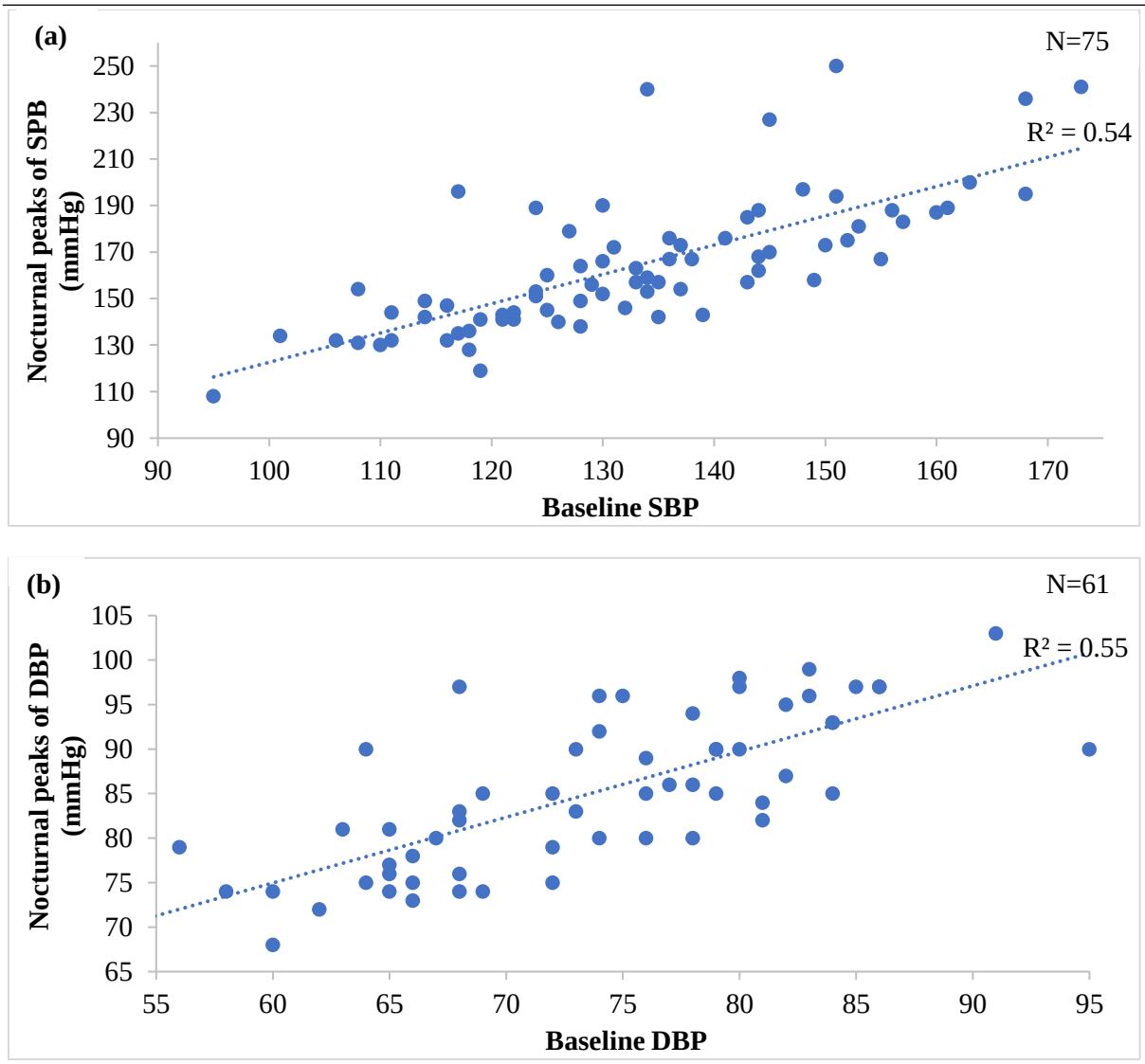

Figure 5.2 Relationship between baseline blood pressure and nocturnal peaks of SBP (a); DBP (b).SBP: systolic blood pressure; DBP: diastolic blood pressure.

It is notable that in all cases, nocturnal peaks of SBP and DBP were higher than resting BP (recorded prior to sleep), indicating that these patients lacked a dipping pattern of BP during sleep as a result of OSA events. In the case of SBP, this difference ranged between +2 and +86 mmHg (mean 33.2, *SD* 18.6); for DBP, the difference ranged from +1 to + 29 mmHg (mean 11.4, *SD* 6.2) (Figure 5.2). The increase in nocturnal BP meant that many patients met the criteria for a higher grade of hypertension, particularly for SBP. For instance, prior to sleep, the majority of participants (68%) had normotension, and none met the criteria for grade 3 hypertension, yet during sleep 25% of participants met this criterion (Table 5.2).

Table 5.2 Descriptive data for hypertension status prior to and during sleep time: number of participants (percentage of sample).

	Normal or pre-hypertension	Grade 1 hypertension	Grade 2 hypertension	Grade 3 hypertension
Resting SBP	51 (68%)	18 (24%)	6 (8%)	0 (0%)
Nocturnal peak SBP	12 (16%)	27 (36%)	17 (23%)	19 (25%)
Resting DBP	72 (96%)	2 (3%)	1 (1%)	0 (0%)
Nocturnal peak DBP	39 (64%)	21 (34%)	1 (2%)	0 (0%)

SBP: systolic blood pressure; DBP: diastolic blood pressure; normal or pre-hypertension (SBP <140 and DBP <90); grade 1 hypertension (SBP 140–159; DBP 90–99); grade 2 hypertension (SBP 160–179; DBP 100–109); grade 3 hypertension (SBP >179; DBP >109).

Sample linear regression analysis showed that the magnitude of the difference between baseline and nocturnal peak SBP was significantly associated with OSA severity as measured by AHI (R^2 = 0.37) (Figure 5.3a). In contrast, the difference between the baseline and peak DBP demonstrated no significant relationship with OSA severity (R^2 = 0.0001) (Figure 5.3b).

Multiple linear regression analyses were performed to examine the associations between nocturnal peaks of SBP and DBP, and BMI and PSG parameters (SaO_2 time <90% and Arousal Index) (Table 5.3). The results showed a significant amount of variation in nocturnal peak SBP (F (4,71) = 9.85, p = .0005), nocturnal peak DBP (F (4,52) = 3.19, p = .02) and mean difference between the baseline and nocturnal peak of SBP (F (4,71)= 4.20, p = .006). However, no significant variation was found in mean difference between baseline and nocturnal peaks of SBP (F (4,52) = 0.09, p = .98). The results showed significant associations between nocturnal peak SBP and BMI and the Arousal Index, while the mean difference between baseline and nocturnal peaks of SB was only linked to the Arousal Index. Although the nocturnal peak of DBP was significantly associated with age, the mean difference between baseline DBP and nocturnal peaks of DBP was not associated with any of the variables included in the model; nor were those other variables associated with the nocturnal peaks of SBP and DBP. In the

absence of any significant relationship with OSA severity, DBP peaks were excluded from further multiple regression analyses related to cognitive tests.

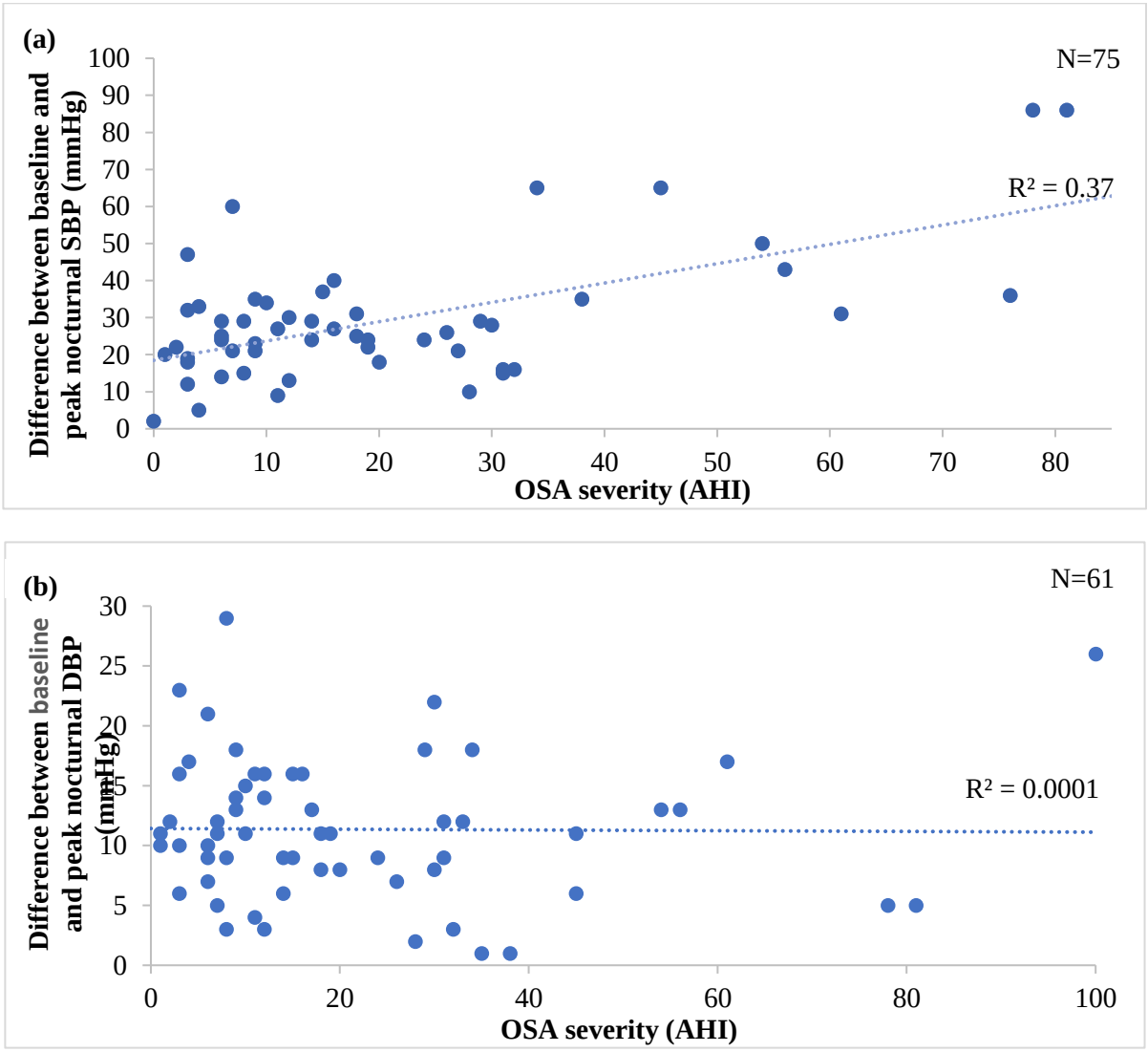

Figure 5.3 Relationship between the severity of OSA (AHI) and mean variance between baseline and peaks of SBP (a) and DBP (b). SBP: systolic blood pressure; DBP: diastolic blood pressure.

Table 5.3 Multiple linear regression analysis including age, SaO_2 time <90%, Arousal Index and BMI modelled to predict nocturnal peaks of blood pressure.

Variable	R^2	p_{model}	*Predictor*	*SE*	*β*	*sr*	*p-value*
Nocturnal peaks of SBP (mmHg)	0.36	**<.01**					
			Age (years)	0.22	0.15	0.14	.15
			Body Mass Index	0.33	0.41	0.37	**<.01**
			Arousal Index	0.25	0.31	0.26	**<.01**
			SaO_2 time <90%	0.00	0.08	0.06	.50
Nocturnal peaks of DBP (mmHg)	0.19	**.02**					
			Age (years)	0.09	0.43	0.40	**<.01**
			Body Mass Index	0.12	0.05	0.05	.68
			Arousal Index	0.09	0.05	0.04	.71
			SaO_2 time <90%	0.00	0.04	0.32	.79
Mean difference between baseline and nocturnal peaks of SBP	0.32	**<.01**					
			Age (years)	0.18	0.11	0.10	.36
			Body Mass Index	0.26	0.21	0.18	.11
			Arousal Index	0.19	0.40	0.36	**<.01**
			SaO_2 time <90%	0.00	0.01	0.01	.91

R^2 = models' multiple correlations; *SE* = standard error; *β* = standardised regression coefficient; sr = semi-partial correlation; SBP: systolic blood pressure; DBP: diastolic blood pressure.

To determine confounders that were correlated with cognitive tests, Pearson bivariate correlation tests were conducted. The results indicated that age was correlated with performance on the mean PVT RT and PVT lapses >500 ms. AM and most AMI episodic memory stages (total episodic memory, episodic early adult life memory and episodic recent life memory) were also linked to age, but age was not linked to any of the semantic memory stages. Smoking was only correlated with AM errors and AMI semantic recent life memory, and daytime sleepiness was not correlated with performance on any of the cognitive tests. The confounding variables that were associated with individual cognitive tests were subsequently included in regression models, in addition to the independent factors.

Prior to reporting the multiple linear regression results, corrections for multiple comparisons were made using the FDR adjustment. All models of PVT, AM indices and some of the AMI measures (total semantic memory and total episodic memory) remained significant ($p < .05$). Moreover, all models showed no multilinearity according to VIF <2.0.

The results revealed no significant associations between any PVT measures and nocturnal peak SBP, or between any PVT measure and the difference between resting and peak nocturnal SBP (Table 5.4). However, a significant relationship was observed between SBP and performance on the AM (Table 5.4). Specifically, time taken on the AM was positively correlated with magnitude of the difference between resting and peak nocturnal SBP. In addition, the number of errors made on the AM was positively correlated with both nocturnal peak SBP and the magnitude of the difference between resting SBP and peak nocturnal BP. For the remaining significant models, no significant associations were found between AMI and BP measures (Table 5.5).

Table 5.4 Multiple linear regression analyses of the association between psychomotor vigilance and Austin maze test indices and blood pressure indices (adjusted for demographic cofounders, hypoxia, sleep fragmentation and depressive symptoms), after applying FDR corrections for multiple comparisons.

Cognitive test	*Model*	R^2	p_{model}	*Predictor*	*SE*	*β*	*sr*	*p-value*
PVT RT-mean								
	1	0.35	**<.01***	Nocturnal peaks of SBP	0.25	0.01	0.00	.93
	2	0.35	**<.01***	Mean difference between baseline and nocturnal peaks of SBP	0.35	0.03	0.02	.81
PVT slowest 10%								
	1	0.28	**<.01***	Nocturnal peaks of SBP	0.89	0.02	0.02	.86
	2	0.26	**.01***	Mean difference between baseline and nocturnal peaks of SBP	0.26	0.01	0.01	.96
PVT RT-lapses >500ms								
	1	0.40	**<.01***	Nocturnal peaks of SBP	0.03	0.01	0.01	.96
	2	0.39	**<.01***	Mean difference between baseline and nocturnal peaks of SBP	0.05	0.03	0.28	.80
AM-time								
	1	0.49	**<.01***	Nocturnal peaks of SBP	0.07	0.10	0.09	.35
	2	0.55	**<.01***	Mean difference between baseline and nocturnal peaks of SBP	0.11	0.27	0.22	**.02**
AM-errors								
	1	0.31	**<.01***	Nocturnal peaks of SBP	0.05	0.20	0.19	**.04**
	2	0.40	**<.01***	Mean difference between baseline and nocturnal peaks of SBP	0.07	0.42	0.30	**<.01**

Note: *indicates a significant model ($p < 0.05$) after FDR adjustment; The model was adjusted for demographic cofounders, hypoxia, sleep fragmentation and depressive symptoms; R^2 = models' multiple correlations; AM: Austin Maze; SE = standard error; β = standardised regression coefficient; *sr* = semi-partial correlation; SBP: systolic blood pressure.

Table 5.5 Multiple linear regression analyses of the association between autobiographical memory interview indices and blood pressure indices (adjusted for demographic cofounders, hypoxia, sleep fragmentation and depressive symptoms), after applying FDR corrections for multiple comparisons.

Cognitive test	*Model*	R^2	p_{model}	*Predictor*	*SE*	*β*	*sr*	*p-value*
Total semantic memory								
	1	0.16	**.01***	Nocturnal peaks of SBP	0.02	0.10	0.09	.42
	2	0.14	.10	Mean difference between baseline and nocturnal peaks of SBP	0.03	0.2	0.02	.89
Childhood semantic memory								
	1	0.13	.06	Nocturnal peaks of SBP	0.02	0.06	0.05	.66
	2	0.07	.44	Mean difference between baseline and nocturnal peaks of SBP	0.01	0.03	0.03	.79
Early adult life semantic memory								
	1	0.10	.10	Nocturnal peaks of SBP	.01	.08	.08	.51
	2	0.13	.15	Mean difference between baseline and nocturnal peaks of SBP	0.02	0.05	0.05	.67

Cognitive test	***Model***	***R^2***	***p_{model}***	***Predictor***	***SE***	***β***	***sr***	***p-value***
Recent life semantic memory								
	1	0.13	.07	Nocturnal peaks of SBP	0.01	0.08	0.07	.51
	2	.13	.22	Mean difference between baseline and nocturnal peaks of SBP	0.01	0.05	0.04	.72
Total episodic memory								
	1	0.16	**.03***	Nocturnal peaks of SBP	0.03	0.05	0.05	.67
	2	0.21	**.03***	Mean difference between baseline and nocturnal peaks of SBP	0.05	0.03	0.03	.84
Episodic childhood memory								
	1	0.04	.59	Nocturnal peaks of SBP	0.01	0.01	0.08	.49
	2	0.07	.47	Mean difference between baseline and nocturnal peaks of SBP	0.02	0.07	.06	.68

Cognitive test	*Model*	R^2	p_{model}	*Predictor*	*SE*	*β*	*sr*	*p-value*
Episodic early adult life memory								
	1	0.13	.08	Nocturnal peaks of SBP	0.01	0.13	0.12	.32
	2	0.15	.16	Mean difference between baseline and nocturnal peaks of SBP	0.02	0.07	0.06	.65
Episodic recent life memory								
	1	0.18	**.01***	Nocturnal peaks of SBP	0.01	0.03	0.02	.84
	2	0.19	.06	Mean difference between baseline and nocturnal peaks of SBP	0.02	0.04	0.04	.63

Note: *indicates a significant model ($p < 0.05$) after FDR adjustment; The model was adjusted for demographic cofounders, hypoxia, sleep fragmentation and depressive symptoms; R^2 = models' multiple correlations; SE = standard error; β = standardised regression coefficient; sr = semi-partial correlation; SBP: systolic blood pressure.

5.5 Discussion

This study investigated associations between nocturnal BP and cognitive impairment in OSA patients. The results show that nocturnal peaks of SBP are significantly associated with visuospatial dysfunction in terms of timing and/or performance errors on the AM. In contrast, performance on tests of sustained attention, RT and autobiographical memory show no significant association with peaks of nocturnal SBP.

High SBP is known to contribute to brain damage through exacerbation of occult micro-strokes (Mensah, 2016), leading to decrements in cognitive performance (Gąsecki et al., 2013). Clinical hypertension is associated with abnormal white matter lesions in most areas of the brain (Kuller et al., 2010). The present findings align with previous studies of non-OSA patients that confirmed the role of elevated BP in cognitive impairments related to visuospatial deficits. A longitudinal study extending over 30 years, controlling for age, education, depression, stroke and antihypertensive medications, and excluding patients with known cognitive impairments found that participants with a higher SBP exhibited poorer performance on cognitive tests involving visuospatial ability (Swan et al., 1998). Similarly, Elias, Robbins, Schultz Jr and Pierce (1990) found that visuospatial deficits, as measured by tactile performance test localisation, were linked to increased BP, after adjusting for age and education level. A follow-up study by Gottesman et al. (2014) of 15,792 participants aged 45–64 years concluded that elevated SBP is associated with cognitive decline, including poorer performance on visuospatial tasks such as the digit symbol substitution test.

Although sustained attention and RT are known to be impaired among OSA patients, the present findings align with previous evidence that slower RT is not associated with high SBP. For instance, Waldstein, Brown, Maier and Katzel (2005) reported that, among normal participants (aged 53–84), high SBP was not associated with delayed RT as measured by the Stroop interference task. Edwards, Ring, McIntyre, Carroll and Martin (2007) have also indicated that RT does not vary between hypertensive and normotensive middle-aged groups. Further, using a simple RT test, Pavlik, Hyman and Doody (2005) found that RT was not associated with hypertension in a sample of 3,385 adult males and non-pregnant females with no history of stroke and ranging in age between 30 and 59 years.

However, the present results conflict with earlier studies regarding the role of high SBP in memory impairment. Swan et al. (1998) reported that adults with a higher lifelong SBP were more likely to perform poorly on verbal learning and memory tasks. Waldstein, Ryan, Manuck, Parkinson and Bromet (1991) compared 40 age-matched midlife males who had either normotension or elevated BP and concluded that those with elevated BP performed worse on memory tasks. In their study of an elderly hypertensive cohort, Sacktor et al. (1999) identified optimal regulation of SBP as a modifiable risk factor in preventing or minimising memory loss. One possible explanation for the difference in the present case is that a majority of participants (68%) did not suffer from chronic daytime hypertension (i.e. their resting SBP was <140 mmHg, and their resting DBP was <90). It follows that nocturnal episodes of hypertension in these OSA patients may not have been of sufficient duration to affect those areas of the brain associated with memory. If this explanation is correct, it suggests that the neural mechanisms that underpin visuospatial function are more sensitive to nocturnal peaks in BP than those underpinning response time and memory.

To the candidate's knowledge, this study is the first to investigate the association between nocturnal peaks in BP and cognitive dysfunction in patients with OSA in independent of hypoxia, sleep fragmentations, and cofounders. While daytime SBP was normotensive in 68% of participants, 84% of participants met the clinical criteria for hypertension (grades 1–3) in terms of their nocturnal peaks of SBP. This finding confirms the association between OSA and elevated nocturnal BP and demonstrates that resting BP is an unreliable indicator of peaks of nocturnal BP in OSA patients. Further, the results show that patients with the most severe OSA exhibit the largest differences between resting and nocturnal SBP. Similarly, Gehring et al. (2018) demonstrated that patients with severe OSA exhibit very high SBP values during sleep, and a cross-sectional study by Jelic et al. (2002) found that mean SBP in sleep apnoea sufferers changed significantly during sleep, including during NREM and REM sleep. Finally, the

substantial difference between resting SBP and peak nocturnal SBP (mean difference: + 33.2 mmHg) and between resting DBP and peak nocturnal DBP (mean difference: +11.4 mmHg) provides a clear indication of the strength of the stress response that is exerted via the SNS in OSA.

The present study has revealed that nocturnal peaks in SBP in OSA are associated with visuospatial dysfunction, even after controlling for age, smoking status, depressive symptoms, hypoxia and sleep fragmentation. This indicates that nocturnal BP is an important, and hitherto overlooked, factor that may contribute to cognitive dysfunction in OSA. Further, the present findings highlight the fact that the risk of organ damage in OSA (especially of the heart and kidneys) can be seriously underestimated if nocturnal BP is not taken into account. Future studies might build on these findings to determine whether treatment with CPAP can improve cognitive outcomes and reduce the risk of organ damage. Future studies should use a larger sample size so that differences in BP peaks in NREM sleep and REM sleep stages can be explored.

Measuring continuous BP has been a big challenge for sleep research because of the inconvenience that accompanies the use of cuff-based BP devices. Hence, the development of a new method (PTT) based on PSG parameters, such as ECG and plethysmography data, makes a notable contribution to clinical research by enabling the continuous measurement of BP during sleep. The present study demonstrated that BP measurements obtained at rest with the PTT method were highly correlated with measurements obtained via a sphygmomanometer, supporting previous studies that reported strong associations between BP estimates from PTT and those obtained from the finger cuff system (Portapress) (Hennig et al., 2012). The present study showed that PTT measurements were an average 3–5 mmHg higher than those obtained via a sphygmomanometer, which confirms a recent report that PTT overestimates BP by an

average of 4–6 mmHg (Krisai et al., 2019; Zachwieja et al., 2020). Other studies have indicated a strong relationship between BP measured by PTT and cuff devices when BP is recorded for a 24-hour period, but there were differences that were most evident during exercise (Gesche et al., 2012; Wong et al., 2009). Since sleep involves minimal movement, continuous BP measurement by the PTT method may be more accurate during sleep than during wakefulness. Further investigation may be required to ascertain how the accuracy of PTT varies during sleep and wakefulness.

Although this study has provided new insights, there are several methodological limitations. First, the sample size of the non-OSA group was less than that of the OSA groups. This limitation reduced the statistical power of the group comparisons but was not a consideration in the comparisons that expressed OSA severity as a continuous variable. Second, using a non-direct method to estimate continuous BP is a potential limitation. Nevertheless, the PTT method has been documented as the best available for estimating continuous nocturnal BP, particularly in sleep research, and the results of the present study support the accuracy of this method. Finally, the current study did not conduct brain imaging, so it was not possible to comment whether structural changes (damage) in the brain were associated with the nocturnal BP spikes. It is hoped that further studies will overcome these limitations.

5.6 Conclusion

This study investigated the association between nocturnal BP spikes (as a manifestation of SNS over-activity) and impairments of sustained attention and RT, visuospatial function and autobiographical memory. The findings indicate that nocturnal peaks in SBP are significantly associated with impairments of visuospatial deficits (timing and performance errors in the AM), whereas performance on tests of sustained attention time, RT and autobiographical memory are not significantly associated with nocturnal peaks of SBP. It remains to be

determined whether the impairments of visuospatial function are permanent or whether they can be alleviated by OSA treatment.

Chapter 6: General Discussion

6.1 Overview

The present study aimed to investigate the factors associated with cognitive dysfunction in OSA, including IH, sleep fragmentation, depressive symptoms, nocturnal over-activity of the SNS including BP spikes, independent of demographic confounder effects that are known to affect cognitive performance. In addition, the characteristics of the study sample and the utility of the Arabic version of the SBQ were analysed. The study yielded novel findings that have not been demonstrated before in previous research. The following section summarises the research aims and findings of the study.

6.2 Review of the Research Findings

Chapter 2 examined the characteristics of the study sample and the capacity of the Arabic version of the SBQ to predict OSA severity among patients referred to a sleep laboratory in Saudi Arabia. Similar to previous studies, most of the study participants were male (69%). The mean age of participants was 43.1 years (range 18–65), while the mean BMI was 33.4 kg/m^2 (range 17–61). This study showed that both age and BMI were correlated with OSA severity, whereas current smoking status was not. The prevalence of depressive symptoms among the cohort was 74% while the prevalence of EDS was 50%. In addition, 60% of those participants with OSA were found to have either IGT or T2D. These findings are very similar to those reported for cohorts of people with OSA in other countries, making it likely that the research findings from this Saudi cohort have relevance to OSA patients globally.

Regarding the utility of the Arabic version of the SBQ, the findings indicated a significant association between SBQ scores and OSA severity. More specifically, the eight items of the

SBQ showed high sensitivity but low specificity in predicting OSA severity according to a ROC curve analysis. The loud snoring item was shown to be superior for detecting mild OSA (AHI >5), while the observed apnoea item provided the best specificity for moderate and severe OSA (AHI >15; Figure 6.1a).

Chapter 3 explored the independent effects of IH, sleep fragmentation and depressive symptoms on cognitive function in OSA. Depressive symptoms were shown to be independently associated with EDS but not with demographic or PSG data. In relation to cognitive performance, the findings indicated that impairments in sustained attention and RT were independently associated with hypoxia and sleep fragmentation. Impairments in visuospatial performance were independently associated with sleep fragmentation only, while impairments in visuospatial function, semantic and episodic memories, sustained attention, and RT were independently associated with depressive symptoms (Figure 6.1b).

Chapter 4 investigated the effects of HRV, PWA and stress response biomarkers (through morning urine samples, blood cortisol and blood glucose levels) as indices of nocturnal over-activity of the SNS, on cognitive dysfunction in OSA. The findings revealed that, in terms of stress response biomarkers, only morning fasting blood glucose levels were significantly associated with time spent with SaO_2 <90%. Further, the findings showed that PWA indices and HRV were linked to OSA severity (AHI) and were strongly correlated with sleep fragmentation, as measured by the Arousal Index. In relation to cognitive performance, the findings indicated a link between nocturnal over-activity of the SNS (PWA and HRV) and visuospatial dysfunction (time performance). However, the findings did not suggest any significant association between nocturnal over-activity of the SNS and sustained attention, RT or autobiographical memory (Figure 6.1c).

Chapter 5 examined associations between nocturnal BP peaks and cognitive impairment. The findings pointed to an association between nocturnal SBP peaks and sleep fragmentation, as measured by the Arousal Index. Nocturnal SBP peaks were strongly correlated with visuospatial dysfunction (timing and error performance). However, significant relationships were not found between nocturnal SBP peaks and performance on measures of sustained attention, RT or autobiographical memory (Figure 6.1d).

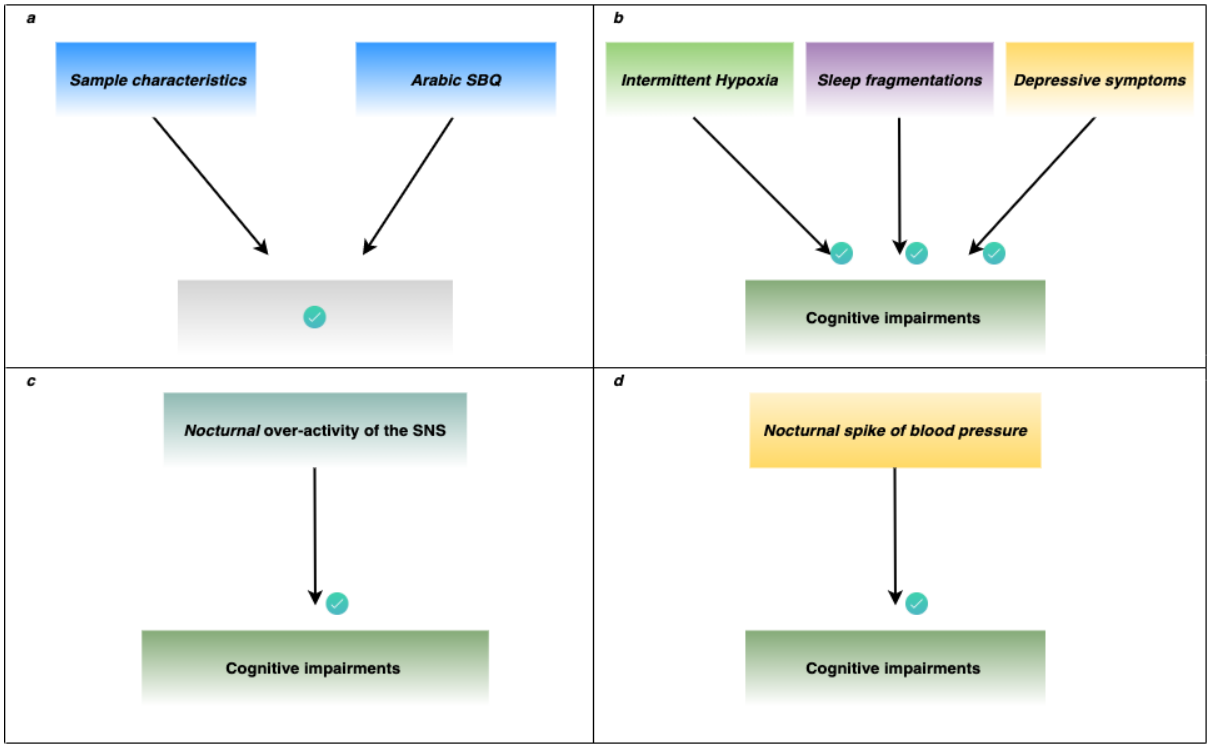

Figure 6.1 Schematic diagrams illustrating the research findings associated with the research aims that formed the basis of Chapters 2–5 (a–d, respectively). In each diagram, an arrow links the dependent variables to the independent variable for each research aim, as discussed in the respective chapter. The green checkmarks denote a statistically significant relationship between the two variables. SBQ: *STOP-Bang questionnaire*; SNS: sympathetic nervous system.

Several of the findings presented in this thesis have implications for clinical practice and suggest directions for future research. These are discussed in the following sections.

6.3 Utility of the Arabic Version of the *STOP-Bang Questionnaire*

In accordance with previous studies of Saudi patients, the present study found that the Arabic version of the SBQ has high sensitivity but low specificity (BaHammam et al., 2015). Studies conducted on non-Arabic populations have also reported that the SBQ has high sensitivity and low specificity (Chung et al., 2016; Vana et al., 2013). The present study found that 29 participants who had no or mild OSA (AHI <15) were assessed by the SBQ (score >2) as having an intermediate or high risk of OSA. On this basis, 42% (29/69) of participants were incorrectly identified as being likely to have OSA. Although the high sensitivity of SBQ ensured that most cases of moderate-to-severe OSA were identified, its low specificity meant that 42% of the patients referred for PSG had no or mild OSA and did not warrant treatment with CPAP. This inconvenienced the patients, wasted scarce resources and prevented patients with moderate-to-severe OSA from undergoing a PSG in a timely fashion.

A more efficient strategy would be to focus on accurately identifying those individuals who are likely to have moderate-to-severe OSA. Based on the data from the current study, identification could be improved by placing weight on one item of the SBQ: observed apnoeic events. A ‘yes’ response to this item predicted an AHI >15 with a sensitivity of 87% and a specificity of 76%, compared with a sensitivity of 98% and a specificity of 32% when using a SBQ score of >2. While focussing on observed apnoeic events should improve the efficiency of PSG referrals, we ought to strive for 100% sensitivity and specificity. However, it is unlikely that this outcome could be achieved without the development of additional screening tools. Including the anatomical features of the airway, such as Mallampati size, in screening tools may increase their specificity. For instance, Avincsal et al. (2017) modified the SBQ version after adding the Mallampati size and reported that the modified SBQ version had the same sensitivity but a higher specificity than the original version.

6.4 Nocturnal Over-activity of the Sympathetic Nervous System in Obstructive Sleep Apnoea

Relatively little research has examined the stress response in OSA. The association between OSA severity and nocturnal over-activity of the SNS was investigated in Chapters 4 and 5. In agreement with previous studies, the present study found that the Arousal Index was associated with nocturnal PWA indices (Adler et al., 2013; Delessert et al., 2010), HRV LF/HF ratio (Bradicich et al., 2020; Kim, Seo, & Kim, 2019) and peaks in SBP (Chouchou et al., 2013). However, while cortisol levels are a strong indicator of SNS over-activity (Tomfohr, Edwards, & Dimsdale, 2012), they were not associated with any of the PSG parameters in the present study. This lack of correspondence could be attributable to the fact that blood was only sampled for cortisol in the morning. Cortisol levels increase during a stressful event (e.g. hypoxia) and then decrease shortly thereafter, as the cortisol is metabolised. It would have been preferable to sample blood throughout the night and then to correlate fluctuations in blood cortisol with the occurrence of severe apnoeic events, but this approach was not possible within the clinical environment of the present study. It is likely that by the time blood samples were obtained in the morning after waking, the cortisol levels had returned to normal circadian rhythm. A similar problem exists for the blood glucose measurements. Hence, morning blood glucose levels as a stress response biomarker, were only associated with time spent with SaO_2 <90%, which is consistent with the results of prior studies (Al-Abri et al., 2011; Priou et al., 2012).

Since all three indices of nocturnal over-activity of the SNS (PWA indices, HRV LF/HF ratio and peaks in SBP) indicated that sleep fragmentation (Arousal Index) but not hypoxia was associated with SNS over-activity, it appears that sleep fragmentation is a stronger driver of the SNS than are episodes of hypoxia. Accordingly, the Arousal Index and morning blood glucose levels may represent useful indicators of nocturnal over-activity of the SNS in OSA.

6.5 Factors Associated with Cognitive Impairment in Obstructive Sleep Apnoea

While it is widely accepted that moderate-to-severe OSA is associated with impaired performance in a variety of cognitive domains, most research into the causes of this impairment has focussed on the contributions of sleep fragmentation and IH. Published data make it clear that these two factors contribute to cognitive impairment in OSA but are only able to account for a fraction of the variance, meaning that additional factors must be involved. To date, few studies have examined whether depressive symptoms, nocturnal over-activity of the SNS or nocturnal spikes in BP are independently associated with cognitive impairment in OSA patients. In the present investigation, these factors were found to have an independent (negative) effect on several cognitive domains (Figure 6.2).

IH was shown to independently contribute to impairments in sustained attention and RT, which is in agreement with the results of previous research (Fowler et al., 1987; Kainulainen et al., 2020; Tanno et al., 2017). These deficits could be partly attributable to damage to the amygdala in OSA (Zhao, Yang, & Cui, 2017), which has been shown to play an important role in attentional processes (Baxter & Murray, 2002). **Sleep fragmentation** was also found to be independently associated with impairments in sustained attention, RT and visuospatial ability. Such findings are in line with those earlier studies that noted a strong association between sleep fragmentation, and sustained attention deficits and delayed RT (Ayalon, Ancoli-Israel, & Drummond, 2009). Previous studies have shown that visuospatial deficits are unique to OSA, and do not occur in other sleep disorders, such as insomnia (Olaithe et al., 2018). The present findings indicate that these visuospatial deficits may be attributable to the combined effects of sleep fragmentation and depressive symptoms, although the underlying neural mechanism remains unclear.

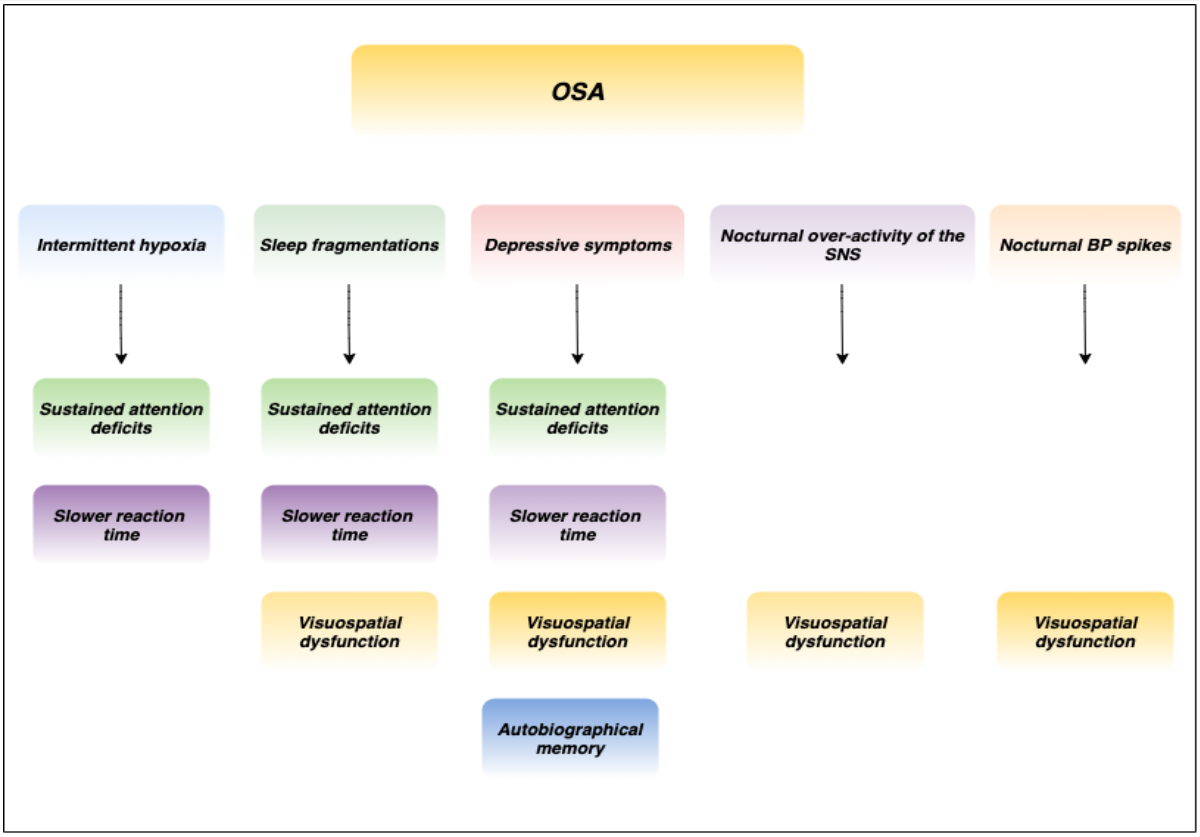

Figure 6.2 Schematic diagram showing the factors identified by the present study to have an independent association with impairments in specific cognitive domains. SNS: sympathetic nervous system; BP**:** blood pressure.

Studies have presented evidence for the role of **depressive symptoms** in impairing cognitive function across different populations, though few studies have examined their relationship in OSA (Faust et al., 2017; Kaser et al., 2017). In the present study, depressive symptoms were found to exert strong independent effects on response times, sustained attention, autobiographical memory and visuospatial performance. Although the influence of depressive symptoms on sustained attention and RT in OSA patients has not previously been examined, the findings of the present study are consistent with findings from studies on depressed patients (Plante et al., 2020; Tsourtos et al., 2002). The findings also support previous research that examined deficits in autobiographical memory recall as a psychological marker of depression (Kuyken & Dalgleish, 1995). In addition, the present findings are consistent with those of Delhikar et al. (2019), who reported that depression was strongly associated with impairment

of semantic memory in OSA patients. However, the present study is the first to identify visuospatial deficits among OSA patients with depressive symptoms. This observation, which suggests that depressive symptoms are an independent factor behind the visuospatial deficits in OSA, supports findings of previous studies on depressed patients (Coello, Ardila, & Rosselli, 1990; Nelson & Shankman, 2016; Paradiso, Hermann, Blumer, Davies, & Robinson, 2001). Given that depressive symptoms were associated with poor performance on all of the cognitive tests used in the present study, depressive symptoms may also be associated with impairments in other cognitive domains that were not assessed in the present study.

Some readers might assume that the depressive symptoms observed in OSA are a secondary consequence of the sleep fragmentation experienced by these patients, yet two findings from the present study argue against this idea. First, the associations between cognitive impairments and depressive symptoms were found to be independent of sleep fragmentation and IH. Second, while a massive 76% of participants with OSA had depressive symptoms, the severity of these symptoms was not correlated with the severity of OSA or the Arousal Index. Taken together, these findings emphasise the importance of viewing depressive symptoms as an independent contributor to cognitive dysfunction in OSA. It is recommended that each time a patient is tested for OSA, they ought to be screened for depressive symptoms, and if these symptoms are detected, a treatment plan should be put in place.

The present study has demonstrated that SNS activity and BP can be reliably and continuously monitored during sleep in OSA patients using sensors that are routinely used during PSG studies. For the first time, and in contrast to previous research (e.g. Idiaquez et al., 2014), the present study demonstrated that lower HRV is linked to visuospatial deficits in OSA. PWA drops, which are a strong indicator of nocturnal over-activation of the SNS, were also linked to poor visuospatial performance. Finally, nocturnal spikes in SBP are another indicator of SNS

over-activity, and the present study found, for the first time, a strong association between high nocturnal SBP and visuospatial impairments. Previous studies in other populations have identified a link between high daytime BP and visuospatial deficits (Elias et al., 1990; Knecht et al., 2008; Swan et al., 1998).

The discovery that multiple indices of **nocturnal over-activity of the SNS** contribute independently to impaired performance on a test of visuomotor function places a spotlight on the effects of overnight stress on the brain. The elevated stress response is probably why 60% of the participants with OSA were found to have IGT or T2D; these disorders of glucose metabolism have been linked to stress and are present at much lower frequencies in the general population. Until now, researchers have considered nocturnal over-activity of the SNS to be a downstream consequence of IH. However, the present results suggest that it is an independent contributor to cognitive dysfunction that is not strongly associated with measures of hypoxia. It is suggested that future PSG studies should routinely assess overnight SNS activity. Such investigations could assist the identification of individuals who suffer from occult spikes of extremely high BP, so that they can receive antihypertensive medication to protect them from the multitude of comorbidities that are associated with elevated BP.

6.6 Limitations

The present study has several limitations that should be addressed in future research. First, the sample size of the non-OSA group was smaller than that of the OSA group. A correlational analysis was conducted to offset this difference; however, the unequal sample size of the two groups could have reduced statistical power. Selection bias is a further limitation of the present study. More specifically, the present study did not use random sampling and instead recruited participants who had been referred to a sleep study after being suspected of having a sleeping disorder. Similarly, the glucose and cortisol samples were collected on waking in the morning

rather than continuously throughout the night, which meant that a less dynamic picture of SNS over-activation was obtained. Nocturnal BP was measured by the PTT method, which is based on ECG and plethysmography data. Although this is the only method that can measure continuous BP in OSA patients without disturbing sleep, it is limited because it does not measure BP directly. Another limitation relates to the fact that fMRI was not conducted in the present study, which prevented determination of whether the cognitive deficits were associated with structural changes in the brain. It should also be noted that it is not possible to know when a patient first develops OSA, as they generally do not undergo a PSG study until their symptoms have begun to interfere with their daily functions. It is likely, therefore, that variation in the time between OSA onset and testing contributed to variability in the data. A further limitation is that a limited battery of cognitive tests was used in the present study, and as these tests did not span all cognitive domains, deficits in other aspects of cognitive function such as executive function and new learning and memory, may have gone undetected.

6.7 Directions for Future Research

Future research that seeks to replicate or build on the results of the present study should consider the following points. First, the present study found that the full version of the Arabic SBQ has a high sensitivity but low specificity. The loud snoring item and observed apnoeic events have high sensitivity and superior specificity for OSA. Larger studies should seek to replicate this observation. Placing greater weight on the above two SBQ items could lead to new ways of improving the efficiency of screening patients for probable OSA.

Second, the present study confirmed that hypoxia and sleep fragmentation are independently associated with impairments in sustained attention and RT, while sleep fragmentation is independently associated with visuospatial ability. Importantly, the present study showed that depressive symptoms are independently associated with impairments in sustained attention,

RT, visuospatial ability and autographical memory. To date, the effect of depressive symptoms has been overlooked; however, the present findings indicate that full recovery of cognition in OSA patients may require interventions that address depressive symptoms, as well as hypoxia and sleep fragmentation. Therefore, future clinical studies ought to treat these three factors and examine whether this assists the recovery of cognitive function.

The present study revealed that nocturnal over-activity of the SNS, including peaks in nocturnal SBP, are associated with OSA severity. Impairment of visuospatial performance was shown to be associated with these factors independently of age, smoking status, depressive symptoms, hypoxia and sleep fragmentation. Henceforth, nocturnal over-activity of the SNS and elevated nocturnal BP should be taken into consideration when seeking to treat cognitive dysfunction in OSA patients.

In summary, the research presented in this thesis has helped to extend understanding of factors that contribute to cognitive impairment in OSA. In addition to confirming the involvement of IH and sleep fragmentation, the present study has highlighted three other factors that appear to independently contribute to cognitive dysfunction. These novel findings point to the need for further basic research and new clinical interventions that target depressive symptoms, nocturnal over-activity of the SNS and spikes in nocturnal BP in OSA.

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Appendices

Appendix 1: RMIT ethics approval

RMIT UNIVERSITY

Human Research Ethics Committee (HREC)
Research and Innovation office
NH&MRC Code: EC00237

Notice of Approval

Date:	**4 July 2018**
Project number:	**21459**
Project title:	***The effect of stress response on cognition, mood and daytime sleepiness in Obstructive Sleep Apnoea***
Risk classification:	**More than low risk**
Chief investigator:	**Professor Stephen Robinson**
Approval period:	From: **4 July 2018** To: **26 February 2021**

The following documents have been reviewed and approved:

Title	Version	Date
21459 Robinson appn	Final	3 July 2018
Participant Information Sheet (Australia)		3 July 2018
Participant Information Sheet (Saudi Arabia)		3 July 2018
Arabic & English DASS 21		
Epworth Sleepiness Scale		
Autobiographical Memory Interview		
Study protocol		
Stop Bang Questionnaire		

The following documents have been noted:

Title	Date
Financial guarantee (Saudi Arabia Ministry of Education)	2 May 2018
Saudi Sleep Lab Acceptance	May 2018

The above application has been approved by the RMIT University HREC as it meets the requirements of the *National statement on ethical conduct in human research* (NH&MRC, 2007).

Terms of approval:

1. **Responsibilities of chief investigator**
   It is the responsibility of the above chief investigator to ensure that all other investigators and staff on a project are aware of the terms of approval and to ensure that the project is conducted as approved by HREC. Approval is valid only whilst the chief investigator holds a position at RMIT University.
2. **Amendments**
   Approval must be sought from HREC to amend any aspect of a project. To apply for an amendment use the request for amendment form, which is available on the HREC website and submitted to the HREC secretary. Amendments must not be implemented without first gaining approval from HREC.
3. **Adverse events**
   You should notify the HREC immediately (within 24 hours) of any serious or unanticipated adverse effects of the research on participants, and unforeseen events that might affect the ethical acceptability of the project.
4. **Annual reports**
   Continued approval of this project is dependent on the submission of an annual report. Annual reports must be submitted by the anniversary of approval (4 July 2018) of the project for each full year of the project. If the project is of less than 12 months duration then a final report only is required.
5. **Final report**
   A final report must be provided within six months of the end of the project. HREC must be notified if the project is discontinued before the expected date of completion.

RMIT UNIVERSITY

Human Research Ethics Committee (HREC)
Research and Innovation office
NH&MRC Code: EC00237

6. **Monitoring**
   Projects may be subject to an audit or any other form of monitoring by the HREC at any time.
7. **Retention and storage of data**
   The investigator is responsible for the storage and retention of original data according to the requirements of the *Australian code for the responsible conduct of research* (section 2) and relevant RMIT policies.
8. **Special conditions of approval**
   Nil.

In any future correspondence please quote the project number and project title above.

Prof Stephen Bird
Chairperson
RMIT HREC

cc: Dr Peter Burke, HREC secretary
Mr Ridwan Alomri, Research student
Prof Gerard Kennedy, Associate supervisor

Appendix 2: Publications and Conference Abstracts Related to the Thesis

Publications

Alomri, R. M., Kennedy, G. A., Wali, S. O., Ahejaili, F., & Robinson, S. R. (2020). Differential associations of hypoxia, sleep fragmentation and depressive symptoms with cognitive dysfunction in obstructive sleep apnoea. *Sleep*. https://doi.org/10.1093/sleep/zsaa213 **(Published)**

Alomri, R. M., Kennedy, G. A., Wali, S. O., Ahejaili, F., & Robinson, S. R. Association between nocturnal sympathetic nervous system activity and cognitive dysfunction in obstructive sleep apnoea. **(Accepted for publication in Scientific Reports Journal - Nature)**

Alomri, R. M., Kennedy, G. A., Wali, S. O., Ahejaili, F., Zelko, M., & Robinson, S. R. Association between nocturnal peaks of blood pressure and cognitive dysfunction in obstructive sleep apnoea. **(Under review in Hypertension)**

Alomri, R. M., Kennedy, G. A., Wali, S. O., Ahejaili, F., & Robinson, S. R. Risk factors and characteristics of obstructive sleep apnoea patients referred for an overnight sleep study in Saudi Arabia: Utility of the *STOP-Bang questionnaire* as a screening tool. **(Prepared for submission)**

Conference Abstracts

Alomri, R. M., Kennedy, G. A., Wali, S. O., Ahejaili, F., & Robinson, S. R. (2019). Hypoxia effects on psychomotor vigilance test performance in obstructive sleep apnoea. *Proceedings of Sleep Down Under,* Sydney, 16–19 October. **(Travel award)**

Alomri, R. M., Kennedy, G. A., Wali, S. O., Ahejaili, F., & Robinson, S. R. (2019). Peaks of systolic blood pressure while sleeping are associated with the severity of impaired cognitive

function in obstructive sleep apnoea. *Proceedings of the World Sleep Congress*, Vancouver, 20–25 September.

Appendix 3: STOP Bang Questionnaire

STOP BANG Questionnaire

Height _____ inches/cm Weight _____ lb/kg
Age _____
Male/Female
BMI _____
Collar size of shirt: S, M, L, XL, or _____ inches/cm
Neck circumference* _____ cm

1. *S*noring
Do you *s*nore loudly (louder than talking or loud enough to be heard through closed doors)?
Yes No

2. *T*ired
Do you often feel *t*ired, fatigued, or sleepy during daytime?
Yes No

3. *O*bserved
Has anyone *o*bserved you stop breathing during your sleep?
Yes No

4. Blood *p*ressure
Do you have or are you being treated for high blood *p*ressure?
Yes No

5. *B*MI
*B*MI more than 35 kg/m^2?
Yes No

6. *A*ge
*A*ge over 50 yr old?
Yes No

7. *N*eck circumference
*N*eck circumference greater than 40 cm?
Yes No

8. *G*ender
*G*ender male?
Yes No

* Neck circumference is measured by staff

High risk of OSA: answering yes to three or more items
Low risk of OSA: answering yes to less than three items

Adapted from:
STOP Questionnaire
A Tool to Screen Patients for Obstructive Sleep Apnea
Frances Chung, F.R.C.P.C., Balaji Yegneswaran, M.B.B.S.,† Pu Liao, M.D.,‡ Sharon A. Chung, Ph.D.,§ Santhira Vairavanathan, M.B.B.S.,_ Sazzadul Islam, M.Sc.,_ Ali Khajehdehi, M.D.,† Colin M. Shapiro, F.R.C.P.C.#*
Anesthesiology 2008; 108:812–21

Appendix 4: The Depression, Anxiety and Stress Scale - 21 Items

DASS21

Name: Date:

Please read each statement and circle a number 0, 1, 2 or 3 which indicates how much the statement applied to you **over the past week**. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:

0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree or a good part of time
3 Applied to me very much or most of the time

1 (s)	I found it hard to wind down	0	1	2	3
2 (a)	I was aware of dryness of my mouth	0	1	2	3
3 (d)	I couldn't seem to experience any positive feeling at all	0	1	2	3
4 (a)	I experienced breathing difficulty (e.g. excessively rapid breathing, breathlessness in the absence of physical exertion)	0	1	2	3
5 (d)	I found it difficult to work up the initiative to do things	0	1	2	3
6 (s)	I tended to over-react to situations	0	1	2	3
7 (a)	I experienced trembling (e.g. in the hands)	0	1	2	3
8 (s)	I felt that I was using a lot of nervous energy	0	1	2	3
9 (a)	I was worried about situations in which I might panic and make a fool of myself	0	1	2	3
10 (d)	I felt that I had nothing to look forward to	0	1	2	3
11 (s)	I found myself getting agitated	0	1	2	3
12 (s)	I found it difficult to relax	0	1	2	3
13 (d)	I felt down-hearted and blue	0	1	2	3
14 (s)	I was intolerant of anything that kept me from getting on with what I was doing	0	1	2	3
15 (a)	I felt I was close to panic	0	1	2	3
16 (d)	I was unable to become enthusiastic about anything	0	1	2	3
17 (d)	I felt I wasn't worth much as a person	0	1	2	3
18 (s)	I felt that I was rather touchy	0	1	2	3
19 (a)	I was aware of the action of my heart in the absence of physical exertion (e.g. sense of heart rate increase, heart missing a beat)	0	1	2	3
20 (a)	I felt scared without any good reason	0	1	2	3
21 (d)	I felt that life was meaningless	0	1	2	3

Appendix 5: Epworth Sleepiness Scale

Epworth Sleepiness Scale

Name: _____ Today's date: _____

Your age (Yrs): _____ Your sex (Male = M, Female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

Appendix 6: Travel Award (Annual Scientific Meeting of the Australasian Sleep Association)

Ref ID: 483
For the attention of: Ridwan Alomri

,Dear Ridwan

On behalf of the Organising Committee, I am pleased to inform you of the success of your student travel grant application to assist you with travel expenses to attend **Sleep DownUnder 2019**, to be .held at the International Convention Centre, Sydney, 16 - 19 October 2019

:You have been awarded the below amount as a student travel grant

Amount Awarded	$400.00