Schizophrenia and Obstructive Sleep Apnoea

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Abstract

Adverse outcomes in schizophrenia are driven by physical ill-health, negative symptoms and neurocognitive decrements. Obstructive sleep apnoea (OSA) comorbid with schizophrenia may worsen these outcomes, because OSA is associated with adverse cardiovascular outcomes and cognitive impairment in general populations. High rates of obesity seen in people with schizophrenia makes it likely that OSA is highly prevalent in this population. There is minimal literature reporting robust prevalence estimates, clinical correlates or treatment outcomes of OSA in people with schizophrenia.

Research addressing these gaps in the literature would be useful to determine the impact OSA has on adverse outcomes in schizophrenia, provide evidence to inform enhanced detection of OSA at the clinical level and quantify treatment outcomes that may be particularly relevant to schizophrenia. The aims of this thesis are to determine the absolute and relative prevalence of OSA in a cohort of people with schizophrenia compared to a matched population control group; undertake exploratory analysis to determine clinical associations with OSA in people with schizophrenia; prospectively determine whether diagnostic tools for OSA are accurate in people with schizophrenia; and whether continuous positive airway pressure (CPAP) treatment of OSA comorbid with schizophrenia is tolerable and associated with improvement in physical health and cognitive outcomes.

The results of this thesis demonstrate that OSA is highly prevalent in schizophrenia occurring at a rate of 40%, which is at the higher end of previous prevalence estimates reported in selected populations that were systematically reviewed. Severe OSA was diagnosed in 27% of the cohort. In comparison to a general population cohort the relative risk of OSA in schizophrenia was 2.9 (95%CI 1.0-8.1, p=0.05). On adjusting for age and BMI the relative risk was reduced to 1.7 (95%CI 0.8-3.7, p=0.17), indicating that risk of OSA in schizophrenia is predominantly

driven by obesity. Exploratory analysis of clinical factors indicated that OSA was associated with reduced odds of employment, increased odds of cardiovascular disease and lower mean quality of life, independent living and psychological well-being scores. Diagnosis of OSA was not significantly associated with adverse psychopathological or cognitive outcomes. Prospective validation of OSA diagnostic tools indicated these had poor discriminatory value. In six participants with severe OSA CPAP treatment was well tolerated at six months of follow-up with mean usage per night adequate for treatment effect. CPAP treatment was associated with normalisation of sleep architecture, mean 7.3kg of weight loss and improvement in cognition as measured by mean change in BACS total Z-score of 0.59.

This thesis demonstrates that OSA is highly prevalent in schizophrenia. The main predictor of OSA appears to be excess rates of obesity, whilst general population screening tools perform poorly and are unlikely to be beneficial for clinical screening. OSA comorbid with schizophrenia is associated with adverse physical health and quality of life outcomes. Importantly treatment of OSA in people with schizophrenia is tolerable, effective and is associated with substantial weight loss and improvement in cognitive measures. These results support the incorporation of OSA into physical health screening guidelines for people with schizophrenia.

Declaration

I, Hannah Myles, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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List of published works

Chapter Two: Paper 1

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Chapter Three: Paper 2

Liu D, **Myles H,** Foley DL, Watts G.F, Morgan V.A, Castle D, Waterreus A, Mackinnon A and Galletly C. (2016) Risk factors for obstructive sleep apnea are prevalent in people with psychosis and correlate with impaired social functioning and poor physical health. *Frontiers in Psychiatry*, 7, 139.

Chapter Four: Paper 3

Myles H, Vincent A, Myles N, Adams R, Chandratilleke M, Liu D, Mercer J, Vakulin A, Wittert G and Galletly C. (2018) Obstructive sleep apnoea is more prevalent in men with schizophrenia compared to general population controls: results of a matched cohort study. *Australasian Psychiatry*, 26(6), 600-3.

Chapter Five: Paper 4

Myles H, Myles N, Vincent A.D, Wittert G, Adams R, Chandratilleke M, Liu D, Mercer J, Vakulin A, Chai-Coetzer C and Galletly C. (2019) Pilot cohort study of obstructive sleep apnoea in community dwelling people with schizophrenia. *Irish Journal of Psychological Medicine,* in press (recommended for publication September 2019).

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Myles H, Myles N, Coetzer C, Adams R, Chandratilleke M, Liu D, Mercer J, Vakulin A, Vincent A, Wittert G, Galletly C. (2019) Cognition in schizophrenia improves with treatment of severe obstructive sleep apnoea: A pilot study. *Schizophrenia Research, Cognition*; 15, 14-20.

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List of abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnoea hyponoea index
AI	Arousal index
ASSET	Assessing Sleep in Schizophrenia and Evaluating Treatment study
BACS	Brief assessment of cognition in schizophrenia
BMI	Body mass index
BPRS	Brief psychiatric rating scale
CBT	Cognitive behavioural therapy
CPAP	Continuous positive airway pressure
DI	Desaturation index
DIP	Diagnostic interview for psychosis
DSM-V	Diagnostic and statistical manual – version five
ECG	Electrocardiogram
EEG	Electroencephalogram
EOG	Electroocculogram
EMG	Electromyogram
ESS	Epworth sleepiness score
FEP	First episode psychosis
FGA	First generation antipsychotic drug
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
ICD-10	International classification of disease – version 10
ISI	Insomnia severity index

MAILES	Men Androgen Inflammation Lifestyle Environment Stress study
MRI	Magnetic resonance imaging
MSLT	Median sleep latency time
N1	Stage 1 sleep
N2	Stage 2 sleep
N3	Stage 3 sleep
NREM	Non-rapid eye movement
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnoea
PANSS	Positive and negative symptom scale
PSG	Polysomnography
PSQI	Pittsburgh sleep quality index
RCT	Randomised controlled trial
RDI	Respiratory disturbance index
REM	Rapid eye movement
REML	REM sleep latency
RERA	Respiratory related arousal
SEI	Sleep efficiency index
SGA	Second generation antipsychotic drug
SHIP	Survey of High Impact Psychosis
SMR	Standardised mortality ratio
SOL	Sleep onset latency
SWS	Slow wave sleep
TST	Total sleep time

Key concepts and definitions

Obstructive sleep apnoea: is a nocturnal breathing disorder characterised by repeated collapse and obstruction of the upper airway during sleep resulting in hypoxia, frequent arousal and disruption to normal sleep architecture. OSA arises as a combination of reduced muscle tone during sleep and extrinsic airway compression due to excessive soft tissue or structural features which give rise to a narrowed airway. Obesity, tobacco smoking and the use of alcohol increase the risk of OSA (Young et al., 2004). OSA is independently associated with a number of adverse physical health outcomes including hypertension, insulin resistance, ischaemic stroke, heart failure and cardiovascular disease (Epstein et al., 2009). Similarly, due to sleep fragmentation OSA is also associated with impaired neurocognitive function (Fulda et al., 2001). OSA is diagnosed on the basis of demonstrating an apnoea hypopnoea index (AHI) of greater than ten events per hour using polysomnography (PSG). Severity of OSA is stratified based on AHI cut-offs: mild AHI 10-20 events/hr, moderate 20-30 events/hr and severe >30 events/hr (Epstein et al., 2009).

Multi-channel polysomnography (PSG): is a multi-parametric study that allows for comprehensive recording of physiological changes that occur during sleep and is the standard diagnostic measure for OSA (Epstein et al., 2009). PSG is recorded during sleep and can be performed in a sleep laboratory attended and monitored by a sleep technician or performed at home using portable equipment. Both methods have similar diagnostic accuracy for OSA (Gagnadoux et al., 2002). At a minimum PSG consists of twelve channels that record electroencephalogram (EEG), respiratory airflow, chin muscle tone, leg movements, eye movements using an electroocculogram (EOG), electrocardiogram (ECG) for heart rate and rhythm, oxygen saturation and abdominal/chest wall belts to measure inspiratory effort. Assessment of these combined parameters allow assessment of sleep architecture,

identification of apnoeas and hypopnoeas, body position during sleep, abnormal leg movements and scoring of sleep related parameters including an apnoea hypopnoea index (AHI) which defines the number of partial or complete apnoeas per hour of sleep. AHI is the diagnostic measure used to define OSA. Scoring and interpretation of PSG data is performed manually by sleep technicians and sleep physicians using standardised criteria published by the American Academy of Sleep Medicine (AASM) (Berry et al., 2015).

Continuous positive airway pressure (CPAP): is a medical device that provides positive pressure ventilation throughout the respiratory cycle. CPAP consists of a mechanical flow generator, pressure hosing and a tight-fitting mask that delivers a constant supply of air above atmospheric pressure during sleep. Masks can be designed to fit over the nose or face to deliver air to the respiratory tract. By providing positive pressure during inspiration CPAP pneumatically splints the airway open, overcomes tissue forces that cause airway collapse and prevents the occurrence of obstructive apnoeas (Sullivan et al., 1981). CPAP is an effective treatment for OSA (Epstein et al., 2009). Use of CPAP is associated with reversal of daytime somnolence and improvement of sleep quality (Patel et al., 2003); improvement of hypertension and hyperglycaemia (Bratton et al., 2015; Iftikhar et al., 2013); and improvements in vigilance and related occupational outcomes (Pan et al., 2015). The pressure required to be delivered by CPAP is determined using a titration study which can either be performed in a monitored sleep laboratory or automated using at-home equipment. Titration studies monitor apnoea events at increasing CPAP pressures to determine the optimal pressure setting at which apnoea and hyponoea events are prevented during sleep.

Chapter 1: Literature review and rationale for subsequent chapters

Introduction

Schizophrenia is a chronic psychotic illness associated with devastating socio-occupational outcomes and severe physical health comorbidity. Adverse socio-occupational outcomes are driven primarily by negative and cognitive symptoms (apathy, cognitive impairment and social withdrawal) of schizophrenia that despite a plethora of antipsychotic drug options, remain resistant to treatment and represent a significant barrier to functional recovery (Fusar-Poli et al., 2015). Physical health comorbidity arises primarily due to the cardiometabolic side-effects of antipsychotic drugs (Correll et al., 2015), high rates of tobacco smoking (Myles et al., 2012) and poor lifestyle (unhealthy diet and lack of exercise) resulting in a 16-18 year reduction in life-expectancy due predominantly to an excess of cardiovascular disease (Laursen, 2011). Both outcomes represent an area of unmet clinical need.

It is likely that obstructive sleep apnoea (OSA) is prevalent in schizophrenia because of high rates of the causative risk factors such as obesity and tobacco smoking. OSA may be relevant in schizophrenia because it both contributes to poorer physical health outcomes and cognitive decrements, and can result in symptoms arising from poor sleep which overlap with the negative symptoms of schizophrenia. Furthermore, OSA has a validated treatment, nocturnal continuous positive airway pressure (CPAP), which mitigates adverse outcomes of the illness. As such the link between OSA and schizophrenia represents a novel and interesting avenue for further research, especially considering the current dearth of evidence in this area.

Currently there is minimal literature reporting on OSA in schizophrenia. Prevalence estimates are limited to small convenience samples using non-standard diagnostic measures. On the other

hand, there is no literature reporting on the physical health and psychiatric correlates of OSA comorbid with schizophrenia nor is there any evidence on the outcomes of OSA treatment in this population. Given these gaps in the literature the overall aims of this thesis are three-fold: firstly, to develop more robust estimates of OSA prevalence in schizophrenia; secondly to explore clinical and psychiatric correlates in this population to informs means of enhanced screening and detection; and thirdly to determine what impact treatment of OSA comorbid with schizophrenia has on physical health and psychiatric outcomes.

Because of the cross-disciplinary nature of this thesis it is pertinent to first background some of the general concepts that form the basis of my thesis. Whilst schizophrenia, it's symptomatology and adverse cardiometabolic outcomes are familiar to the majority of psychiatrists, the pathobiology, diagnostic nuances and management of sleep apnoea are unlikely to be familiar subject matter. In reference to cardiometabolic disease this lack of knowledge is likely to be particularly acute given that prior to beginning this thesis OSA was not mentioned in any clinical guidelines for the prevention of physical health morbidity in people with schizophrenia. Similarly, it is reasonable to assume that whilst sleep physicians are well acquainted with OSA and its management, they are unlikely to appreciate the unique symptomatic impact that OSA may have on psychiatric and physical health outcomes in people with schizophrenia.

In one sense a key aim of this thesis is to bridge a knowledge gap between two seemingly unrelated disciplines in an attempt to inform novel strategies to improve functional recovery and the physical health of people with schizophrenia. This thesis follows in the footsteps of a wealth of recent literature addressing the physical health inequalities of people with schizophrenia and the responsibility psychiatrists have in managing risk factors for preventable cardiometabolic disease once considered outside of their field of practice (Lambert et al.,

2009). In this context it is pertinent to recognise that siloing of expertise is likely to result in misconceptions or deficiencies in the literature or a lack of research translation between specialties. This is particularly relevant in mental health where treatment nihilism abounds and a psychiatric diagnosis has, and remains a barrier to effective medical care (Knaak et al., 2017).

This literature review will first background the key concepts of schizophrenia and its relationship with cardiometabolic morbidity and negative symptoms. Subsequently OSA and its relationship with physical health morbidity and cognitive decrements will be discussed. Finally, a mechanistic relationship between schizophrenia and OSA will be discussed and recent literature reviewed.

Schizophrenia and poor physical health

Schizophrenia is a highly disabling psychotic illness that has an approximate 0.4% lifetime prevalence in the general population (Saha et al., 2005). It is a clinical diagnosis codified by the DSM-V and is defined by the presence of positive symptoms (delusions, hallucinations, disorganised speech and/or catatonia) with or without negative symptoms (social withdrawal, diminished emotional expression, apathy and poverty of speech) that have been present for greater than six months and result in socio-occupational impairment. Peak incidence occurs in adolescence and early adulthood (McGrath et al., 2008) with some suffering a chronic and relapsing course with incomplete remissions. People living with schizophrenia experience high levels of unemployment (Evensen et al., 2016), poor quality of life (Eack et al., 2007) and have a life expectancy 10-15 years less than the general population (Laursen, 2011).

Apart from psychiatric symptoms, people with schizophrenia have mortality rates substantially higher than the general population. This differential mortality gap was first demonstrated by Saha and colleagues (2007) in a systematic review that demonstrated a standardised mortality

ratio (SMR) of 2.58 indicating that a person with schizophrenia has more than a doubling in risk of death compared to age and sex matched people in the general population. Further analysis indicates this differential mortality is driven by an excess of cardiovascular disease (SMR 1.79) and endocrine disease such as diabetes (SMR 2.63); and has worsened over time given higher SMRs reported over successive decades. Other literature has confirmed an excess of metabolic syndrome and cardiovascular risk factors in people with schizophrenia which is the primary driver of cardiovascular morbidity and mortality in this population. The metabolic syndrome refers to a cluster of related risk factors comprising abdominal obesity, hypertension, impaired insulin sensitivity, elevated triglycerides and reduced high density lipoprotein (HDL) cholesterol that promote cardiovascular disease. Data from the US CATIE study demonstrated that 42.7% of subjects met criteria for metabolic syndrome which equated to a relative risk of 1.38 for men and 2.51 for women in comparison to the age-matched general population (McEvoy et al., 2005). Australian data has similarly indicated a prevalence of metabolic syndrome in people with psychotic illness of 54.8% (Galletly et al., 2012). Epidemiological evidence also demonstrates increased odds of hard cardiovascular endpoints in people with schizophrenia compared to the general population including diabetes, heart failure and stroke, and death from these outcomes (Curkendall et al., 2004). As such, people with schizophrenia have metabolic profiles similar to that seen in people 10-15 years older in the general population (Bobes et al., 2007).

Lifestyle and medication drive cardiovascular disease in schizophrenia

The determinants of increased cardiometabolic risk in people with schizophrenia are likely to be multifactorial. Firstly, traditional lifestyle factors play an important role. There is extensive evidence that people with schizophrenia engage in low rates of physical activity (Stubbs, Firth, et al., 2016) and have poor cardiorespiratory fitness compared to healthy controls (Vancampfort et al., 2017). Meta-analytic estimates suggest people with psychotic illness

spend up to eleven hours of their waking day undertaking no physical activity at all (Stubbs, Williams, et al., 2016). The determinants of physical inactivity are poorly understood but may correlate with lower socioeconomic status and the negative symptoms of psychotic illness (Vancampfort et al., 2017). Similarly, rates of smoking are extremely high in people with psychotic illness (Myles et al., 2012) and are up to three times that seen in the general population (Newcomer, 2007). Theories to account for this association include the lower socioeconomic status of people with schizophrenia, neurobiological vulnerabilities to nicotine dependence and use of nicotine as self-treatment for medication side-effects or symptoms of psychosis (de Leon et al., 2005). Some authors have noted an excess prevalence of family history of diabetes and cardiovascular disease in people with schizophrenia (Holt et al., 2006). Whilst this association may support shared genetic risk factors for schizophrenia and poor physical health it may also implicate intergenerational environmental factors.

Aside from traditional lifestyle factors, a unique determinant of risk for cardiovascular disease in people with schizophrenia is long term treatment with antipsychotic medications that are known to promote weight gain and metabolic syndrome. Meta-analysis of data from randomised-controlled trials (RCTs) of 15 antipsychotic drugs found both first generation (FGA) and second generation (SGA) agents, apart from haloperidol, ziprasidone and lurasidone, were independently associated with weight gain to a varying extent (Leucht et al., 2013). Subsequent analysis indicates that this effect is dose dependent and has a linear relationship with duration of exposure (Spertus et al., 2018). Various mechanisms have been posited to explain antipsychotic-induced weight gain. There is empirical evidence that olanzapine and clozapine alter leptin and ghrelin levels centrally resulting in a direct orexigenic effect (Lu et al., 2015), whilst antagonism of central 5-HT2C and H1 receptors correlate with increased weight gain due to direct orexigenic effects and sedation respectively (Henderson et al., 2015). Antipsychotic drugs have also been demonstrated to directly dysregulate lipid and

glucose metabolism further compounding their effect on promoting impaired glucose tolerance and hyperlipidaemia independent of weight gain alone (Goncalves et al., 2015; Skrede et al., 2012).

Physical health comorbidity in schizophrenia is under-recognised and under-treated

Despite overwhelming evidence of a disproportionate burden of cardiovascular risk factors, cardiometabolic disease and premature mortality, people with schizophrenia have historically accessed preventative health care and management of established disease at lower rates than the general population. There is an abundance of data indicating that the detection of physical health comorbidity is poor. One early US study that screened 2,090 inpatients with major mental illness indicated that 43% suffered one or more physical illnesses and that half of these diagnoses had not been contemporaneously identified in the primary healthcare or mental healthcare setting (Koranyi, 1979). Evidence of under-recognition is also reflected in more recent case-controlled primary care data from the UK (Smith et al., 2013) and the US (Carney et al., 2006) demonstrating people with schizophrenia have lower odds of diagnosis with ischaemic heart disease, hypertension, cardiac failure and peripheral vascular disease than the general population despite clear evidence of an excess prevalence of these diseases in screened populations. Interestingly registry data from Sweden (Crump et al., 2013) (where free universal access to healthcare reduces confounding influences) indicates that whilst people with schizophrenia had double the number of healthcare contacts and mortality from ischaemic heart disease, they were less likely than the general population to have a diagnosis of ischaemic heart disease prior to death. As such it can be inferred that people with schizophrenia are prone to inefficient and poor-quality preventative management of cardiovascular disease despite a clear preponderance of risk factors. This assumption also holds true for the management of established disease. One large US cohort study of people undergoing treatment for confirmed myocardial infarction demonstrated that schizophrenia conferred a 34% increase in twelve-

month mortality, an association that became insignificant when the statistical model was adjusted for five quality indicators (Druss et al., 2001). Longitudinal Australian data also confirms an excess of cardiovascular morbidity in people with schizophrenia and demonstrates that hospitalisation, mortality and revascularisation rates for comorbid ischaemic heart disease had not diminished over time (Lawrence et al., 2003). The unfortunate healthcare experience for a person with schizophrenia has thus been the neglect of early detection and intervention followed by inequitable access to management of acute illness when severe symptomatology or life-threatening disease supervenes (Muck-Jorgensen et al., 2000).

Cardiometabolic disease is ultimately preventable and thus it is unsurprising that access to primary prevention through management of risk factors has also been poorly available to people suffering schizophrenia. Data from a number of countries indicate that simple clinical measures are often neglected in the routine clinical care of people with psychotic illness. One large survey in the US noted that BMI and waist circumference were not recorded in 95% of patients with psychotic illness under routine primary care and mental health assessment (Buckley et al., 2005). Similarly, blood pressure was not routinely recorded in 45-65% of outpatients chronically treated with antipsychotic medications, whilst glucose and lipid monitoring were not performed in 60-65% and 70-75% respectively in the same population despite clinician awareness of risk (Barnes et al., 2007; Buckley et al., 2005; Newcomer et al., 2004). A controlled study comparing metabolic monitoring between people prescribed antipsychotic medications for psychotic illness and antiretroviral medications for HIV (which have an analogous cardiometabolic side-effect profile) demonstrated similar figures for subjects with psychosis. Conversely this study reported over 90% compliance with monitoring for people on antiretroviral medications (Jennex et al., 2008) which highlights both the achievability of preventative monitoring and the inadequacy of simple medical care that people with schizophrenia encounter. Once cardiovascular risk factors have been established, people

with schizophrenia also experience significant under-prescribing as a means of secondary prevention. As an example, a large survey of people with psychosis in Australia reported that only 40% of people with established type two diabetes were prescribed hypoglycaemic medication, 52% with hypertension were prescribed blood pressure lowering medication and 39% with hypercholesterolaemia were prescribed statins (Galletly et al., 2012).

In regard to OSA more specifically, there may be unique barriers to both preventing risk factors for the development of OSA and accessing treatment for people with schizophrenia. Hesitancy of mental health clinicians to participate in physical health assessment in people with major mental illness may result in lack of detection or management of risk factors for OSA. Lack of integration between physical health and psychiatric services plays into this possible deficit and is an area of substantial need. Furthermore, in this setting there may be significant diagnostic overshadowing that further impairs recognition of physical health comorbidity. Unique to people with schizophrenia cognitive and psychosocial deficits arising from negative symptoms make it difficult to establish and maintain the lifestyle changes necessary to prevent OSA. In addition, psychiatrists may not see themselves as responsible for the institution of treatment for OSA nor be aware of evidence-based diagnosis and management pathways.

Physical health guidelines in schizophrenia neglect OSA

Recognition of the disproportionate burden of cardiometabolic risk and morbidity has led to an increasing concern amongst mental health clinicians in regard to physical health comorbidity (Correll, 2007), numerous editorialised calls to action (Crompton et al., 2010; Langan et al., 2013) and an explosion of literature informing systematic and protocolised strategies for screening and preventative management at the clinical level. A large number of major society guidelines (American Diabetes Association, 2004; De Hert et al., 2009; National Institute for Health and Care Excellence, 2014) have been published describing specific monitoring protocols which have been systematically reviewed (De Hert et al., 2011). Generally, all of

these address identification and management of obesity, diabetes and hyperglycaemia, hyperlipidaemia, cardiovascular disease and hyperprolactinaemia. As a result, standardised protocols for anthropometric, glycaemic and lipid monitoring have been implemented widely in mental health services across Australia and internationally. Furthermore, these guidelines also provide evidence-based lifestyle and pharmacological strategies that are safe and effective at preventing cardiometabolic morbidity in this population (M et al., 2009). Although uptake of such strategies has been variable at a clinical and population level (Mitchell et al., 2012; Moeller et al., 2011; Morrato et al., 2010) there is at least an abundance of literature which has established a broad evidence base and translational research emphasis on recognition and management of these common risk factors in people with schizophrenia.

Whilst the monitoring and management of weight gain, diabetes, hypertension and hyperlipidaemia have been extensively described in physical health guidelines for schizophrenia, strategies regarding OSA are neglected. At the time of writing this literature review, OSA had not been included in any major guidelines for the management of physical comorbidity in schizophrenia. This is despite risk factors such as obesity (Mitchell et al., 2013), tobacco smoking (Myles et al., 2012) and alcohol consumption (Moore et al., 2012), which are directly causative of OSA, being highly prevalent in people with schizophrenia. As discussed further below OSA is associated with secondary physical health morbidity, poor quality of life and neurocognitive changes that may remain under-recognised and unaddressed given the presumptive prevalence of OSA in people with schizophrenia. Further research is required to effectively incorporate OSA screening and management into schizophrenia management guidelines to further optimise preventive metabolic management of this population.

Sleep and its measurement

In humans sleep-wake cycles are controlled by the circadian clock, which is a complex neurohormonal system that generates a 24-hour rhythm which is the primary regulator of sleep and wakefulness. Melatonin, secreted by the pineal gland, is the major signalling molecule that entrains an individual's circadian rhythm. Secretion of melatonin is regulated by the sensory input of light from the suprachiasmatic nucleus and to a lesser extent other physiological and genetic factors (Farhud et al., 2018). The circadian rhythm influences the ideal timing of restorative sleep and is disrupted by non-environmental light (Schomerus et al., 2005) and unsynchronised socio-occupational behaviour such as shift-work (James et al., 2017). Disruption to circadian rhythms has a detrimental effect on physical and mental health being associated with an increase in depressive symptoms, cognitive impairment and increased risk of cardiovascular disease (Bedrosian et al., 2017; Ortiz-Tudela et al., 2014).

Sleep is a highly regulated process that can be divided into various phases, based on electroencephalogram (EEG), electromyogram (EMG) and electrooculogram (EOG) data, which cycle in a normal pattern throughout a period of sleep. Broadly sleep can be divided into rapid eye movement (REM) and non-REM (NREM) sleep. In an awake alert individual EEG demonstrates a low-amplitude low frequency pattern defined as alpha waves. Initiation of sleep results in the establishment of NREM stage 1 (N1) sleep resulting in the loss of alpha rhythm and the development of lower frequency delta waves. Individuals awakened from N1 sleep are subjectively unaware of being asleep. N1 sleep quickly transitions to NREM stage 2 sleep (N2) characterised by persistence of delta waves interrupted by sleep spindles and K-complexes. Sleep spindles denote burst-like episodes of oscillatory activity lasting greater than 0.5 seconds which presumably function in the consolidation of long-term memory through the integration of new information into existing knowledge (Tamminen et al., 2010) and the directed retention or discarding of existing memory (Saletin et al., 2011). K-complexes consist of a brief high

voltage biphasic waves recorded predominantly over the frontal cortex; these are proposed as a mechanism to prevent cortical arousal (and wakefulness) during sleep and also to strengthen synaptic pathways established during the preceding period of wakefulness (Cash et al., 2009). N2 sleep is followed by NREM stage 3 (N3) sleep (also termed slow wave sleep (SWS)) characterised by high voltage low amplitude waves termed delta waves. The N3 stage may be associated with dreaming and functions as the restorative period of sleep that may also promote the consolidation of long-term memory. Generally skeletal muscle tone reduces progressively throughout subsequent phases of NREM sleep. REM sleep is a unique phase of sleep characterised by random or rapid movement of the eyes (detected by EOG) with complete skeletal muscle paralysis accompanied by alpha waves on EEG. The function of REM sleep is poorly understood (Shrivastava et al., 2014), but is associated with vivid dreaming and a propensity to brief waking with lucid recall of dream subject matter (Hobson et al., 2000). Normal sleep undergoes ultradian cycling with initial descent from N1 to N3 sleep followed by alteration between NREM and REM sleep every 60-90 minutes for the duration of sleep. Generally, the bulk of N3 sleep occurs during the early period of sleep with REM sleep occurring during the later period of sleep. The biological relevance of this ultradian rhythm is unknown. A pictorial representation of sleep phases in comparison to EEG data is presented in figure 1.

Clinical and symptomatic measurement of sleep

Self-reported questionnaires are frequently used to measure subjective quality of sleep with the most commonly used tools being the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) and Epworth Sleepiness Scale (ESS) (Johns, 1991). Importantly these tools are not a screening test for clinical diagnosis of a sleep disorder, but are rather designed as research, population health or clinical tools for identification of sleep disturbance or daytime somnolence that deviates from the normal population.

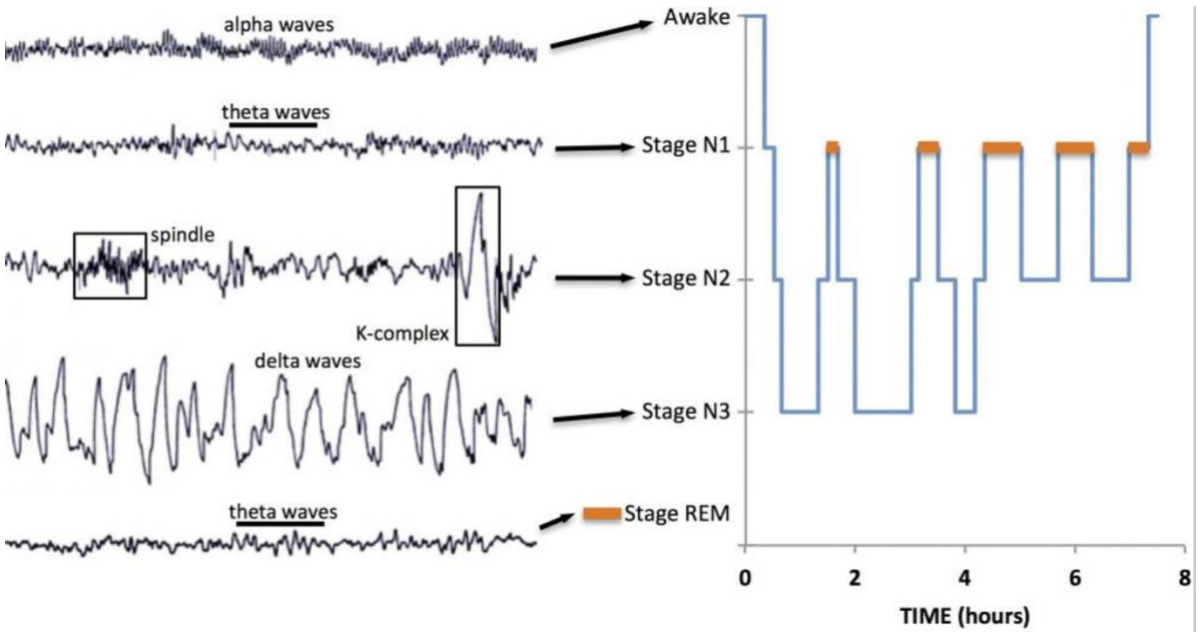

Figure 1: EEG sleep data in comparison to sleep stages (Carley, D.W. and Farabi, S.S., 2016) American Diabetes Association (2020) with permission.

The PSQI is the most widely used measure in clinical and research settings (Mollayeva et al., 2016) and was originally developed in 1988 in a cohort of patients with major depression as a standardised method of differentiating those with good and poor-quality sleep. It applies to sleep symptoms in the last month and consists of nine questions that are summated into seven subscale scores and an overall score between 0-21. The subscale scores individually assess sleep duration, latency, disturbance, efficiency, quality; daytime impairment and use of hypnotic medication. A total score of greater than five defines poor sleep quality. The PSQI is useful in that it has been validated across a number of clinical and non-clinical populations (Mollayeva et al., 2016), including cohorts with schizophrenia (Ritsner et al., 2004). However, there is some evidence that subscale scores may be of more relevance in the assessment of people with schizophrenia (Faulkner et al., 2019) rather than the total score due to the prominence of circadian rhythm disturbance in this population (Pritchett et al., 2012) and differences in aligning sleep with socio-occupational expectations between the general population and people with schizophrenia (Faulkner et al., 2017).

The ESS is another widely used questionnaire which was first described in 1990 and developed as a means of identifying abnormal daytime sleepiness. It was developed in a group of 150 people with a variety of diagnosed sleep disorders and compared to a control group of 30 (Johns, 1991). It consists of eight questions with a score greater than ten being indicative of excessive daytime sleepiness. The ESS has been validated across a large number of populations (Chan et al., 2009; Izci et al., 2008; Manni et al., 1999), but has not been specifically validated in populations with schizophrenia. In terms of external validity the ESS is shown to have moderate correlation with measures of psychological symptom severity (Olson et al., 1998), is moderately predictive of a diagnosis of OSA (Manni et al., 1999), and is strongly predictive of a diagnosis of narcolepsy (Parkes et al., 1998) but correlates poorly with objective measures of daytime sleepiness such as the median sleep latency time (MSLT) (Chervin et al., 1997; Johns, 1992). In schizophrenia the questions used in the ESS may lack internal validity given that people with schizophrenia may not partake in the activities queried due to low rates of employment and socio-occupational disadvantage. As such it is important that sleep symptom scores reported in people with schizophrenia be interpreted in this context and with a broader caveat that these scores correlate poorly with more objective measures of architectural sleep disturbance.

Scoring systems also exist for the purpose of determining risk or as a surrogate diagnostic tool for various sleep disorders. There are a large number of screening tools developed to diagnose OSA – these include the Berlin (Netzer et al., 1999), OSA50 (Chai-Coetzer et al., 2011), STOP-BANG (Chung, Subramanyam, et al., 2012) and Wisconsin Sleep (Young et al., 1993) questionnaires. Generally, these questionnaires utilise combinations of self-reported and partner-reported snoring or apnoeas, obesity or increased neck circumference and symptoms of daytime sleepiness as criteria to generate a score which is then dichotomised to a binary diagnostic outcome. These tools have been recently systematically reviewed by the US

Preventative Services Task Force, which concluded that currently there is insufficient evidence that any published tool has sufficient accuracy to be of benefit in screening general populations for OSA (Gamaldo et al., 2018). As such these tools are useful only for the identification of subjects in selected groups who would benefit from further diagnostic assessment, not as a measure of diagnosis alone. Of relevance to this thesis, no published diagnostic tool has been validated in cohorts of people with schizophrenia, making their clinical value in this situation even less clear and their use for population estimates of OSA prevalence unreliable.

Objective measurement of sleep

The most objective measure for assessment of sleep is multichannel PSG and actigraphy which allow for unambiguous quantitative measures of sleep architecture and circadian rhythm. The commonly reported parameters for PSG are outlined in table 1. PSG involves the measurement of oxygen saturation, EEG, EOG, ECG, body position, nasal air flow, limb movement and abdominal and thoracic inspiratory effort and allows for the objective measurement of sleep architecture and respiratory parameters during sleep. EEG data collected during PSG also allows for the measurement of various parameters, that whilst not diagnostic of a sleep disorder, are associated with a variety of cognitive and psychological outcomes in health and disease. Actigraphy involves use of a wearable accelerometer to record movement over 24 hours periods and derive periods of activity versus inactivity based on sustained acceleration above a threshold. These periods, or epochs, reliably correlate with physical activity/inactivity, onset of sleep and onset of wakefulness with the generated data able to report parameters such as total sleep time, sleep efficiency, number of nocturnal awakenings, sleep latency and sleep-wake cycling. Whilst actigraphy measurements are moderately correlated with diagnosis of a sleep-disorder, they are not a substitute for PSG and have most benefit in objectively assessing insomnia, circadian rhythm dysregulation and side-effects of hypnotic or sedative drugs (Ancoli-Israel et al., 2003). Furthermore, there is moderate quality evidence that sleep

disturbance as measured by actigraphy in populations with psychiatric illness correlates with psychiatric outcomes (Ancoli-Israel et al., 2003). As an example, one cohort study of 28 people with schizophrenia demonstrated that circadian rhythm, mean daytime activity levels and nocturnal awakening were significantly disrupted in comparison to a control cohort. Similarly, day-time napping, poor sleep efficiency and mean nocturnal awakenings correlated strongly with overall neuropsychological function in those with schizophrenia (Martin et al., 2001).

Sleep in schizophrenia

Before discussing the pathophysiology of OSA and its possible relationship to schizophrenia, it is first pertinent to review the sleep symptoms and architectural changes in sleep experienced by people with schizophrenia more generally. Mechanistically objective alterations in sleep or the subjective experience of sleep symptoms may be driven by both neurobiological changes intrinsic to schizophrenia and the pharmacodynamic effects of antipsychotic medications. As such it is important to consider the sleep outcomes experienced by people with untreated schizophrenia in comparison to those with established disease who are taking antipsychotic medications.

It is likely that the relationship between sleep disturbance and psychotic symptoms is bidirectional. There is good quality evidence that sleep deprivation and disturbance provokes subclinical psychotic symptoms in normal populations (Hennig et al., 2018; Scott et al., 2017). Similarly, actigraphic measures of sleep disturbance and circadian rhythm disturbance have been demonstrated to predict the development of positive symptoms and overt psychosis in adolescent populations at ultra-high risk of psychosis (Lunsford-Avery et al., 2017; Lunsford-Avery et al., 2015). In established disease, measures of sleep disturbance are also shown to worsen after antipsychotic drug withdrawal and predate overt psychotic relapse (Chemerinski et al., 2002). As a corollary objective PSG measures of REM sleep disruption correlate with

longitudinal psychiatric outcomes and global functioning after one year of treatment for recently diagnosed schizophrenia (Goldman et al., 1996). Similarly, treatment of sleep disturbance is effective at reducing psychotic symptomatology of paranoia and hallucinations as demonstrated in a large randomised controlled trial (RCT) of cognitive behavioural therapy for treatment of insomnia (Freeman et al., 2017). Taken as a whole these observations suggest that sleep disturbance is a core feature of schizophrenia and mirrors current psychosis symptomatology, whilst also being a risk factor itself for the development or worsening of psychotic symptomatology.

Whilst not a diagnostic criterion *per se,* sleep disturbance in schizophrenia is consistently reported with subjective sleep symptoms being highly prevalent. One cohort study of 214 men with treatment naïve schizophrenia reported that 63% described persistent 'sleep loss symptoms' which included difficulty maintaining sleep, early waking and trouble initiating sleep (Sweetwood et al., 1976). Other cohort studies of patients treated with antipsychotic drugs have reported lower rates of sleep disturbance of between 32-37% (Haffmans et al., 1994; Serretti et al., 2004), which may reflect an effect of antipsychotic treatment in ameliorating positive symptoms that contribute to sleep disruption (Krystal et al., 2008).

Standardised measurement of sleep in people with schizophrenia also demonstrates significant sleep disturbance in this population. Royuela et al. (Royuela et al., 2002) assessed

Table 1: Common PSG parameters, definition according to AASM criteria and clinical or diagnostic relevance (Berry et al., 2015)

Sleep parameter	Definition	Clinical relevance
Sleep measures		
Sleep onset latency (SOL)	Time from lights off to 10 consecutive minutes of stage 2 sleep (in minutes)	Measure of vigilance or degree of day-time sleepiness. Repeated testing is termed median sleep latency time (MSLT) which is gold-standard diagnostic tool for narcolepsy and idiopathic hypersomnia. Sleep latency is reduced when a subject is increasingly sleepy.
Total sleep time (TST)	Minutes of sleep during recorded period of sleep	May be reduced or prolonged by variety of pathological factors. Differing normal ranges for ages, total sleep time reduces with increasing age.
Sleep efficiency index (SEI)	Total time spent asleep per time period of recording (expressed as percentage)	Normal sleep efficiency index is >80%. Reduced with frequent awakenings during the night. Reduced sleep efficiency is an indicator of non-restorative sleep.
Arousal index (AI)	Number of arousals or awakenings per hour	Arousals are caused by disruption to sleep may be due to primary sleep fragmentation or because of apnoeas causing arousal due to hypoxia.
N1	Time (in minutes) or percentage of total sleep time in stage 1 sleep	Transition between wakefulness and sleep. Reduced with excessive sleepiness. Normal range in adults is ~5% of total sleep.
N2	Time (in minutes) or percentage of total sleep time in stage 2 sleep	First stage of true sleep. Accounts for ~50% of total sleep in adults. Increasing N2 is an age-related change and also seen with some medications. Reduced due to sleep fragmentation or increased N3 or REM sleep.
N3 (also termed slow wave sleep (SWS))	Time (in minutes) or percentage of total sleep time in stage 3 sleep	Deep restorative sleep. Accounts for ~20% of total sleep in adults. Predominates in first third of the night. Increases after sleep deprivation and with hypnotic/sedative medications.
REM	Time (in minutes) or percentage of total sleep time in REM sleep	Function of REM sleep uncertain. Accounts for ~25% of total sleep in adults. Suppressed by alcohol, tricyclic antidepressants and amphetamines. Increased REM occurs during treatment of OSA.
REML	Time (in minutes) from initiation of N1 to first REM epoch	Reduced REML is seen in withdrawal from antidepressant drugs and alcohol, clinical depression and in diagnosable sleep disorders such as OSA and narcolepsy.

Sleep parameter	Definition	Clinical relevance
Respiratory measures		
Hypopnoea	10 seconds of reduced nasal airflow with accompanying oxygen desaturation	Seen in OSA and central causes of sleep apnoea (i.e. reduced central nervous respiratory drive)
Apnoea	10 seconds of complete cessation of nasal airflow	Seen in OSA and central causes of sleep apnoea (i.e. reduced central nervous respiratory drive)
Apnoea hyponoea index (AHI)	Number of apnoeas and hypopnoeas during each hour of PSG recording	Diagnostic measure of OSA
Respiratory effort related arousal (RERA)	Reduction in nasal airflow with increased respiratory effort and arousal without oxygen desaturation	Seen in OSA
Respiratory disturbance index (RDI)	Number of apnoeas, hypopnoeas and RERAs per hour of PSG recording	Alternative diagnostic measure of OSA
Oxygen desaturation index (ODI)	Number of ≥3% oxygen desaturation events per hour of PSG recording	Indicator of apnoea or hypopnoea, but unable to differentiate central versus obstructive causes. May be used as a screening test for OSA.

44 people with treated schizophrenia with the PSQI in comparison to a general population control group. Mean PSQI was elevated in the schizophrenia group compared to the control group (mean PSQI 6.6 versus 4.5, $p<0.01$) which was accounted for by significant elevation of sleep latency, sleep duration and hypnotic drug use subscales. Interestingly, sleep disturbance was not significantly elevated in the schizophrenia group. These findings suggest that people with schizophrenia spend more time in bed and have poor sleep efficiency, but do not subjectively recognise nocturnal interruption to sleep or report excessive daytime somnolence. A similar cohort study in a mixed first episode psychosis (FEP) and chronic schizophrenia cohort of 100 people reported ESS and PSQI with comparisons across the two groups (Sharma et al., 2016). PSQI aggregate scores were elevated in 83% of the total cohort, whilst ESS scores were only elevated in 32%. In contrast with previous studies, elevated PSQI scores were significantly higher in the chronic cohort compared to the FEP cohort whilst mean duration of illness was significantly higher in those with an elevated PSQI compared to those without across the entire cohort. These findings were not replicated with the ESS data.

On the whole, the literature reporting symptom data indicates that sleep disturbance, as measured by difficulty initiating efficient sleep, is highly prevalent in people with schizophrenia. However, there are inconsistencies in whether these symptoms improve or worsen with duration of illness or initiation of antipsychotic treatment. Interestingly, whilst sleep disturbance is common this does not necessarily translate into a measurable signal on standardised assessment of daytime somnolence using PSQI subscales or the ESS which may reflect a lack of symptomatic awareness of these symptoms by people with schizophrenia or alternatively that these tools perform poorly in this population.

Objective sleep disturbance in schizophrenia

The clinical observation of sleep symptoms in schizophrenia has led to the development of extensive literature reporting PSG data in people with schizophrenia compared to healthy controls. This literature has been extensively reviewed with three meta-analyses published reporting architectural sleep alterations in newly diagnosed, medication-withdrawn and medication treated patients with schizophrenia (Benca et al., 1992; Chan et al., 2017; Chouinard et al., 2004). In summary these meta-analyses have some broadly comparable findings but also key differences as a result of inclusion criteria, specifically whether schizophrenia cohorts were antipsychotic naïve or exposed, and statistical heterogeneity across the included studies. The most recently published meta-analysis (Chan et al., 2017) reported aggregate effect size data indicating prolonged sleep onset latency and N1, and reduced N3, REM sleep latency, total sleep time and sleep efficiency index in cohorts with schizophrenia. Restriction of analysis to medication naïve patients indicated that whilst differences in sleep onset latency, total sleep time and sleep efficiency index remained similar, there was no detectable difference in effect size of sleep architecture (i.e. reduced N3 and REM sleep latency). These findings are consistent with an earlier meta-analysis (Chouinard et al., 2004) which included only medication naïve cohorts. Restriction of analysis to medication-withdrawn cohorts demonstrated a consistent reduction in total sleep time, sleep efficiency index, REM sleep latency and N3 with a concomitant increase in sleep onset latency. Analysis of medicated cohorts indicated significantly prolonged sleep onset latency and N2 with a concomitant reduction in REM duration. In an older meta-analysis of predominantly medicated cohorts effect size was significantly higher for sleep onset latency and reduced for total sleep time and sleep efficiency index (Benca et al., 1992). Interestingly moderator analysis of duration of illness indicated that longer duration of illness correlated with a progressive reduction in N3 and normalisation in REM sleep latency.

These meta-analytic findings suggest that sleep disturbance in schizophrenia is a dynamic process dependent on and modified by both the duration of illness and exposure to antipsychotic medication. Consistent findings are that sleep disruption (as measured by total sleep time, sleep efficiency index and sleep onset latency) is a pervasive feature of schizophrenia both early and late in disease. This observation is unsurprising given evidence of severe circadian rhythm disturbance in schizophrenia which has been replicated across multiple studies using actigraphic measures, sleep diaries and serial melatonin measurement (Afonso et al., 2014; Martin et al., 2001; Poulin et al., 2010; Wulff et al., 2012). Furthermore, some authors have reported neurochemical data demonstrating objective changes in regulatory pathways indicative of a biological basis to circadian rhythm disruption in this population (Rao et al., 1994; Wulff et al., 2012). On the other hand, changes to sleep architecture in schizophrenia (as measured by REM and non-REM sleep duration, and REM sleep latency) are more inconsistent and appear to depend more on medication exposure and duration of illness. As such it is difficult to definitively determine whether single architectural parameters are pathobiologically related to schizophrenia or whether they represent a surrogate of response to treatment or marker of long-term outcome.

The major confounding effect of PSG data in schizophrenia is the impact that antipsychotic drugs may play in altering normal sleep architecture. There is extensive data reporting the effect of antipsychotic drugs on sleep architecture in both normal volunteers and people with schizophrenia, the bulk of which has been extensively reviewed (Cohrs, 2008). FGAs on the whole appear to consistently prolong total sleep time and improve sleep efficiency in people with schizophrenia but have an inconsistent effect on these parameters in healthy controls. Exposure also prolongs N3 sleep, however this impact is variable with low potency, more sedating drugs (e.g. chlorpromazine) exerting a significant influence and high potency, less sedating drugs (e.g. haloperidol) having minimal effect. Similarly, the impact of FGAs on REM

sleep duration appears to be agent specific. Of note, withdrawal effects have more consistent effects on sleep architecture. Abrupt drug withdrawal of haloperidol results in reduction of total sleep time, N3 sleep, REM duration and sleep efficiency with relative increase in N2 sleep (Neylan et al., 1992; Nofzinger et al., 1993; Thaker et al., 1989). Evidence also suggests that the degree of reduction in total sleep time and sleep efficiency after antipsychotic withdrawal were strongly correlated with risk of psychosis relapse, whilst degree of increase in N3 sleep was inversely correlated (Chemerinski et al., 2002; Neylan et al., 1992).

In regard to SGAs their effect on sleep varies considerably based on the individual agent, reflecting the diverse receptor profile of these drugs. Most SGAs, with the exception of risperidone, increase total sleep time and sleep efficiency, whilst their effects on REM and non-REM sleep are variable. Olanzapine and ziprasidone are consistently reported to prolong N3 sleep in people with schizophrenia, clozapine is associated with a reduction in N3 sleep, whilst other individual drugs have minimal effect. Similarly, REM sleep duration is variably impacted; clozapine and paliperidone are reported to prolong REM sleep, risperidone and ziprasidone are reported to reduce REM sleep, whilst olanzapine and quetiapine have inconsistent or clinically meaningless effects. As such it is difficult to generalise an effect of all antipsychotic drugs on sleep architecture, beyond a relatively consistent effect on prolonging total sleep time and sleep efficiency which is likely a function of their ability to ameliorate positive symptoms which impact directly on sleep quality (Cohrs, 2008).

The effect of sleep on symptomatology in schizophrenia

It is likely that changes in sleep architecture are associated with clinical outcomes in schizophrenia, particularly neurocognitive performance. There is a preponderance of PSG data that indicates abnormalities in REM sleep are a predictor of more severe symptomatology, using general rating scales such as the positive and negative symptom scale (PANSS) and brief

psychiatric rating scale (BPRS). As an example, reduction in REM latency is consistently reported to be strongly correlated to BPRS scores in untreated schizophrenia (Poulin et al., 2003; Tandon et al., 1992) and is responsive to antipsychotic drug treatment (Taylor et al., 1991). REM sleep density (the frequency of eye movements during REM sleep) is also reported to be reduced in schizophrenia compared to general populations and is inversely correlated with BPRS (Poulin et al., 2003) and total PANSS scores (Yang et al., 2006). The effect of REM sleep disturbance is most pronounced in its association with positive symptomatology. Severity of positive symptoms is inversely correlated with REM density (Benson et al., 1993; Rotenberg et al., 1997) which is independent of antipsychotic medication effects (Yang et al., 2006). Similarly, reductions in REM sleep latency (the time between onset of sleep and the first episode of REM) are predictive of more severe positive symptomatology both in drug naïve cohorts (Lauer et al., 1997; Poulin et al., 2003) and in treated cohorts recently withdrawn from antipsychotic medications (Tandon et al., 1992; Taylor et al., 1991; Thaker et al., 1989). Whilst beyond the scope of this thesis, some authors suggest these associations indicate the physiology of REM sleep shares a common biological basis with the symptomatology of schizophrenia (Poulin et al., 2003).

Conversely the main PSG measure associated with negative symptomatology is alterations in slow wave sleep (SWS). Findings across multiple studies of treatment naïve (Ganguli et al., 1987; Keshavan, Miewald, et al., 1995; Keshavan, Pettegrew, et al., 1995; van Kammen et al., 1988) and antipsychotic medicated (Kajimura et al., 1996; Kato et al., 1999; Tandon et al., 2000) cohorts consistently demonstrate an inverse relationship between slow wave sleep duration and negative symptoms throughout all phases of illness. This finding is independent of age and depressive symptomatology (which can also be associated with reduced slow wave sleep) (Ganguli et al., 1987). Some studies also suggest that reduction in delta wave activity (defined as reduction in voltage and frequency of delta waves) is also correlated with negative

symptoms independent of absolute slow wave sleep duration (Ganguli et al., 1987; Kato et al., 1999; Keshavan, Miewald, et al., 1995). These findings are indicative of a direct neurobiological link between sleep and functional outcomes in schizophrenia. As such, treatment directed at normalising slow wave sleep in schizophrenia may represent a novel means of modifying negative symptoms of schizophrenia, which often remain resistant to antipsychotic treatment.

It is perhaps unsurprising that alterations in sleep architecture are also associated with cognitive deficits in schizophrenia. Cognition encompasses multiple aspects of intellectual functions including working, short-term and long-term memory, judgement, reasoning, procedural learning, attention, comprehension and language. As such, comparability of literature reporting the effect of sleep on cognition in schizophrenia is impacted on by the variety of outcomes that can be measured. Decrements in gross measures of vigilance as measured by reaction time were shown to be correlated with reduction in slow wave sleep duration and sleep spindle density in a small cohort of drug-naïve patients with schizophrenia (Forest et al., 2007). Other lines of research support the role of disordered sleep architecture as playing a role in sleep-dependent memory consolidation. In cohorts of treated patients with schizophrenia reductions in slow wave sleep and sleep spindle density have been correlated with measures of visuospatial memory (Goder et al., 2004), declarative memory (Goder et al., 2008) and procedural learning (Goder et al., 2006), however results were inconsistent across these studies, possibly as a result of the different antipsychotic treatments that the cohorts were prescribed (Manoach et al., 2009).

Whilst the absolute amount of time spent in various phases of sleep correlates with outcomes in individual cognitive domains, there is evidence that global measures of complex cognitive processes are more dependent on dynamic aspects of sleep architecture. In healthy people this

can be thought of as a multi-step process whereby consolidation of declarative memory is achieved predominantly through the effects of early slow wave sleep with subsequent integration and enhancement of these memories into larger integrative networks dependent on later N2 and REM sleep. As such higher level or abstract cognitive processes such as procedural learning, emotional memory and judgement are likely to be more dependent on the normal progression throughout sleep stages (i.e. predominant slow wave sleep early in the night followed by later N2 and REM sleep) than on absolute or relative changes in the amount of time spent in slow wave sleep, REM or N2 sleep (Manoach et al., 2009). Empirical evidence for this assertion is supported by two studies in normal populations. One study demonstrated that overnight improvement in visio-perceptual learning correlated strongly with absolute slow wave sleep early in the night and REM sleep late in the night, and that this correlation was strengthened by a regression model combining these two parameters (Stickgold et al., 2000). Another study of day-time napping on visio-perceptual learning indicated that deterioration in performance was reduced with naps containing slow wave sleep, but was improved with naps that contained slow wave sleep followed by periods of REM (Mednick et al., 2002). In schizophrenia there is evidence that disruptions in this multi-step process similarly drive deficits in procedural memory learning. One polysomnographic study demonstrated that in comparison to healthy controls, people with schizophrenia spent a significantly shorter period of time in N2 in the last quarter of sleep and had significantly reduced sleep spindle density. The motor sequence task was used as measure of procedural learning and was measured before and after a night of sleep. Quantity of N2 sleep in the last quarter of sleep and early slow wave sleep duration were predictive of improvement, a correlation that was strengthened when these two parameters were combined in a logistic regression model (Manoach et al., 2010).

Impairment across a variety of cognitive domains is a central feature of schizophrenia and persists throughout all phases of the disease (Rund, 1998). Furthermore, cognitive deficits

remain stable over the course of disease independent of acute change in positive symptoms (Harvey et al., 1990) and are a strong predictor of functional outcome (Green et al., 2000). Disappointingly, antipsychotic agents have only modest effect on cognitive measures in schizophrenia with FGAs having no measurable impact and SGAs having statistically significant but clinically meaningless effects in comparison to placebo (Bowie et al., 2006). It is likely that sleep disruption is intrinsic to schizophrenia and plays a complex role in driving cognitive deficits and negative symptoms. As such modification of the architectural changes and disruption of sleep in schizophrenia may represent a novel means of improving treatment-resistant symptoms and functional outcomes. However as yet there is almost no literature describing specific interventions to achieve this or outcomes of such a therapeutic approach.

How might OSA and its treatment be relevant in schizophrenia

There is a wealth of evidence indicating that sleep disturbance and sleep architecture is disrupted in schizophrenia, however there is comparatively little high-quality literature describing what role comorbid OSA plays in driving sleep disturbance in schizophrenia. As previously discussed, it is probable that OSA is prevalent in schizophrenia due to shared risk factors. As a corollary, it is plausible that sleep disturbance described in schizophrenia may therefore be driven or exacerbated by OSA. Unsurprisingly, many of the sleep symptoms and architectural changes in sleep described in schizophrenia are analogous to those seen with OSA. It is important therefore to consider the pathophysiology, symptomatology and treatment outcomes of OSA and how these may be aetiologically linked to schizophrenia.

OSA is the most common of the diagnosable sleep disordered breathing syndromes. OSA results from repeated collapse or obstruction of the pharyngeal airway during sleep resulting in hypoxia and frequent arousals that cause sleep fragmentation and disruption to normal sleep architecture (Osman et al., 2018). The pathophysiology of OSA is driven by excessive soft

tissue surrounding the upper airway, negative intraluminal pressure generated by inspiratory effort and a failure of pharyngeal dilator muscles to counterbalance these opposing forces and maintain airway patency. During wakefulness people with OSA are able to maintain adequate tone to preserve airway patency, however during sleep physiological reduction in muscle tone can result in collapse of the airway with resultant hypoxia, then arousal, to normalise airway tone. Dilator muscle tone and reflex responsiveness to negative airway pressure is most ablated during transition of N1 to N2 sleep and during REM sleep and therefore apnoeas are most common during these phases of sleep (Eckert et al., 2008).

The major risk factors for OSA are obesity, male sex, increasing age and tobacco smoking, all of which mediate risk mainly through mechanical effects. Deposition of fat around the pharynx in obesity increases collapsibility of the airway (Horner et al., 1989) and also has direct effects on pharyngeal dilator muscle function resulting in increased fatigability (Carrera et al., 2004). Compared to women, men demonstrate sex-related propensity for fat distribution around the pharyngeal airway (Whittle et al., 1999) and a longer pharynx length (Malhotra et al., 2002) – both factors promote airway collapsibility. Similarly increasing age is associated with preferential deposition of pharyngeal fat, independent of total body fat, whilst muscular reflexes to negative airway pressure also deteriorate with age (Malhotra et al., 2006). Tobacco smoking is reversibly associated with an increased risk of OSA as a result of pharyngeal lymph-adenoid hyperplasia in response to particulate irritants, and nicotine withdrawal during sleep can result in a reduced arousal threshold to hypoxia (Young et al., 2004). Obesity (Mitchell et al., 2013) and tobacco smoking (Myles et al., 2012) are highly prevalent in schizophrenia making it likely that OSA is therefore over-represented in this population.

Various classes of drugs are also associated with increased risk or exacerbation of underlying OSA, generally mediated by reduction in muscle tone or a central reduction in respiratory drive

during sleep. Meta-analysis has demonstrated alcohol is strongly associated with risk and severity of OSA, an effect that is independent of obesity (Simou et al., 2018). Mechanistically, there is evidence that alcohol both reduces pharyngeal muscle tone and increases upper airway resistance predisposing to airway collapse (Krol et al., 1984). Alcohol use may be a significant factor in driving OSA risk in people with schizophrenia, given that alcohol use disorders are over-represented in this population (Moore et al., 2012). Historically benzodiazepines have also been implicated in increasing risk of OSA through the purported mechanism of reducing muscle tone. However, this association has not survived recent meta-analysis which demonstrates that benzodiazepines do not objectively worsen apnoeas or hypopnoeas, but do have a significant effect on worsening nocturnal hypoxia associated with apnoeas likely as a result of an increased arousal threshold (Mason et al., 2015).

Of particular relevance to schizophrenia, there is emerging evidence that SGA medications are another drug-related risk factor for OSA. Chronic SGA use induces significant weight gain and pharmacodynamically interact with a receptor profile that may have effects on central respiratory drive and airway muscle tone providing a mechanistic link with OSA. There is minimal empirical evidence, but some authors suggest that serotonergic antagonism of SGAs may ablate central nervous system control of airway patency and resistance during sleep (Kanamaru et al., 2007). One retrospective cohort study of patients referred to a sleep disorders clinic reported mean apnoea hyponoea index as a measure of OSA severity between patients exposed and unexposed to SGAs. This study reported a significantly higher apnoea hyponoea index in those exposed to SGA agents which remained significant when controlling for BMI, age, sex and benzodiazepine use (Rishi et al., 2010). Another single-arm intervention study reported change in apnoea hyponoea index after eight weeks of treatment with olanzapine, risperidone and quetiapine initiated as treatment in otherwise healthy patients for insomnia. At follow-up there was a substantial and statistically significant increase in apnoea hyponoea

index from pre-treatment values, which occurred despite no acute change in BMI or neck circumference during the treatment period (Khazaie et al., 2018). Another retrospective cohort study of patients exposed to SGAs using a control group of people with depression not exposed to SGAs, demonstrated that whilst apnoea hyponoea index was elevated in the schizophrenia group, this effect became non-significant on a regression model incorporating age, sex and BMI (Shirani et al., 2011). Together these studies suggest that SGAs may contribute to an increased risk of OSA, however it is unclear whether or not this risk is attributable to off-target pharmacodynamic properties or reflects a secondary effect from antipsychotic-induced weight gain. Certainly, the literature specifically examining effect of SGA in schizophrenia is limited by retrospective methodology, and the literature more generally suffers from small sample size that may be insufficiently powered to detect an effect independent of obesity. Larger prospective studies using unselected populations are required to definitively determine whether SGAs have an independent effect on increasing risk of OSA.

The symptomatic impact of OSA relevant to schizophrenia

The main symptomatic outcome of OSA is excessive daytime sleepiness, fatigue and non-restorative sleep as a result of nocturnal sleep fragmentation. These symptoms are associated with reduced socio-occupational performance (Omachi et al., 2009), increased risk of motor vehicle accidents (Teran-Santos et al., 1999) and reduced quality of life (Lacasse et al., 2002). Beyond subjective symptoms, untreated OSA is also associated with significant neurocognitive and affective dysfunction. Case-controlled studies have demonstrated an excess of diagnosable depressive disorders in people with OSA compared to general population controls (Aikens et al., 1999; Ramos-Platon et al., 1992), an association which has also been demonstrated in larger epidemiological cohorts (Ohayon, 2003) and confirmed on meta-analysis (Garbarino et al., 2018). Whilst the relationship between affective symptoms and OSA is likely to be bi-directional, OSA is probably in part aetiological given that CPAP treatment is demonstrated to

normalise affective symptoms (Giles et al., 2006). Similarly, there is extensive evidence describing cognitive decrements in people with OSA compared to the general population, an association that appears to affect subdomains selectively. Reviews and meta-analyses of case-controlled data (Beebe et al., 2003; Bucks et al., 2013; Olaithe et al., 2013; Wallace et al., 2013) indicate that vigilance, long-term episodic memory and executive functioning (which includes shifting between tasks, efficiently accessing semantic memory, fluid reasoning and problem solving) are the predominant cognitive domains affected. Cognitive outcomes also appear to occur as a threshold effect of OSA, evidenced by a lack of conclusive evidence demonstrating a liner correlation between severity of cognitive symptoms and apnoea hyponoea index (Wallace et al., 2013). Importantly, CPAP treatment is associated with an improvement in cognitive outcomes in OSA, particularly vigilance and executive functioning (Olaithe et al., 2013).

Neurocognitive and affective symptoms of OSA may be particularly relevant in schizophrenia where they may compound negative symptoms and pre-existing cognitive decrements related to the schizophrenia. Negative symptoms are generally considered to encompass five primary domains: blunted affect, alogia, asociality, anhedonia and avolition (Kirkpatrick et al., 2006). They are highly predictive of real-world functioning (Harvey et al., 2012) and are poorly responsive to antipsychotic treatment (Galderisi et al., 2018). Cognitive decrements in schizophrenia are also highly prevalent, stable over the course of illness and considered to be a trait marker (Rund, 1998). Affected cognitive domains are broad, but predominantly include attention, vigilance, executive functioning and verbal memory (Heinrichs et al., 1998). Similar to negative symptoms, severity of cognitive decrements corelate strongly with functional outcomes and are resistant to antipsychotic treatment (Fett et al., 2011). Whilst cognitive symptoms are distinct from negative symptoms in schizophrenia, there is likely to be some degree of overlap. For example, some authors (Marder et al., 2017) have suggested that

paradigms of attention and vigilance share commonality with standardised measures of negative symptoms; impairment of executive function is a key factor in avolition; and poor verbal fluency underlies alogia to a significant extent.

It is clear that the adverse neurocognitive outcomes of schizophrenia and OSA overlap considerably, particularly in the cognitive domains of attention, vigilance and executive functioning. It follows therefore that because of pre-existing neurocognitive decrements, people with schizophrenia are likely to be particularly vulnerable to the adverse cognitive and affective outcomes of comorbid OSA which in turn may indirectly exacerbate negative symptoms and functional outcomes intrinsic to psychiatric disease. Given that CPAP is validated to improve cognitive outcomes of OSA in the general population, treatment of OSA comorbid with schizophrenia may offer a means of improving functional recovery in a subset of patients. As yet there is no published evidence to support this assumption.

Possible effects of treatment of OSA comorbid with schizophrenia

As previously discussed, disruption of sleep architecture is a pervasive feature of schizophrenia, which may be exacerbated by comorbid OSA. In general populations with OSA, frequent arousal due to hypoxia results in significant sleep fragmentation and an overall reduction in sleep efficiency. Improvements in sleep efficiency after treatment of OSA with CPAP therapy are a strong predictor of improvement in vigilance (Conradt et al., 1998). Similarly, sleep architecture is grossly disrupted by OSA with consistent reports of reduced slow wave sleep, reduction in REM and increase in N1 sleep which are normalised by CPAP treatment (Bonsignore et al., 1987; Collard et al., 1996; Fietze et al., 1997; Lamphere et al., 1989). CPAP treatment has also been reported to normalise sleep spindle density in OSA, which is another strong predictor of improvement in vigilance (Yetkin et al., 2018). Of note decreases in slow wave sleep and sleep spindle density seen in OSA mirror those described in

schizophrenia and as such may compound the associated neurocognitive decrements in comorbid disease. There is a preponderance of data demonstrating that CPAP normalises sleep architecture in general populations with OSA, but to what extent this occurs in people with schizophrenia is yet to be determined.

Finally, it is possible that treatment of comorbid OSA could improve cardiometabolic parameters and quality of life in people with schizophrenia, which as previously discussed is an area of unmet clinical need. CPAP treatment has been consistently shown to improve blood pressure control and quality of life in people with OSA (Jonas et al., 2017). Whilst large randomised studies have not demonstrated an effect of CPAP in the secondary prevention of cardiovascular end-points such as stroke or myocardial infarction (McEvoy et al., 2016), there is evidence that CPAP does improve recurrence of atrial fibrillation (Kanagala et al., 2003), reduces mortality associated with heart failure (Kasai et al., 2008; Wang et al., 2007) and results in increased rates of physical activity (Jean et al., 2017).

Perhaps the largest caveat in interpreting outcomes related to CPAP is that the magnitude of treatment effect is dependent on adequate adherence. A therapeutic threshold of CPAP is generally considered to be between 5-6 hours per night (Rotenberg et al., 2016), whilst improvements in physical health outcomes appear to occur with 4 hours of use per night (Barbe et al., 2012; Peker et al., 2016). Disappointingly, general population estimates of adherence are between 30-40% with up to 10% of people unable to undertake CPAP at all (Rotenberg et al., 2016). Although no empirical evidence exists, it is possible that people with schizophrenia may undertake CPAP even less than general populations due to changes in mental state. There is data in people with major depression and comorbid OSA that CPAP adherence is poorer than the general population (Law et al., 2014). As such, despite the theoretical benefit of ideal CPAP usage in improving cognitive symptoms, quality of life and physical health outcomes in people

with schizophrenia, it is important also to determine whether the treatment is acceptable as an indicator of its real-world benefit.

Prevalence and identification of OSA in schizophrenia

In general populations identification of OSA is typically based on the symptomatic complaint of poor sleep quality or daytime somnolence, which may be objectively assessed using scoring systems such as the ESS and PSQI. Similarly, a number of diagnostic scoring systems are available that may be useful in identifying high risk groups where PSG assessment is warranted to further investigate for OSA. As previously discussed, these clinical measures of OSA symptoms are likely to perform poorly in people with schizophrenia. It is plausible that diagnostic overshadowing may obscure detection of OSA in people with schizophrenia as both patient and clinicians may attribute sleep symptoms, cognitive impairment and daytime somnolence to sleep disruption intrinsic to psychotic illness or to the sedating effects of antipsychotic medications. Diagnostic tools for OSA and objective measures of sleep symptoms or daytime sleepiness are also likely to perform poorly, especially as none have been validated in people with schizophrenia. As previously discussed sleep symptoms related to socio-occupational activities assessed in these tools may not be particularly relevant to people with schizophrenia given socioeconomic deprivation in this population and pervasive negative symptoms of apathy and avolition. Similarly, a number of tools rely on bed-partner reported snoring or pausing during sleep, which is likely to be insensitive to the detection of symptoms given the majority of people with schizophrenia lack a bed partner (Morgan et al., 2011).

One cohort study (Anderson et al., 2012) of people with schizophrenia undergoing PSG assessment for OSA indicated that mean ESS and PSQI were not significantly elevated in those subjects who were diagnosed with sleep apnoea using PSG. Whilst this study did not attempt to specifically validate these symptom tools, it is pertinent to note that mean PSQI and ESS

scores across the entire cohort were only 6.5 and 5.6 respectively despite 52% of the cohort having a diagnosis of OSA. These scores are lower than means reported in general population controls (Johns, 1991) which is indicative of how poorly sensitive these measures may be. Apart from this single study there is no other literature reporting the validity of sleep symptom scores or diagnostic questionnaires in schizophrenia and as such minimal evidence to guide clinicians on how best to identify OSA at the clinical level. Poor clinical awareness of OSA may lead to the under-provision of sleep services to people with schizophrenia and a missed opportunity to intervene in a reversible condition that may aggravate cognitive deficits, impaired quality of life and adverse physical health outcomes.

It is important then to interpret published estimates of OSA in this context. There are three main methods for reporting prevalence of OSA: estimates based on diagnostic screening tools, estimates based on healthcare registry data and estimates based on diagnostic tools such as PSG. Two studies have reported estimates based on screening tools. The first study (Alam et al., 2012) utilised the STOP-BANG questionnaire (Chung, Subramanyam, et al., 2012) in a cohort of 100 subjects comprised mainly of people with schizophrenia or schizoaffective disorder and reported a 69% prevalence of OSA. Of the entire cohort 16% had a prior diagnosis of OSA confirmed by PSG and of those considered to have OSA based on STOP-BANG scores only 32% had OSA previously mentioned as a diagnostic possibility by their treating doctors. A second study (Annamalai et al., 2015) reported on a cohort of 175 patients with schizophrenia or schizoaffective disorder being assessed for insomnia and utilised a simplified STOP questionnaire (Chung et al., 2008) as a measure of OSA. 57.7% of subjects were considered to have OSA based on the STOP questionnaire and similarly only 14.9% of the total cohort had a previous diagnosis of OSA. Given the limitations of diagnostic screening tools, it is unlikely that these prevalence estimates are accurate. However, the results do suggest that clinical recognition and detection of OSA risk is low in people with schizophrenia. One large

data linkage study using outpatient data from the US Veterans Health Database reported prevalence of OSA in people with a current diagnosis of psychosis based on ICD-10 codes (Sharafkhaneh et al., 2005). This large study reported a prevalence rate of OSA of 1.6%, which is likely to be a gross underestimation given this rate is much lower than that seen in the general population (Heinzer et al., 2015). These results thus only provide further evidence that OSA comorbid with schizophrenia is likely to be significantly under-recognised at the clinical level.

To date there are only four cohort studies that provide estimates of OSA in schizophrenia using objective diagnostic measures and from which clinical associations can be determined. The details of each study, their inclusion criteria, diagnostic measures and prevalence estimates are outlined in table 2. On the whole all of these studies have limitations in methodology which limit their extrapolation to populations with schizophrenia more generally. Of note only one study (Anderson et al., 2012) utilised the gold-standard measure of apnoea hyponoea index >5 on overnight PSG as a threshold for diagnosis. Two other studies (Ancoli-Israel et al., 1999; Winkelman, 2001) defined respiratory disturbance index (RDI) >10 on overnight PSG as the threshold for diagnosis of OSA, which is not recommended in preference to the apnoea hyponoea index by the American Academy of Sleep Medicine (AASM) (Berry et al., 2015). The final study (Takahashi et al., 1998) utilised overnight oximetry and desaturation index (DI), defined as the mean number of desaturation episodes of >4% per hour of sleep, as the diagnostic measure of OSA. Whilst desaturation index does correlate with apnoea hyponoea index, it does not reliably differentiate obstructive from central apnoeic episodes (Chung, Liao, et al., 2012).

Similarly, variation in populations recruited across these studies is likely to have substantial impact on the reported estimates of OSA prevalence, limits comparability of the literature and precludes generalisation of results to broader populations of people affected by schizophrenia.

As an example, two studies (Takahashi et al., 1998; Winkelman, 2001) screened inpatients with schizophrenia; inpatients are likely to have acute changes in mental state and antipsychotic or sedative medication usage that may have impacted on sleep quality and confounded sleep study results. Similarly, differences in risk factors present in reported populations are also likely to have impacted on the reported prevalence estimates. The rates reported in one study (Ancoli-Israel et al., 1999) of older patients with schizophrenia may not be generalisable to younger groups of people because age is a risk factor for OSA. Another study (Winkelman, 2001) probably suffers from a positive selection bias because it only included participants referred to a sleep disorders clinic based on clinical suspicion of OSA, whilst another study (Anderson et al., 2012) is confounded by heterogeneity of psychiatric diagnosis with only 48% of participants having a diagnosis of schizophrenia. Ethnic differences may also be at play in the final study which reported the lowest prevalence of OSA across the literature (Takahashi et al., 1998). The mean BMI of 23.9 across this cohort of Japanese patients were in the normal range which is atypical of people with schizophrenia generally and is likely the reason why rates were not substantially elevated in comparison to a cohort of general population controls.

Despite these limitations these studies indicate that OSA is likely to be prevalent in schizophrenia with rates of between 14-57%. These studies also reported that age, male sex,

Table 2: Comparison of studies reporting prevalence of OSA in cohorts of people with schizophrenia using diagnostic measures

Study	Population	Methods	OSA diagnostic criteria	OSA prevalence
Ancoli-Israel (1999)	Older (mean age 60 years) outpatients with schizophrenia or schizoaffective disorder	Polysomnography	Respiratory disturbance index >10	48%
Anderson (2012)	Group of patients with major mental illness, 48% had schizophrenia or schizoaffective disorder	Polysomnography	Apnoea hyponoea index >5	52%
Takahashi (1998)	Inpatients with schizophrenia	Overnight oximetry	Desaturation index >5	21.9% in men 13.5% in women
Winkelman (2001)	Inpatients with schizophrenia referred to a sleep disorders clinic for clinical suspicion of OSA	Polysomnography	Respiratory disturbance index >10	57.1% in men 46.2% in women

BMI and increased neck circumference were associated with a diagnosis of OSA. Beyond these traditional risk factors, these studies were not able to provide information as to whether antipsychotic medications or psychiatric symptoms were associated with a diagnosis of OSA. In light of the existing literature it is clear that further research is required to determine robust prevalence estimates of OSA in schizophrenia that are not confounded by acute changes in mental state or selection bias due to convenience sampling. Similarly, more detailed datasets are also required to determine whether there are psychiatric disease specific predictors of OSA, beyond traditional risk factors, that may enhance recognition of OSA or facilitate targeted diagnostic screening at the clinical level.

Overview and approach of subsequent chapters

As outlined, it is likely that OSA is prevalent in schizophrenia and may have an adverse impact on quality of life, physical health morbidity and psychiatric outcomes, particularly negative symptoms and cognitive function. OSA has a validated treatment and it is possible that CPAP may provide a novel means of improving these adverse outcomes in people with schizophrenia and comorbid OSA. Whilst these assertions can be indirectly inferred from existing literature, there is a dearth of evidence reporting robust estimates of OSA in unselected cohorts, physical health and psychiatric outcomes associated with OSA, and treatment outcomes with CPAP in schizophrenia. Of concern, it is likely that OSA in under-recognised and under-treated at the clinical level. Further research is also required to identify population-specific clinical factors that are predictive of diagnosis to facilitate improved recognition at a clinical level.

In the context of these gaps in the existing literature the aims of this thesis are firstly to determine more accurate and generalisable estimates of OSA prevalence in schizophrenia; secondly to investigate physical health and psychiatric disease correlates in this population to enhance clinical detection of OSA; and thirdly to determine the impact that CPAP treatment of

severe OSA comorbid with schizophrenia has on physical health and psychiatric measures. To achieve these aims I present five manuscripts, all published or accepted for publication in peer-reviewed journals, with each manuscript forming a substantive chapter of this thesis. Each manuscript is presented in the format and referencing style as required by the publishing journal. This exegesis reviews each of the five manuscripts, why the research was warranted, and the specific research aim it addresses.

Three datasets reporting original data were analysed to provide results in this thesis. The first was data derived from the Survey of High Impact Psychosis (SHIP), the second was the Assessing Sleep in Schizophrenia and Evaluating Treatment (ASSET) dataset and the third was data derived from the Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) study. The SHIP dataset is derived from a survey of people in contact with mental health services across five Australian states conducted in 2010. This survey included people aged 18-64 years and covered a catchment area including approximately 10% of the Australian population. The survey was conducted using a two-phase methodology whereby a brief screening tool was first used to identify a cohort of 7,955 people with psychotic illness. Of this cohort 1,825 were subsequently interviewed, had diagnosis of a psychotic illness confirmed using the Diagnostic Interview for Psychosis (DIP) and underwent a battery of assessments covering psychopathology, cognitive ability, physical health, medication use and socioeconomic measures. Assessments included measures of OSA based on the University of Maryland Medical Centre Questionnaire for Sleep Apnea and severity of sleep disruption using the Assessment of Quality of Life Questionnaire. The full study methodology has been reported previously (Morgan et al., 2011). This dataset allows for the exploratory analysis of associations between OSA symptoms and psychiatric outcomes in people with schizophrenia, it forms the experimental basis of the manuscript presented in chapter 3.

The ASSET dataset was developed as an independent experiment of this thesis and had not previously been published. Briefly, the dataset was developed in two phases. The first phase involved prospective recruitment of a population of outpatients in the Northern Adelaide Local Health Network aged 18-64 years with a current diagnosis of schizophrenia, who were prescribed clozapine. These participants underwent baseline assessment of anthropometric measures, physical health screening, psychopathological measures, cognition using the Brief Assessment of Cognition in Schizophrenia (BACS), sleep symptoms using the ESS, PSQI, Insomnia Severity Index (ISI) and OSA screening tools OSA50 and STOP-BANG. Following baseline assessment subjects undertook diagnostic at-home PSG with OSA defined by apnoea hyponoea index >10. In the second phase subjects with severe OSA (defined as apnoea hyponoea index >30) were commenced on CPAP and were followed up at six months of treatment with repeat assessment of anthropometric, psychopathological, cognitive and sleep symptoms measures. This data set allows for estimation of OSA prevalence, prospective validation of sleep symptoms and OSA diagnostic scores and follow-up data to assess the impact of CPAP treatment on physical health measures, psychosis symptoms and cognitive outcomes, it forms the experimental basis of the manuscript presented in chapter 5 and 6.

The MAILES dataset is composed of an observational cohort of randomly selected community dwelling males in metropolitan Adelaide recruited between 2000 and 2010. The cohort has been prospectively followed with a variety of physical health, laboratory and sociodemographic measures occurring at various time points of follow-up. A subset of this cohort underwent at-home PSG to screen for OSA based on an apnoea hyponoea index >10. The full study methodology has been reported previously (Grant et al., 2014). This dataset provides a male general population control group for the ASSET study to determine relative prevalence of OSA and explore factors independently associated with OSA in the

schizophrenia cohort. In conjunction with the ASSET dataset it forms the experimental basis of the manuscript presented in chapter 4.

Chapter 2 (paper 1)

The purpose of this first paper was to undertake a systematic review of literature reporting diagnostic measures of OSA in cohorts of people with a diagnosis of schizophrenia. In regard to the narrative of this thesis the rational for this paper is two-fold. Firstly, this manuscript allows me to critically examine the literature to determine what is already known in regard to the aim of this thesis, namely prevalence, predictors and outcomes of OSA comorbid with schizophrenia. Primarily the results of this manuscript will establish a baseline estimate of prevalence to which primary data reported in later chapters of this thesis can be compared, but also allows for deficiencies in the literature to be identified, where original research would be informative and offer the greatest impact. Secondly, this manuscript aimed to provide a synthesis of the literature to inform improved detection of OSA at the clinical level which is the overarching aim of this thesis.

As discussed above there is a paucity of literature reporting diagnostic measures of OSA in cohorts with schizophrenia, with existing literature confounded by convenience sampling and recruitment bias. As such it is anticipated that existing literature will only provide limited information on the aims of this thesis. The pre-specified outcomes of this systematic review are to determine the prevalence of OSA, relative prevalence of OSA in comparison to general population control groups, the physical health and psychiatric correlates of OSA, the utility of OSA screening tools and outcomes of OSA treatment on physical health and psychiatric outcomes.

This systematic review builds on and provides novel information in comparison to existing literature. As an example, previous narrative reviews have been published (Cohrs, 2008;

Kaskie et al., 2017) but only provide a description of prevalence without critical analysis of confounding factors and how this might influence estimates in more representative populations of people with schizophrenia. As a corollary these reviews also report minimal analysis of factors predictive for diagnosis. Similarly, a meta-analysis reporting prevalence of OSA in schizophrenia has also been published (Stubbs, Vancampfort, et al., 2016). However, because of variability in recruitment strategies in the existing literature there was significant heterogeneity in the effect size reported in this meta-analysis which was not explained by subgroup analysis. As such it was felt that systematic review was of more relevance in determining prevalence and predictors of OSA in light of these methodological limitations, rather than replication meta-analysis. On the whole the existing literature does not adequately address any of the aims of this thesis which justifies further original research reported in subsequent chapters.

*The systematic review was published in Schizophrenia Research as a brief report. The submission was originally made as a full-length paper and was recommended for publication by peer review. An editorial decision was made to reduce the paper significantly in length, for the purposes of this thesis the original submission is available in appendix one.

Chapter 3 (paper 2)

This paper is a prospective cohort study using data from the SHIP study to determine prevalence of OSA related sleep symptoms in a cohort of people with psychotic illness. The study performs exploratory analysis of the association between sleep symptoms and physical health, psychopathological and quality of life outcomes. The results of this paper will inform the narrative arc of my thesis by providing inferential evidence of the symptomatic burden that people with schizophrenia experience as a result of OSA and determine what impact these symptoms have on physical health and psychiatric outcomes. Specifically, this paper defines

sleep symptoms using criteria from the University of Maryland Medical Centre Questionnaire for Sleep Apnoea which quantifies the frequency and severity of snoring and witnessed apnoea during sleep over the preceding 12 months; and sleep disturbance using a criterion in the Assessment of Quality of Life Questionnaire which quantifies the subjective quality of sleep into various categories of severity. The SHIP dataset reports an extensive range of physical health, psychiatric, sociodemographic and medication data, and as such allows for broad exploratory analysis of associations and multivariate analysis.

Whilst existing literature has reported on sleep disturbance in schizophrenia (Haffmans et al., 1994; Serretti et al., 2004; Sweetwood et al., 1976), indicating that it is highly prevalent, there is minimal literature that reports sleep disturbance specific to OSA. This chapter builds in this evidence base by specifically examining to what extent OSA is likely to drive sleep disturbance in people with schizophrenia. The SHIP dataset also has a substantially larger sample size than that of existing literature and as such is likely to provide much more robust prevalence estimates across a more generalisable cohort of people with psychotic illness. The size of the SHIP dataset also allows for extensive exploration of how sleep disturbance and OSA symptomatology impacts or is impacted on by a broad array of factors. This is particularly important in regard to the second aim of this thesis, because little is currently known in regard to the physical health and psychiatric correlates of OSA. Importantly, the SHIP dataset allows for multivariate analysis to control for factors such as obesity, age and sex which confound these associations, providing a clearer picture of independent associations that may be modifiable with CPAP treatment. The results of this paper will help to substantiate, or refute, the hypothesis that OSA is associated with poorer psychiatric outcomes and clarify specific associations that will be further explored in subsequent chapters reporting more robust diagnostic measures of OSA using PSG.

Chapter 4 (paper 3)

Building on the evidence generated in chapter 3, the paper presented in chapter 4 aims to determine whether there are increased odds of OSA in people with schizophrenia compared to general population controls. In regard to the narrative of this thesis, this paper is directly relevant to the investigation of prevalence (in providing evidence that OSA occurs more frequently in schizophrenia) and predictive factors (by exploring whether the relative odds of OSA is explained by an excess of the traditional risk factors of age and obesity). This paper reports a matched cohort study of people screened for OSA using diagnostic PSG. The schizophrenia cohort is derived from the ASSET trial which consecutively screened a group of people with schizophrenia who were prescribed clozapine, whilst the control cohort is derived from a randomly selected population of men screened with PSG as part of the MAILES study. Because the comparator cohort is composed completely of men, only the male subjects of the ASSET study were analysed. This study will report the odds of severe OSA (apnoea hyponoea index >30) in the schizophrenia cohort compared to the control cohort and allow for logistic regression analysis using models matching for age and BMI to determine to what extent these factors explain an excess of OSA in the schizophrenia cohort.

Whilst there are a number of cohort studies that report the prevalence of OSA in schizophrenia, this paper will be the first to determine whether this prevalence is significantly higher than the general population using a matched cohort. One previous study has reported no increased odds of OSA in people with schizophrenia compared to a control cohort (Takahashi et al., 1998). However, this study did not use PSG for diagnosis of OSA, reported an unusually low mean BMI in the schizophrenia cohort and performed measures on inpatients with schizophrenia where sleep measures may have been confounded by acute changes in mental state. The paper in this chapter avoids these factors and will provide the only current evidence that robustly demonstrates or refutes an increased risk of OSA in schizophrenia. The overarching importance

of demonstrating increased odds of OSA in schizophrenia validates the importance of enhanced screening for OSA in this population. As such the secondary aim of this paper, that is exploring to what extent obesity and age drive risk of OSA, is also important because it provides evidence on how best to identify people who should undergo screening for OSA at the clinical level. Alternatively, if age and BMI do not explain risk of OSA, this result would generate the hypothesis that medication or psychiatric disease specific factors may play an aetiological role in OSA. As yet there is no literature reporting what clinical factors drive risk of OSA in schizophrenia.

Chapter 5 (paper 4)

This paper reports the main observational results of the ASSET dataset and addresses the aims of determining a robust prevalence estimate of OSA in schizophrenia and how diagnosis of OSA is associated with physical health, cognitive, psychiatric and functional outcomes, and objective sleep quality using the ESS and PSQI. Furthermore, this paper also prospectively determines the diagnostic efficacy of OSA screening tools previously validated in general populations. Briefly, this paper reports a prospective cohort study of stable community dwelling people with schizophrenia recruited from a clozapine clinic. Diagnosis is based on at-home PSG with OSA defined by apnoea hyponoea index >10.

This paper reports the first study to determine prevalence of OSA using gold standard diagnostic measures in a cohort composed completely of people with schizophrenia and avoids biases in recruitment to which previous literature is liable. As such the results generated will be comparatively more generalisable and accurate. Similarly, it will allow for the exploratory analysis of a large variety of factors that may be associated with a diagnosis of OSA and offers an opportunity to empirically validate associations identified in chapter 4 of this thesis. This paper will also determine mean PSQI and ESS scores across the cohort and determine whether

these are increased in those with a diagnosis of OSA. Previous literature has reported these scores in cohorts of people with schizophrenia generally (Royuela et al., 2002; Sharma et al., 2016), however this paper will be the first to determine whether comorbid OSA is responsible for these sleep symptoms and whether or not they are predictive of diagnosis of OSA. Similarly, this paper will be the first to prospectively validate diagnostic screening tools for OSA in people with schizophrenia, which has not been previously reported and will provide an evidence base as to whether these questionnaires are useful at the clinical level.

Chapter 6 (paper 5)

This chapter addresses the final aim of this thesis which is to investigate the acceptability of CPAP treatment for severe OSA and to determine the effect CPAP has on physical health, sleep architecture, psychiatric measures and cognitive outcomes. The paper constituting this chapter reports on subjects in the ASSET trial with a diagnosis of severe OSA based on apnoea hyponoea index >30. These subjects were commenced on CPAP treatment and underwent assessment of sleep architecture (using PSG), CPAP usage, physical health measures, psychiatric symptoms scales, sleep quality measures and cognitive measures at baseline and at six months of treatment.

To date this is the only study that reports on CPAP treatment of comorbid OSA in schizophrenia and is novel in many aspects. Firstly, it allows for the robust assessment of CPAP acceptability. As previously discussed, people with schizophrenia access physical healthcare at a substantially lower rate than the general population. One factor contributing to this may be treatment nihilism. Objectively demonstrating CPAP acceptability would go some way to refuting this perception in the minds of clinicians. Secondly, this is the only study which provides evidence as to whether treatment of OSA with CPAP modifies negative and cognitive symptoms in people with schizophrenia. This outcome is of particular importance, because

these symptoms are treatment resistant and a significant barrier to functional recovery. On the basis that as OSA is prevalent in schizophrenia, a positive finding would indicate that CPAP treatment is a feasible means of improving functional outcomes in a highly disadvantaged population. Thirdly, optimisation of physical health is a priority for people with schizophrenia, given that cardiovascular morbidity is the primary determinant of reduced life-expectancy in this population. This paper provides evidence as to whether treatment of OSA comorbid with schizophrenia is able to modify cardiovascular risk factors as a novel means of addressing physical health inequality.

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Chapter 2: Paper 1

Obstructive sleep apnea and schizophrenia: a systematic review to inform clinical practice

Citation: Myles H, Myles, N, Antic N.A, Adams R, Chandratilleke M, Liu D, Mercer J, Vakulin A, Vincent A, Wittert G and Galletly C. (2016). Obstructive sleep apnea and schizophrenia: A systematic review to inform clinical practice. *Schizophrenia Research*, 170(1), 222-5.

Abstract

Background: Risk factors for obstructive sleep apnea (OSA) are common in people with schizophrenia. Identification and treatment of OSA may improve physical health in this population; however there are no guidelines to inform screening and management.

Objectives: Systematic review to determine, in people with schizophrenia and related disorders: the prevalence of OSA; the prevalence of OSA compared to general population controls; the physical and psychiatric correlates of OSA, associations between antipsychotic medications and OSA; the impact of treatment of OSA on psychiatric and physical health; and the diagnostic validity of OSA screening tools.

Data sources: Medline, EMBASE, ISI Web of Science and PsycINFO electronic databases. Cohort, case–control and cross-sectional studies and RCTs reporting on prevalence of OSA in subjects with schizophrenia and related disorders were reviewed.

Results: The prevalence of OSA varied between 1.6% and 52%. The prevalence of OSA was similar between people with schizophrenia and population controls in two studies. Diagnosis of OSA was associated with larger neck circumference, BMI N 25, male sex and age N 50 years. There were no data on physical or psychiatric outcomes following treatment of OSA. The diagnostic utility of OSA screening tools had not been investigated.

Conclusion: OSA may be prevalent and potentially under-recognized in people with schizophrenia. Further research is required to determine utility of OSA screening tools, the relationships between antipsychotic medications and OSA and any benefits of treating OSA. We propose a strategy for the identification of OSA in people with schizophrenia and related disorders.

1. Introduction

Cardiovascular disease causes a 16–18 year reduction in life- expectancy in people with schizophrenia (Laursen, 2011). Obstructive sleep apnea (OSA) may contribute to this disease burden as it is associated with heightened risk of hypertension, diabetes, stroke and heart failure (Epstein et al., 2009). High rates of obesity (Galletly et al., 2012; Mitchell et al., 2013), tobacco smoking (Myles et al., 2012), alcohol consumption (Moore et al., 2012), and sedative medication use (Al Lawati et al., 2009; Galletly et al., 2012) may increase risk of OSA in people with schizophrenia. Whilst diagnosis may go unrecognized when sleep disturbance, daytime somnolence and cognitive impairment are mistaken for negative symptoms or medication side effects. Recent reviews on OSA in schizophrenia (Alam and Chengappa, 2011; Gupta and Simpson, 2015; Kalucy et al., 2013) and physical health guidelines do not provide recommendations on screening for OSA in schizophrenia.

2. Methods

A systematic review was undertaken of English language publications in peer-reviewed journals. We searched Medline, EMBASE, PsycINFO, and ISI Web of Science using: (psychosis or schizophrenia) and (obstructive sleep apnea or obstructive sleep apnoea or sleep disordered breathing). 148 papers were identified and examined; five original articles reporting applicable data were identified (see Table 1).

Papers were included if they reported: prevalence of OSA in a psychosis cohort alone or compared to a matched general population cohort; psychiatric, physical health or anthropometric measures and quantitative assessment of how these related to a current diagnosis of OSA; prospective assessment of OSA or daytime sleepiness screening tools and; physical health or psychiatric disease measures before and after treatment of OSA.

We included studies that specified the proportion of participants with a diagnosis of schizophrenia, schizoaffective disorder, or schizophreniform disorder in each cohort. Overnight multichannel polysomnography (PSG) is the gold standard for diagnosis of OSA (Epstein et al., 2009), however we included broader diagnostic definitions including modified PSG, and overnight oximetry.

3. Results

3.1. Prevalence of OSA

OSA prevalence varied between 13.5% and 57.1% across four cohort studies screening subjects using overnight multichannel PSG, modified PSG or overnight oximetry. These studies varied in diagnostic criteria and no study reported on a generalizable psychosis cohort. Winkelman (2001) was prone to selection bias as subject recruitment was based on suspicion of OSA. Anderson et al. (2012) excluded subjects with previous OSA diagnosis, potentially reducing prevalence estimates. Ancoli- Israel et al. (1999) studied an older age group (mean 59.6 years), whilst low rates reported by Takahashi et al. (1998) may result from the cohorts' low mean BMI (23.9).

3.2. Relative prevalence of OSA

Takahashi et al. (1998) reported a non-significant comparison of OSA in inpatients with schizophrenia (18.8%) matched to controls recruited from hospital staff (22%). Sharafkhaneh et al. (2005) compared prevalence of OSA in subjects with schizophrenia (1.2%) to subjects without schizophrenia (1.6%) through retrospective review of 4,060,504 veteran case records, reporting an unadjusted odds ratio of 1.49 (95% CI 1.05–1.92). This study potentially under-estimates the prevalence of OSA due to opportunistic methodology, non-standardized diagnostic criteria and lack of data on non-VHA health contact.

3.3. Physical and psychiatric correlates of OSA

Anderson et al. (2012) reported that age ($r = 0.47$, $p = 0.001$) and neck circumference ($r = 0.311$, $p = 0.028$) were positively correlated with apnea–hypopnea index (AHI). Multivariate analysis revealed male sex (OR = 21.9, 95%CI 1.3–370.3) and BMI >25 (OR 36.1, 95%CI 1.3–990.1) as significant predictors of OSA using AHI >5 as the dependent variable. Using multivariate analysis, Winkelman (2001) reported significant associations for male sex (OR = 5.76, 95%CI 2.08–15.27), age (OR = 1.03, 95%CI 1.00–1.06) and BMI (OR = 1.14, 95%CI 1.08–1.21) with RDI >10 as the dependent variable.

Takahashi et al. (1998) reported no significant correlation between dose of antipsychotic medication (mg equivalent dose of haloperidol) and oxygen desaturation index (ODI), but reported a positive correlation with hypnotic medication (number of pills per day) in the subgroup of women. Winkelman (2001) demonstrated no significant association between categorical antipsychotic use and an RDI >10 on multivariate analysis. However, the association was significant at an RDI threshold of >20 (OR = 5.02, 95% CI 1.44–17.56). Anderson et al. (2012) reported a negative correlation between quantitative measures of antipsychotic use (percentage of maximum dose) and AHI >5 ($r = -0.382$, $p = 0.014$) on univariate analysis, but no significant interaction between categorical benzodiazepine use and AHI on multivariate analysis.

No studies report on measures of quality of life, psychiatric symptoms, cognitive function, or social and occupational function.

3.4. Utility of OSA screening tools

Anderson et al. (2012), examined measures of daytime sleepiness and sleep disturbance with the Epworth Sleepiness Score (ESS) (Johns, 1991) and the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The mean ESS was 5.6 (SD = 5.04) and the mean PSQI was 6.5

(SD = 3.5), lower than general population controls (Johns, 1991). Sensitivity and specificity were not reported.

3.5. OSA treatment

No study reported acceptability of CPAP treatment; or measures of physical health, psychopathology or social functioning before and after treatment.

4. Discussion

OSA is common in people with psychotic illness with rates in screened populations between 13.5–57.1%. This is comparatively higher than general population estimates between 2%–4% (Young et al., 2008). Variations in age, degree of obesity, patient selection and diagnostic measures however, make no single study widely generalizable to psychiatric populations. Unfortunately, one large case–control study potentially underestimates both general and relative prevalence of OSA due to its opportunistic methodology given 80% of OSA remains undiagnosed despite access to healthcare (Kapur et al., 2002; Young et al., 1997) and that people with psychotic illness have reduced access to healthcare reducing diagnosis in this group further. Prevalence of OSA in stable community patients and the impact of shared risk factors including obesity, sedative medication use and alcohol abuse remain to be determined.

The significant association of age, BMI >25 and male sex in two studies (Anderson et al., 2012; Winkelman, 2001) and neck circumference in one (Anderson et al., 2012) are consistent with the American Academy of Sleep Medicine general population guidelines (Epstein et al., 2009) that identify BMI and neck circumference as primary predictors of OSA. Similarly, the STOP-BANG questionnaire validated in general populations (Chung et al., 2008) utilizes criteria of BMI >35, age >50 years, neck circumference >40 cm and male sex; along with observed apneas, hypertension, snoring, and symptoms of daytime sleepiness. This provides indirect

evidence that the STOP-BANG could identify at-risk patients, with the caveat that it has not been specifically validated and a lower BMI of >25 constitutes a risk factor in people with psychosis.

The low mean scores of the ESS and PSQI reported in one study (Anderson et al., 2012) is consistent with other literature (Rishi et al., 2010) indicating a minority of patients with schizophrenia and comorbid OSA report sleeping difficulties or snoring at diagnosis. High rates of unemployment (Waghorn et al., 2012) and low rates of de facto relationships (Morgan et al., 2011) may limit observation of daytime and nocturnal symptoms in people with schizophrenia. Furthermore, sleep symptoms may be mistaken for antipsychotic side effects or negative symptoms. These findings suggest OSA may be under-recognized in schizophrenia, with available evidence emphasizing physical risk factors over sleep symptoms as a means of identifying OSA.

Inconsistent associations between OSA and antipsychotic and hypnotic medications were reported in available studies and potentially arise from variation in medication use measures. Other literature reports higher prevalence (Shirani et al., 2011) and severity of OSA (Rishi et al., 2010) in people taking antipsychotic medications. Similarly, there is a recognized association between benzodiazepine use and OSA in the general population (Dolly and Block, 1982; Hanly and Powels, 1993). Whilst both drug classes are potentially implicated their specific etiological role in OSA is as yet unclear and requires further evaluation.

No study assessed patients before and after treatment of OSA to determine impact on physical health, psychopathology or other functional domains in people with psychosis. In the general population OSA is associated with depression, anxiety, reduced quality of life and decrements in daytime work performance (Lal et al., 2012; Patil et al., 2007); whilst treatment of OSA can improve quality of life (Rizzi et al., 2014). OSA could potentially compound the negative

symptoms of amotivation, apathy and social withdrawal in schizophrenia. The degree to which OSA contributes to these symptoms is unclear and should be a research priority.

We suggest that OSA screening be considered as part of the physical health assessment of people with schizophrenia. OSA is prevalent, potentially under-recognized and a risk factor for poor physical health, whilst treatment may potentially improve cardio-vascular risk and quality of life. OSA screening should be conducted with emphasis on neck circumference >40 cm, BMI >25, male sex, age >50, and witnessed apneas or loud snoring. The OSA50 (Chai-Coetzer et al., 2011) is an appropriate tool for this purpose validated in a primary care setting. An OSA50 score ≥ 5 should prompt referral for PSG as the preferred diagnostic test. We propose sleep symptoms as a subordinate criterion for considering PSG referral, given patients with schizophrenia are unlikely to report symptoms of daytime sleepiness, these symptoms may be confounded by medication side effects or psychiatric symptoms, and most lack partners to report snoring or nocturnal apneas.

Further research should be directed towards estimates of OSA prevalence in community samples with stable schizophrenia, validation of population-specific screening tools and investigation of OSA treatment outcomes.

Table 1: Studies reporting prevalence of OSA in populations with schizophrenia

Study	Population	Diagnostic measure	OSA criteria	Prevalence
Anderson et al. 2012	52 outpatients with major mental illness, of which 25 (48%) had a diagnosis of schizophrenia or schizoaffective disorder	Polysomnography	Severity based on AHI Mild — AHI 5–15 Moderate — AHI 15–30 Severe — AHI >30	52% prevalence 32% mild 14% moderate 6% severe
Sharafkhaneh et al. 2005	4,060,504 outpatients identified through retrospective review of case notes in the Veteran's Health Database, patients with psychosis compared to general population	Previous diagnosis of OSA documented in database, diagnostic measures not specified	ICD-10 codes, AHI cut-off not defined	1.6% prevalence
Winkleman 2001	46 inpatients with schizophrenia or schizoaffective disorder considered at high risk of OSA referred to sleep disorders clinic	Polysomnography	RDI >10	57.1% in males 46.2% in females
Ancoli-Israel et al. 1999	52 geriatric outpatients (mean age 59.6 years) with schizophrenia or schizoaffective disorder	Modified polysomnography	RDI >10	48% prevalence
Takehashi et al. 1998	101 inpatients with schizophrenia	Overnight oximetry	DI	21.9% in males 13.5% in females

Abbreviations: AHI apnea–hypopnea index as defined by AASM (Kushida et al., 2005); RDI respiratory desaturation index as defined by the ASDA criteria (ASDA, 1992; Timms et al., 1988) and DI desaturation index as defined by >4% oxygen desaturations at least 5 times per hour.

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Chapter 3: Paper 2

Risk factors for obstructive sleep apnea are prevalent in people with psychosis and correlate with impaired social functioning and poor physical health

Citation: Liu D, Myles H, Foley D.L, Watts G.F, Morgan V.A, Castle D, Waterreus A, Mackinnon A, Galletly C. (2016). Risk factors for obstructive sleep apnoea are prevalent in people with psychosis and correlate with impaired social functioning and poor physical health. *Frontiers in Psychiatry*, 7: 139

Abstract

Background: Obstructive sleep apnea (OSA) in the general community is associated with obesity, smoking, alcohol, and sedative medication use and contributes to depressed mood, daytime sedation, and sudden cardiovascular deaths. Poor cardiovascular health, impaired social functioning, and negative and cognitive symptoms are also among the common clinical features of psychotic disorders. People with psychosis have higher rates of sleep disturbance; however, OSA has not been extensively investigated in this population.

Aims: This study aimed to determine the prevalence of OSA and general sleep disruption symptoms in a representative Australian sample of people with psychosis. We investigated the prevalence of potential risk factors for OSA, including obesity, psychotropic medications, and substance abuse in this population. Finally, we evaluated associations between symptoms of OSA, symptoms of general sleep disruption, and various clinical features in people with psychosis.

Methods: Participants took part in the Second National Australian Survey of Psychosis, a population-based survey of Australians with a psychotic disorder aged 18–64 years. Symptoms associated with OSA (snoring and breathing pauses during sleep) in the past year were assessed using questions from the University of Maryland Medical Centre Questionnaire and symptoms associated with general sleep disruption in the past week using the Assessment of Quality of Life Questionnaire. Data collected included psychiatric diagnosis and symptoms, education, employment, medications, smoking status, physical activity, drug and alcohol use, and cognitive function. Physical health measures included body mass index, waist circumference, blood pressure, fasting blood glucose, and lipids.

Results: Snoring was reported by 41.9%; 7% stating they frequently stopped breathing (pauses) during sleep. Univariate logistic regressions show OSA symptoms (pauses and snoring) were associated with older age, female gender, lower levels of social participation or employment, cardiovascular risk factors, sedentary lifestyle, and poorer quality of life, while symptoms of general sleep disruption were more likely in people with depressive symptoms.

Conclusion: Australians with psychosis have high levels of sleep disturbance, including OSA. OSA symptoms were associated with cardiovascular disease risk factors, reduced social participation and employment, and poorer quality of life. Whether correction of OSA can improve these factors in people with psychosis remains to be determined.

Keywords: risk factors, obstructive sleep apnea, psychosis, social functioning, physical health

Introduction

Obstructive sleep apnea (OSA) affects 2–4% of the general adult population (1). OSA is characterized by repeated pharyngeal obstructions during sleep, resulting in airflow cessation (apnea) or reduction (hypopnea), frequent disruption of sleep, and hypoxic episodes. While obesity is the most significant risk factor, other risk factors, including smoking and use of sedative medications, have been found to play a significant role in OSA (2–4). OSA is associated with poor cardiometabolic outcome (5), increased risk of depression and anxiety, and impaired neurocognitive function (6).

People living with psychosis experience poor physical health and shortened life expectancy, with high prevalence of cardiometabolic risk factors, including obesity, hypertension, and diabetes (7, 8); impaired social and occupational function (9–11); and cognitive impairment (11, 12). Although OSA and psychotic disorders have many risk factors and poor clinical outcomes in common, few studies have focused on OSA in people with psychosis (13, 14). Several small studies have found a high prevalence of OSA in people with schizophrenia (15–18). High rates of obesity and smoking and frequent use of sedative medications observed in people with psychotic illnesses may con- tribute to the development of OSA. Alternatively, the pathological sequelae of OSA, including repeated episodes of hypoxia, sleep fragmentation, and oxidative stress, may precipitate or perpetuate psychopathological symptoms, metabolic disturbance, and impairment of neurocognitive and social functions in people with psychotic illness.

Aims

Our primary aim was to examine the prevalence of OSA symptoms in a large representative sample of people with psychosis. Secondary aims included exploring the associations between

OSA symptoms and variety of clinical outcomes, including physical health, risk factors for cardiovascular diseases, quality of life, social functioning, cognitive functioning, vocational engagement, and psychiatric symptoms. Finally, we examined the association between OSA symptoms in this population and known risk factors for OSA (e.g., obesity, alcohol and tobacco consumption, and sedative medication).

Our hypothesis was that clinical symptoms of OSA would be highly prevalent in people with psychosis and that clinical symptoms of OSA would correlate with increased cardiometabolic risk, poor cognitive and social functioning, and poor quality of life. Clinical symptoms of OSA would be associated with obesity, substance abuse, and the use of antipsychotic medications in a representative sample of people with psychotic disorders.

Material and methods

Sample

The 2010 Survey of High Impact Psychosis (SHIP) was the second Australian National survey of psychotic disorders. The survey catchment covered a population of 1.5 million people aged 18–64 years, approximately 10% of the Australian population in this age group. A two-phase design was used. In Phase 1, screening for psychosis took place in public mental health services and in non-governmental organizations supporting people with a mental illness. In Phase 2, people who screened positive for psychosis in Phase 1 were randomly selected and stratified by age group (18–34 years and 35–64 years) for interview and assessment. This process identified 7955 people who were screened positive for psychosis and eligible for interview. Potential participants were randomly selected and approached for participation in the study; 1825 participants who screened positive for psychosis were included and interviewed in Phase 2 of the study. The study was approved by the human research ethics committees at each of the

seven study sites, and all participants provided written informed consent. Full details of the survey methodology are described elsewhere (10, 12).

Demographics and social participation

Gender, age, marital status, formal study educational level, and current employment were recorded. Item to assess the participant's involvement in meaningful activity was extracted from the main interview schedule to assess: 0 = employed in any job in last 12 months; 1 = home duties/caring for own children; 2 = caring for relatives; 3 = retired; 4 = volunteer/unpaid work; 5 = student; and 6 = no formal activity. Participants were divided into two groups: no formal activity and others. Diagnostic assessment was based on a semi-structured clinical research interview, the Diagnostic Interview for Psychosis (DIP) (19). Diagnoses were made according to the ICD-10 classification system (20).

Sleep apnea risk assessment

Questions assessing sleep apnea were taken from the University of Maryland Medical Centre Questionnaire for Sleep Apnea. These were self-rated assessments of the frequency and severity of snoring and pauses in breathing during sleep (a more severe symptom of OSA) over the previous 12 months. To assess the severity of the snoring, the following question was asked: "In the last 12 months, how frequently do you experience or have you been told about snoring loud enough to disturb the sleep of others?" [0 = never; 1 = rarely (less than once a week); 2 = occasionally (1–3 times a week); 3 = frequently (>3 times a week)]. To assess the severity of pauses, the following question was asked: "In the last 12 months, how often have you been told that you have "pauses" in breathing or stop breathing during sleep?" [0 = never; 1 = rarely (less than once a week); 2 = occasionally (1–3 times a week); 3 = frequently (>3 times a week)].

The assessment of the severity of disrupted sleep in the past week was made using Question 13 from the Assessment of Quality of Life (AQoL) Questionnaire-4D (21). The severity of

disrupted sleep was rated as 1 = “I am able to sleep without difficulty most of the time”; 2 = “My sleep is interrupted some of the time, but I am usually able to go back to sleep without difficulty”; 3 = “My sleep is interrupted most nights, but I am usually able to go back to sleep without difficulty”; 4 = “I sleep in short bursts only. I am awake most of the night.” Dichotomous categories for sleep measurement were created as follows: snoring (yes = reported snoring, no = no snoring); pauses (yes = reported pauses, no = no pauses); disrupted sleep (yes = at least some of the time, no = rarely).

Physical activities and physical health

Physical activity in the past 7 days was assessed using the International Physical Activity Questionnaire (IPAQ) short form (22). Electronic scales measuring up to 200 kg were used to assess weight (kilograms); height (metres) was taken against a measure on a wall. Body Mass Index (BMI) was calculated as weight/height^2. Participants were categorized according to WHO criteria (23) as underweight (BMI < 18.5), normal (BMI 18.5–24.99), overweight (BMI 25–29.99) or obese (BMI ≥ 30). Participants’ absolute 5-year cardiovascular disease risk was determined by Framingham risk equation (24). Participants’ history of diagnosed cardiovascular disease was ascertained by asking participants if they had ever been told by a doctor that they had any of the following: heart attack, angina, stroke/ transient ischemic attack (TIA), or other heart disease, e.g., arrhythmias. They were asked to bring all medications to the interview, and those relevant to cardiometabolic conditions were identified. Details of all medication used in the 4 weeks prior to interview was recorded; this was based on self-report or review of medication charts (25).

Participants were also asked to provide a fasting blood sample for analysis of high-density lipoprotein cholesterol, triglyceride, and plasma glucose levels. Metabolic syndrome was defined using the harmonized criteria developed by the International Diabetes Federation Task

Force on Epidemiology and Prevention and related expert organizations (26). These criteria for metabolic syndrome require three of the following five risk factors to make the diagnosis: abdominal obesity (at-risk waist circumference ≥94 cm for men and ≥80 cm for women); at-risk diastolic and/ or systolic blood pressure (systolic blood pressure ≥130 mmHg and/or a diastolic pressure ≥85 mmHg); at-risk levels of fasting blood glucose (≥5.6 mmol/L), triglycerides (≥1.7 mmol/L), or HDL-C (<1.0 mmol/L for men and <1.3 mmol/L for women). Abdominal obesity was defined as a waist circumference ≥94 cm for men and ≥80 cm for women. Hypertension was diagnosed if the person had a systolic blood pressure ≥130 mmHg and/or a diastolic pressure ≥85 mmHg. The thresholds for blood glucose, triglycerides, and lipids were: glucose ≥5.6 mmol/L; triglycerides ≥1.7 mmol/; HDL-C <1.0 mmol/L for men and <1.3 mmol/L for women. People receiving medications for hypertension, hyperlipidemia, or hyperglycemia were considered to meet the relevant criterion.

The IPAQ short form (22) was used to assess the amount of time participants spent in both vigorous and moderate exercise, and the amount of time they spent sitting on a typical weekday, during the last 7 days. The total time spent in various activities over the previous 7 days was classified according to Australian Bureau of Statistics criteria as applied in the National Survey of Mental Health and Wellbeing (27) into four levels of activity: very low, low, moderate, and high.

Psychotropic medications

Information about antipsychotics, mood stabilizers, antidepressants, and other sedative medications taken in the 4 weeks prior to the interview was collected. Outpatients were asked to bring their medications to the interview, and for inpatients, the drug charts were reviewed. Antipsychotic medications were sub-classified as typical antipsychotics and atypical antipsychotics.

Substance use

Respondents were asked how often they had used alcohol, cannabis, amphetamines, and other drugs in the previous year, and were classified as: 1 = not used; 2 = monthly or less than monthly; 3 = weekly/daily (19). Alcohol dependence and risk categories were measured using the Alcohol Use Disorders Identification Test (AUDIT) (28). Lifetime diagnoses of alcohol, cannabis, and other substance abuse/dependence were assessed using the DIP (19). Caffeine consumption was quantified based on amount per day on average in the previous 4 weeks.

Diagnosis, psychopathology, and cognitive function assessment

Diagnostic assessment was based on a semi-structured clinical research interview, the DIP (19). Diagnoses were made according to the ICD-10 classification system (20). Psychiatric symptoms were systematically interrogated using the DIP. Symptoms of hallucinations, delusions, or subjective thought disorder in the past 1 month and symptoms of anxiety, including worry, panic, anxiety, and obsession over the past 12 months were recorded. A brief cognitive assessment tool was employed. This comprised the: (i) National Adult Reading Test (NART) Revised (29) and (ii) Digit-Symbol Coding Test (DSCT) from the RBANS battery (30). Participants' subjective experience of forgetfulness over the past 12 months prior to the interview was assessed and the results were classified as: 1 = able to remember most things; 2 = somewhat forgetful; 3 = very forgetful.

Quality of life assessment

The quality of life in the past week was assessed using The AQoL-4D 12-item instrument (21). The AQoL-4D independently models all the sub-dimensions of health (independent living, social relationships, physical senses, psychological well-being, and illness) and combines sub-models to obtain a multi-attribute utility score. Scores from the first four dimensions form the multi-attribute utility score. Algorithms for AQoL scoring were obtained from

http://www.aqol.com.au/index.php/scoring-algorithms?id=82. Where negatively skewed (AQoL utility scores), data were trans- formed using the appropriate log transformations.

Statistical analyses

Descriptive statistics were reported as means and SDs. Dichotomous categories were created: age (18–34 vs. 35–64); obesity – BMI ≥ 30 (no vs. yes); absolute 5-year cardiovascular disease risk by Framingham risk equation (low vs. high = medium risk or high risk); any formal activity, including paid or unpaid work, or study (no vs. yes); subjective memory forgetfulness (no = able to remember most things vs. yes = somewhat forgetful or very forgetful); Fagerstrom nicotine dependence categories (low = low or very low vs. high = moderate, high, or very high); AUDIT risk (low vs. high = hazardous, harmful, or dependent). Univariate logistic regression was performed to explore associations between and among potential risk factors (independent variables) and the dependent variables (sleep apnea – snore, sleep apnea – pause, and disrupted sleep). Independent samples *t*-test was used to compare the mean scores for the AQoL. A binary logistic regression analysis was conducted to explore potential predictors of OSA symptoms. Variables were divided into four categories (cardiovascular risks; physical activity; social function; and substance abuse) and were entered into the model to estimate multivariate associations, with and without adjusting for age, gender, and BMI. Variables were included in the regression analyses, if they demonstrated significant association with OSA symptoms in the univariate analyses. All statistical analyses were performed with SPSS 22.0. The α value taken to indicate statistical significance was adjusted using Bonferroni correction for multiple comparisons of variables of the same category.

Results

Sociodemographic data

The study sample comprised 1825 participants. Their mean age was 38.4 ± 11.2 years, and 59.6% were male. Most participants were single (61.2%); only 17% were married or in *de facto* relationships. More than half (53.2%) of the participants were not currently engaged in any meaningful activity such as paid or unpaid employment, volunteer job, career, home duty, or study. Most did not engage with any vigorous or moderate physical activity (76.9 and 69.2%, respectively); around half (48.5%) had engaged in any form of physical activity for less than 2 h per week. Nearly all participants (96.7%) had very low to low levels of exercise, according to ABS classification (31). The majority of participants were overweight, with 46.4% being obese (BMI ≥ 30), and the mean BMI was in the obese range (30.5 ± 7.5 SD) (Table 1).

Prevalence of symptoms of sleep disturbance

Nearly half of participants reported snoring during sleep (41.9%), while 17.4% reported that they stopped breathing during sleep and 7% reported frequent (>3 times per week) episodes of stopping breathing during sleep. Over half of participants reported disrupted sleep at least some of the night (Table 2).

The association between symptoms of sleep disturbance and sociodemographic characteristics

Women reported snoring more frequently than men ($p < 0.001$). Individuals aged 35–64 years had significantly higher odds of snoring ($p < 0.001$), pauses (stopped breathing during sleep) ($p < 0.05$), and disrupted sleep ($p < 0.05$), compared with those aged 18–34 years. People reporting pauses in breathing during sleep were less likely to have any formal work or study activity ($p < 0.05$), be in paid employment in the previous year ($p < 0.01$), or be in paid employment in the previous week ($p < 0.001$) (Table 3).

Associations between cardiovascular risks and symptoms of sleep disturbance

People who reported snoring or pause had 1.5–3 times odds than those who did not to meet at-risk criteria for most key cardiometabolic risk factors, including elevated plasma triglycerides and fasting glucose, low HDL cholesterol, and hypertension. Participants reported snoring had odds ratio (OR) of 1.84 [confidence interval (CI) 1.46, 2.32], while those reported pause had OR of 2.26 (CI 1.66, 3.08) to meet criteria for metabolic syndrome and they had a higher 5-year risk of cardiovascular disease [snore OR 1.56 (CI 1.23, 1.98); pause OD 1.65 (CI 1.23, 2.22), respectively]. Snorers were more likely to have reported a history of cardiovascular disease, including angina, heart attack, other heart disease, e.g., arrhythmias, hypertension, and stoke/TIA [OR 2.03 (CI 1.64, 2.52)], as did those who reported pauses in breathing during sleep [OR 2.19 (CI 1.69, 2.84)]. Participants with disrupted sleep were more likely to meet the at-risk criteria for triglyceride levels, but not for other cardiovascular risk factors. Those with disrupted sleep were more likely to have a history of cardiovascular disease [OR 1.47 (CI 1.19, 1.82)] (Table 4).

Associations between level of physical activities, quality of life, psychopathology, and symptoms of sleep disturbance

Participants with pauses in breathing during sleep, but not snoring or interrupted, had higher odds of not to engage in any vigorous activity [OR 1.6 (CI 1.14, 2.26)] or total physical activity [OR 1.53 (CI 1.09, 2.16)]. Participants reporting pauses in breathing during sleep had lower scores on measures of total quality of life ($p < 0.001$), independent living ($p < 0.05$), and psychological wellbeing ($p < 0.001$) when compared with those without pauses (Table 5).

Participants with disrupted sleep but not snoring or pauses in breathing during sleep had higher odds of experiencing hallucinations, delusions or subjective thought disorder ($p < 0.001$), depressive symptoms ($p < 0.001$), and manic symptoms ($p < 0.001$) in the past month. Anxiety

symptoms were more likely to occur in those whose sleep was characterized by snoring ($p < 0.01$), pauses ($p < 0.001$), and disruption ($p < 0.001$) (Table 6).

Associations between psychotropic medications and symptoms of sleep disturbance

Participants taking atypical antipsychotic medications (including clozapine) had lower odds of reporting disrupted sleep than those not taking atypical antipsychotics ($p < 0.001$, respectively). Atypical antipsychotics were not associated with snoring or pauses in breathing during sleep. Mood stabilizers were associated with increased odds of snoring ($p < 0.001$) and pauses in breathing during sleep ($p < 0.05$), but there was no association with disrupted sleep. Taking an antidepressant was associated with an increased likelihood of snoring ($p < 0.001$) and a reduced likelihood of disrupted sleep ($p < 0.001$) but had no significant association with pauses in breathing during sleep (Table 7).

Associations between substance use and symptoms of sleep disturbance

People who were at risk of hazardous/harmful/dependent drinking or who were current smokers were more likely to have pauses in breathing during sleep and disrupted sleep, while those who used cannabis or tranquilizers monthly or more frequently were more likely to have disrupted sleep. Monthly or more frequent amphetamine use was associated with lower incidence of pauses. Caffeine intake of <200 mg/day was associated with a lower incidence of snoring and pauses in breathing during sleep (Table 8).

Multiple logistic regression models adjusting for multiple confounders

After adjusting for gender, age, and BMI in multiple logistic regression models, the odds of pauses in breathing during sleep in participants with a positive history of cardiovascular disease remained 1.96 times (95% CI, 1.19, 3.48) higher than those with- out the history of cardiovascular disease. Participants who were at high risk of hazardous/harmful/dependent

drinking had odds ratio of snoring 1.59 times (CI 1.07, 2.38) and pause in breathing during sleep 1.882 times (CI 1.15, 3.09) in low risk participants (Table 9).

Discussion

In this representative sample of people with psychotic illness, symptoms of OSA were highly prevalent, with rates of pauses in breathing during sleep and snoring 17.4 and 41.9%, respectively. However, these results are likely to be underestimates given that 83% of patients were neither married or in a *de facto* relationship and, thus, likely had no regular bed partner to notice these symptoms during sleep. Our results confirm and add precision to findings from previous studies with small samples of selected patients with schizophrenia (15–18). Further, the prevalence of OSA in our study sample was much higher than the prevalence of OSA in general population, which is estimated to be 3–5% (1, 32–36).

Our study has demonstrated that symptoms of OSA (snoring and pauses in breathing during sleep) were associated with higher likelihood of meeting at-risk criteria for key cardiometabolic risk factors. Symptoms of OSA were associated with a higher rate of a reported history of cardiovascular diseases. The association between pause in breathing during sleep and reported history of cardiovascular disease remained significant after adjusting for BMI, age, and gender. Previous studies in the general population have found that OSA is a significant independent risk factor for CVD-related mortality and a composite endpoint of all-cause mortality and incident stroke (37). Additionally, obesity, male gender, older age, and increased neck circumference are the most significant risk factors for OSA. Thus, it is likely that OSA and obesity may impact on each other to set up a vicious cycle, thereby creating severe cardiometabolic disease.

We found that OSA symptoms, such as snoring and pauses in breathing during sleep, did not impact on the severity of psychopathology, including depressive, psychotic, and manic symptoms, except anxiety symptoms. Disrupted sleep was associated with more severe symptoms in all domains measured. We are not aware of any previous studies examining the associations between OSA and psychopathology in people with psychosis; however, a number of case studies have reported a reduction in positive and negative symptoms of psychosis when Continuous Positive Airway Pressure (CPAP) treatment was initiated (38–41).

Our results revealed an unexpected finding. People prescribed with more obesogenic and sedative atypical antipsychotics were less likely to report subjective sleep disturbances, than those who were prescribed other psychotropic drugs. This contradicts an earlier retrospective study, which found that atypical antipsychotic medications were independently associated with OSA, and that individuals taking atypical antipsychotics had more severe sleep apnea when adjusted for BMI, sex, and use of benzodiazepines and sleeping aids (42). It has been suggested that the sedative actions of atypical antipsychotics may reduce activity of the hypoglossal and recurrent laryngeal nerve on upper airway musculature; however, this is not reflected in our data. The finding that the use of atypical antipsychotics is associated with reduced odds of disrupted sleep could be explained by the hypnotic effects of these medications, which could possibly cause a reduction in reported sleep symptoms. Another explanation for the difference between our results and Rishi et al. (42) is that Rishi compared people taking atypical antipsychotics with participants who were not taking any hypnotic medication, whereas we have compared people with psychotic illnesses on a variety of typical antipsychotics, atypical antipsychotics, mood stabilizers, and benzodiazepines. Interestingly, our study showed that the use of mood stabilizers and antidepressants was associated with symptoms of OSA. As mood stabilizers and antidepressants are commonly used as adjunctive medications in psychosis, this finding suggests that the prescribing of these drugs may increase the risk of OSA. Another

possible explanation for this new finding is, people with OSA may be more depressed and fatigued and, therefore, more likely to be prescribed antidepressants and mood stabilizers.

Pauses in breathing during sleep, indicating the more severe form of OSA, were associated with lower rates of employment or study. Evaluation of health-related quality of life showed that our participants reporting more severe form of symptoms of OSA had significant impairments in the domains of independent living and psychological well-being. It is possible that current sleep symptoms may negatively impact on social participation; alternatively, people who are disengaged from social activity may also sleep poorly, perhaps as a result of depression or poor physical health. However, if sleep disorders do cause a reduction in social function, treatment of these disorders could be associated with improved function and productivity. This hypothesis could be tested in clinical trials.

In this study, we found that symptoms of sleep apnea and symptoms of disrupted sleep impact on different clinical domains in people with psychosis. Symptoms of sleep apnea are more likely to have negative relationship with people's cardiometabolic risk, social participation, and physical activity, while disrupted sleep has stronger association with active psychiatric symptoms. This suggests that the mechanism of the effect of sleep apnea on patients' clinical outcomes is different from sleep deprivation alone.

In conclusion, this study provides robust evidence that sleep disorders are prevalent in people with psychotic illness and may contribute a further risk factor for cardiovascular disease. The disease-specific determinants of OSA in people with psychosis should be elucidated in future studies. Further investigation and treatment of OSA in people with psychosis may be beneficial in reducing the burden of cardiovascular disease, productivity, and quality of life.

Limitations

This study had several limitations: The inherent biases of observational data without clear objectives apply to this study. The measures of symptoms of sleep apnea are indirect and self-reported. This study did not specifically examine the polypharmacy interaction or the medication compliance. Due to the nature of cross-sectional study, we can only identify associations in the data.

Ethics statement

This study was approved by the appropriate institutional human research ethics committees at each of the study sites and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants provided written, informed consent prior to participation.

Table 1: Social demographics

	N	%	Mean ± SD
Gender			
Men	1039	59.3	
Women	714	40.7	
Age			38.4 ± 11.2
18-34	773	42.4	
35-64	1052	57.6	
Marital status			
Single, never married	1117	61.2	
Married/de facto	312	17.0	
Separated	376	20.6	
Widowed	20	1.1	
Education level			
Complete year 9	410	22.5	
Complete year 10	535	29.3	
Complete year 11	283	15.5	
Complete year 12	574	31.5	
Physical activity			
Vigorous (none)	1448	79.6	
Moderate (none)	1255	69.2	
Walking (≤ 2hr/wk)	942	52.3	
Total activity (≤2 hr/wk)	881	48.5	
Sitting (hrs/week)			45.7 ± 23.2
Level of exercise (ABS Classification)			
Very low	611	33.6	
Low	1148	63.1	
Moderate	54	3	
High	6	0.3	
Meaningful activity (paid or unpaid work, or study)			
Yes	854	46.8	
No	971	53.2	
Difficulty reading, writing or both			
Yes	335	18.4	
No	1490	81.6	

	N	%	Mean ± SD
BMI - criteria from Wold Health Organization			30.5 ± 7.5
Underweight	26	1.5	
Normal	409	23.1	
Overweight	516	29.1	
Obese	823	46.4	
Any history of cardiovascular disease (including hypertension and stroke)	505	28.5	
Diagnosis			
Schizophrenia	857	47.0	
Schizoaffective disorder	293	16.1	
Bipolar disorder with psychotic features	319	17.5	
Depression with psychosis	81	4.4	
Delusional disorder	92	5.0	
Major depression without psychosis	158	8.7	
Screen positive but did not meet full criteria for ICD-10 psychosis	25	1.4	

Table 2: Sleep data of the study population (present state)

	N	%
Sleep apnoea snoring		
Never	1018	58.1
Rarely	185	10.6
Occasionally	213	12.2
Frequently	337	19.2
Sleep apnoea (pause)		
Never	1418	82.6
Rarely	100	5.8
Occasionally	78	4.5
Frequently	121	7.0
Disrupted sleep		
Rarely	837	46.3
Some of the night	415	23.0
Most of the night	318	17.6
Short bursts sleep	236	13.1

Table 3: Univariate associations between participant characteristics and symptoms of sleep disturbance

	Snore				Pause				Disruptive sleep			
	N	**%**	**X^2 (p)**	**OR (95%CI)**	**N**	**%**	**X^2 (p)**	**OR (95%CI)**	**N**	**%**	**X^2 (p)**	**OR (95%CI)**
Gender												
Men	399	38.4	13 ***	1.43 (1.18, 1.73)	117	17.4	0.01	1.01 (0.78, 1.30)	557	51.8	3.6	1.20 (0.99, 1.45)
Women	336	47.1			122	17.5			412	56.4		
Age												
18-34	259	34.1	33.5 ***	1.77 (1.46, 2.16)	110	14.9	5.8 *	1.37 (1.06, 1.77)	390	50.7	4.7 *	1.23 (1.02, 1.48)
35-64	476	47.9			189	19.3			579	55.8		
Lives alone												
Yes	208	39.4	2.3	0.85 (0.69, 1.05)	82	15.9	1.2	0.86 (0.65, 1.13)	314	56	1.5	1.13 (0.93, 1.39)
No	514	43.3			210	18.1			637	52.8		
Formal activity (paid or unpaid work, or study)												
Yes	345	41.5	0.14	0.97 (0.8, 1.17)	122	15	6.5 *	0.72 (0.56, 0.93)	450	52.9	0.39	0.94 (0.78, 1.15)
No	390	42.3			177	19.6			519	54.3		
Paid employment - past year												
Yes	232	39.9	1.4	0.88 (0.72, 108)	75	13.2	10.7 **	0.62 (0.47, 0.83)	308	51.9	1.2	0.9 (0.74, 1.09)
No	503	42.9			224	19.5			661	54.5		
Paid employment - past week												
Yes	156	40.9	0.2	0.95 (0.75, 1.2)	43	11.4	12.1 ***	0.55 (0.39, 0.77)	194	49.6	3.3	0.81 (0.65, 1.12)
No	579	42.2			256	19.1			775	54.8		

OR – odds ratio; CI; confidence interval; *, p<0.05; **, p<0.01; ***, p<0.001

Table 4: Univariate associations between participant cardiovascular risk factors and symptoms of sleep disturbance

	Snore				Pause				Disruptive sleep			
	N	**%**	**X^2 (p)**	**OR (95% CI)**	**N**	**%**	**X^2 (p)**	**OR (95%CI)**	**N**	**%**	**X^2 (p)**	**OR (95%CI)**
Triglycerides level - criteria from IDF criteria												
At risk	287	48.2	12.4	1.5	141	24.2	33.4	2.44	350	57.3	6.5	1.33
Not at risk	247	38.2	***	(1.2, 1.88)	73	11.6	***	(1.79, 3.33)	333	50.2		(1.07, 1.66)
Fasting Plasma Glucose level -criteria from IDF criteria												
At risk	177	49.6	8.9	1.45	76	22	6	1.47	205	56	1.2	1.15
Not at risk	357	40.3	**	(1.14, 1.86)	139	16		(1.08, 2.02)	478	52.6		(0.9, 1.47)
Blood Pressure Systolic and diastolic - IDF criteria												
At risk	406	48.8	30.9	1.73	168	20.7	11	1.54	465	54.5	0.6	1.08
Not at risk	310	35.5	***	(1.43, 2.1)	125	14.6	***	(1.19, 1.98)	474	52.7		(0.89, 1.3)
BMI: overweight - IDF criteria												
Yes	599	46.5	41.2	2.16	263	20.8	37.5	3.17	701	52.8	0.8	0.91
No	122	28.7	***	(1.7, 2.7)	32	7.7	***	(2.16, 4.66)	240	55.3		(0.73, 1.13)
HDL level - IDF criteria												
At risk	286	46.4	5.8	1.32	130	21.6	13.1	1.74	343	54.5	0.4	1.08
Not at risk	244	39.5		(1.05, 1.66)	82	13.6	***	(1.29, 2.36)	336	52.7		(0.86, 1.34)
Metabolic syndrome - IDF criteria												
At risk	308	50.6	27.4	1.84	140	23.6	27.2	2.26	347	55.6	1.7	1.16
Not at risk	218	35.7	***	(1.46, 2.32)	72	12	***	(1.66, 3.08)	327	52		(0.93, 1.45)

	Snore				Pause				Disruptive sleep			
	N	**%**	**X^2 (p)**	**OR (95% CI)**	**N**	**%**	**X^2 (p)**	**OR (95%CI)**	**N**	**%**	**X^2 (p)**	**OR (95%CI)**
Absolute cardiovascular disease 5 year risk - Framingham risk equation												
High	205	52	13.4 ***	1.56 (1.23, 1.98)	92	24	11 ***	1.65 (1.23, 2.22)	245	60.3	9.5 *	1.45 (1.15, 1.84)
Low	361	41			138	16			461	51.2		
Any history of cardiovascular disease (including hypertension and stroke)												
Yes	263	54.6	43.2 ***	2.03 (1.64, 2.52)	124	26.3	35.5 ***	2.19 (1.69, 2.84)	300	60.4	12.9 ***	1.47 (1.19, 1.82)
No	459	37.1			170	14.0			644	50.9		

OR – odds ratio; CI - confidence interval; IDF - International Diabetes Federation; BMI – body mass index; HDL – high density lipoprotein; *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$

Table 5: Univariate associations between participant physical activities, quality of life and symptoms of sleep disturbance

	Snore				Pause				Disruptive sleep			
	N	**%**	**X^2 (p)**	**OR (95% CI)**	**N**	**%**	**X^2 (p)**	**OR (95% CI)**	**N**	**%**	**X^2 (p)**	**OR (95% CI)**
Vigorous activity (hr/week)												
0	598	43.2	3.8	1.27 (1.0, 1.6)	254	18.7	7.5 **	1.6 (1.14, 2.26)	770	53.7	0.0	1.0 (0.8, 1.27)
>0	137	37.5			45	12.6			198	53.5		
Moderate activity (hr/week)												
0	493	41.2	1.0	0.9 (0.74, 1.11)	207	17.6	0.9	1.03 (0.79, 1.36)	664	53.3	0.2	0.96 (0.78, 1.17)
>0	239	43.7			91	17.1			301	54.4		
Walk (hr/week)												
≤ 2	389	43.4	2.0	1.15 (0.95, 1.39)	169	19.3	4.2	1.3 (1.0, 1.68)	510	54.6	0.8	1.1 (0.9, 1.31)
>2	336	40.1			128	15.5			449	52.5		
Total activity (hr/week)												
0	105	47.7	3.4	1.3 (0.98, 1.73)	50	23.4	6.0 *	1.53 (1.09, 2.16)	122	54.2	0.0	1.03 (0.77, 1.36)
>0	630	41.2			249	16.6			846	53.6		

		Snore				Pause				Disruptive sleep			
		N	**%**	**X^2 (p)**	**OR (95% CI)**	**N**	**%**	**X^2 (p)**	**OR (95% CI)**	**N**	**%**	**X^2 (p)**	**OR (95% CI)**
			Mean	**SD**			**Mean**	**SD**					
AQol (log)	No	985	-0.39	0.38	NS	1377	-0.37	0.35	P <0.001				
	Yes	713	-0.40	0.36	NS	285	-0.47	0.41					
Indep living (log)	No	1008	-0.07	0.14	NS	1407	-0.07	0.14	P<0.05				
	Yes	728	-0.08	0.14		293	-0.09	0.15					
Social rel (log)	No	991	-0.26	0.32	NS	1389	-0.25	0.31	NS				
	Yes	718	-0.24	0.29		287	-0.26	0.30					
Physic sense (log)	No	1012	-0.03	0.06	NS	1412	-0.03	0.05	NS				
	Yes	732	-0.03	0.05		296	-0.03	0.06					
Psy wellbeing (log)	No	1009	-0.09	0.15	NS	1409	-0.09	0.14	P = 0.000				
	Yes	730	-0.10	0.14		294	-0.13	0.18					

OR – odds ratio; CI - confidence interval; AQol (log): algorithms for the Assessment of Quality of Life-4D multiattribute utility score; Indep living (log): algorithms for independent living; Social rel (log): algorithms for social relationships; Phsic sense (log); algorithms for physical senses; Psy wellbeing (log); algorithms for psychological well-being ; *, p<0.05; **, p<0.01; ***, p<0.001

Table 6: Univariate associations between subjects' psychopathology at present state and symptoms of sleep disturbance

	Snore				Pause				Disruptive sleep			
	N	**%**	**X^2 (p)**	**OR (95% CI)**	**N**	**%**	**X^2 (p)**	**OR (95% CI)**	**N**	**%**	**X^2 (p)**	**OR (95% CI)**
Hallucinations, delusions or subjective thought disorder in the past one month												
Yes	404	41.0	0.1	1.02 (0.85, 1.24)	182	19.1	4.4	1.28 (0.99, 1.64)	576	57.4%	12.9 ***	1.41 (1.17, 1.7)
No	331	42.4			117	15.3			393	48.9%		
Any depressive symptoms in the past one month												
Yes	210	41.5	0.1	0.98 (0.79, 1.2)	97	19.8	2.7	1.25 (0.96, 1.64)	366	70.2%	81.1 ***	2.67 (2.15, 3.32)
No	525	42.1			202	16.5			603	46.9%		
Screen for mania over the past one month												
Yes	75	48.4	2.9	1.33 (0.96, 1.85)	23	15.4	0.4	0.85 (0.54, 1.36)	114	72.2%	23.8 ***	2.4 (1.68, 3.45)
No	660	41.3			276	17.6			855	51.9%		
Positive general rating of anxiety or phobia in the past 12 months												
Yes	466	44.6	7.8 **	1.32 (1.09, 1.6)	209	20.4	15.7 ***	1.71 (1.31, 2.24)	663	61.3%	63.8 ***	2.17 (1.79, 2.63)
No	269	37.9			90	13.0			306	42.2%		

OR – odds ratio; CI - confidence interval; *, p<0.05; **, p<0.01; ***, p<0.001

Table 7: Univariate associations between participants' psychotropic medications and symptoms of sleep disturbance

	Snore				Pause				Disruptive sleep			
	N	**%**	**X^2 (p)**	**OR (95% CI)**	**N**	**%**	**X^2 (p)**	**OR (95% CI)**	**N**	**%**	**X^2 (p)**	**OR (95% CI)**
Typical antipsychotics												
Yes	156	44.4	1.1	1.14 (0.9, 1.44)	63	18.4	0.3	1.1 (0.8, 1.48)	186	51.7	0.7	0.91 (0.72, 1.14)
No	579	41.3			236	17.2			783	54.1		
Atypical antipsychotics												
Yes	526	41.9	0.0	1.0 (0.81, 1.23)	203	16.5	2.3	0.81 (0.62, 1.06)	651	50.5	18.5 ***	0.63 (0.52, 0.78)
No	209	42.0			96	19.6			318	61.6		
Mood stabiliser												
Yes	237	50.7	20.3 ***	1.63 (1.32, 2.02)	92	20	3.9 *	1.32 (1.0, 1.73)	251	51.8	1.0	0.9 (0.73, 1.11)
No	498	38.7			207	16.3			718	54.4		
Antidepressant												
Yes	307	47.7	11.1 ***	1.39 (1.15, 1.69)	126	19.7	3.7	1.28 (0.99, 1.65)	405	60.1	17.9 ***	1.52 (1.25, 1.84)
No	428	38.9			173	16.1			564	49.8		
Clozapine												
Yes	118	41.7	0.0	1.0 (0.76, 1.28)	49	17.6	0.0	1.0 (0.72, 1.42)	126	42.6	17.5 ***	0.59 (0.46, 0.75)
No	617	42.0			250	17.4			843	55.8		

OR – odds ratio; CI - confidence interval; *, p<0.05; **, p<0.01; ***, p<0.001

Table 8: Univariate associations between substance use and symptoms of sleep disturbance

	Snore				Pause				Disruptive sleep			
	N	**%**	**X^2 (p)**	**OR (95% CI)**	**N**	**%**	**X^2 (p)**	**OR (95% CI)**	**N**	**%**	**X^2 (p)**	**OR (95% CI)**
Alcohol risk (AUDIT)												
Low	496	41.7	0.1	1.03 (0.84, 1.26)	185	15.9	5.5 *	1.36 (1.05, 1.76)	627	51.1	9.7 **	1.37 (1.12, 1.68)
High	239	42.5			114	20.5			342	59		
Current smoker												
No	242	42.2	0.0	0.99 (0.81, 1.21)	75	13.2	10.8 ***	1.6 (1.21, 2.13)	297	49.6	5.6 *	1.27 (1.04, 1.54)
Yes	490	42.0			223	19.6			663	55.5		
Cannabis use - past year												
<monthly	304	40.6	0.0	1.02 (0.8, 1.3)	136	18.7	0.0	1.0 (0.75, 1.38)	391	51.0	9.8 **	1.46 (1.15, 1.86)
≥monthly	176	41.1			79	18.9			264	60.4		
Amphetamine use - past year												
<monthly	256	41.6	0.6	0.84 (0.54, 1.31)	130	21.7	6.3 *	0.43 (0.22, 0.84)	347	54.8	2.5	1.42 (0.92, 2.2)
≥monthly	36	37.5			10	10.5			62	63.3		
Tranquilizers use - past year												
<monthly	77	45.6	2.2	0.6 (0.3, 1.19)	43	26.1	0.0	0.95 (0.44, 2.03)	108	62.1	5.8 *	2.58 (1.17, 5.68)
≥monthly	15	33.3			11	25.0			38	80.9		
Caffeine (mg/day)												
<200mg	252	37.3	9.8 **	1.37 (1.15, 1.67)	95	14.3	7.4 **	1.44 (1.11, 1.88)	372	53.6	0.0	1.0 (0.83, 1.21)
≥200mg	483	44.8			204	19.4			597	53.7		

OR – odds ratio; CI - confidence interval; AUDIT - Alcohol Use Disorders Identification Test ; *, p<0.05; **, p<0.01; ***, p<0.001.

Table 9: Logistic regression model for the relationship between subjects' OSA symptoms and disease factors

	Snore				Pause			
	Unadjusted OR (95% CI)	**P**	**Adjusted OR (95%CI)**	**P**	**Unadjusted OR (95% CI)**	**P**	**Adjusted OR (95%CI)**	**P**
Physical Health								
Metabolic syndrome IDF criteria	1.84 (1.46, 2.32)	<0.001	0.67 (0.41, 1.05)	NS	2.26 (1.66, 3.08)	<0.001	.632 (0.37, 1.09)	NS
Absolute cardiovascular disease 5-year risk equation	1.56 (1.23, 1.98)	<0.001	1.16 (0.67, 2.01)	NS	1.65 (1.23, 2.22)	<0.001	1.325 (0.69, 2.54)	NS
Any history of cardiovascular disease	2.03 (1.64, 2.52)	<0.001	1.40 (0.85, 2.30)	NS	2.19 (1.69, 2.84)	<0.001	1.959 (1.19, 3.48)	P<0.05
Physical activities								
Vigorous activity (hr/week)	1.27 (1.0, 1.6)	NS	1.22 (0.72, 2.06)	NS	1.6 (1.14, 2.26)	<0.01	.935 (0.48, 1.83)	NS
Walk (hr/week)	1.15 (0.95, 1.39)	NS	1.01 (0.58, 1.75)	NS	1.3 (1.0, 1.68)	<0.5	.771 (0.39, 1.52)	NS
Total activity (hr/week)	1.3 (0.98, 1.73)	NS	0.81 (0.43, 1.50)	NS	1.53 (1.09, 2.16)	<0.5	.834 (0.39, 1.77)	NS
Social function								
Formal activity (paid or unpaid work, or study)	0.97 (0.8, 1.17)	NS	1.38 (0.77, 2.50)	NS	0.72 (0.56, 0.93)	<0.05	1.161 (0.59, 2.30)	NS
Paid employment - past year	0.88 (0.72, 108)	NS	0.97 (0.47, 2.00)	NS	0.62 (0.47, 0.83)	<0.01	.927 (0.39, 2.19)	NS
Paid employment - past week	0.95 (0.75, 1.2)	NS	0.86 (0.43, 1.71)	NS	0.55 (0.39, 0.77)	<0.001	.399 (0.16, 1.01)	NS

	Snore				Pause			
	Unadjusted OR (95% CI)	**P**	**Adjusted OR (95%CI)**	**P**	**Unadjusted OR (95% CI)**	**P**	**Adjusted OR (95%CI)**	**P**
Substance abuse								
Alcohol risk (AUDIT)	1.03 (0.84, 1.26)	NS	1.59 (1.07, 2.38)	P<0.05	1.36 (1.05, 1.76)	<0.05	1.882 (1.15, 3.09)	P<0.05
Current smoker	0.99 (0.81, 1.21)	NS	.77 (0.43, 1.37)	NS	1.6 (1.21, 2.13)	<0.001	.746 (0.37, 1.51)	NS
Amphetamine use - past year	0.84 (0.54, 1.31)	NS	1.53 (0.81, 2.89)	NS	0.43 (0.22, 0.84)	<0.05	.562 (0.22, 1.42)	NS
Caffeine (mg/day)	1.37 (1.15, 1.67)	<0.01	1.60 (1.03, 2.51)	P<0.01	1.44 (1.11, 1.88)	<0.001	1.643 (0.94, 2.89)	NS
Gender	1.43 (1.18, 1.73)	<0.001	1.17 (0.76, 1.80)	NS	1.01 (0.78, 1.30)	NS	1.507 (0.89, 2.54)	NS
Age	1.77 (1.46, 2.16)	<0.001	2.21 (1.45, 3.39)	P<0.001	1.37 (1.06, 1.77)	<0.05	1.141 (0.68, 1.91)	P<0.05
BMI	2.16 (1.7, 2.7)	<0.001	1.21 (0.73, 2.00)	NS	3.17 (2.16, 4.66)	<0.001	2.236 (1.09, 4.58)	P<0.05

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Chapter 4: Paper 3

Obstructive sleep apnoea is more prevalent in men with schizophrenia compared to general population controls: results of a matched cohort study

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Abstract

Objectives: Obstructive sleep apnoea (OSA) may be more common in people with schizophrenia compared to the general population, but the relative prevalence is unknown. Here, we determine the relative prevalence of severe OSA in a cohort of men with schizophrenia compared to representative general population controls and investigate the contribution of age and body mass index (BMI) to differences in prevalence.

Methods: Rates of severe OSA (apnoea–hypopnoea index > 30) were compared between male patients with schizophrenia and controls from a representative general population study of OSA.

Results: The prevalence of severe OSA was 25% in the schizophrenia group and 12.3% in the general population group. In subgroups matched by age, the relative risk of severe OSA was 2.9 ($p = 0.05$) in the schizophrenia subjects, but when adjusted for age and BMI, the relative risk dropped to 1.7 and became non-significant ($p = 0.17$).

Conclusions: OSA is prevalent in men with schizophrenia. Obesity may be an important contributing factor to the increased rate of OSA.

Keywords: schizophrenia, psychosis, obstructive sleep apnoea, obesity, BMI, apnoea–hypopnoea index

Introduction

Obstructive sleep apnoea (OSA) may be more prevalent in people with schizophrenia compared to the general population, given the high rates of risk factors for OSA such as obesity, tobacco smoking, alcohol consumption and sedative medication use.[1] Studies assessing OSA in people with schizophrenia provide prevalence estimates between 13.5 and 57.1%,[2–4] which is higher than the general population.[5] However, these studies may not provide generalisable or consistent data due to biases in recruitment and variability in assessment measures and diagnostic thresholds for OSA. There is no literature reporting the comparative prevalence of OSA in people with schizophrenia with matched general population controls.

Analysis of registry data suggests that diagnosis of a psychotic illness is predictive of OSA.[6] Similarly, Rishi et al.[7] reported an increased prevalence of severe OSA in a cohort exposed to atypical antipsychotic drugs compared to controls (odds ratio = 1.9, 95% confidence interval (CI) 1.1–3.3). Causes of these associations are unclear. The most important risk factor for OSA is obesity, which is highly prevalent in people with schizophrenia.[1] Whilst obesity ostensibly increases the risk of OSA in this group, pharmacological factors such as hypnotic and central-apnoeic effects of antipsychotics[8] or sleep architecture changes intrinsic to schizophrenia[9] may independently increase the risk of OSA beyond traditional risk factors. Furthermore, determining whether, and to what extent, OSA is over-represented in people with schizophrenia would help enhance clinical awareness and recognition, and enable evidence-based provision of treatment services.

To further explore the relationship between OSA and schizophrenia, we aimed to determine the relative prevalence of OSA in men with schizophrenia taking clozapine compared to a general population control group matched for age and body mass index (BMI). We

hypothesised that rates of OSA would be higher in men with schizophrenia when matched for the traditional risk factors of increased age and BMI.

Methods

Population

The data compared two cohorts: a community sample of men with stable schizophrenia (the Assessing Sleep in Schizophrenia and Evaluating Treatment (ASSET) study); and a comparison cohort of male general population controls (the Men Androgen Inflammation Lifestyle Environmental and Stress (MAILES) study).

The ASSET subjects were recruited between 2015–2016 from a psychiatric outpatient clinic in Adelaide. Inclusion criteria included a current diagnosis of schizophrenia or schizoaffective disorder, age 18–64 years and current treatment with Clozapine as an outpatient. Ethics approval was provided by The Queen Elizabeth Hospital Human Research Ethics Committees (HREC). All participants gave written informed consent.

Control subjects were drawn from the MAILES database, the details of which have been previously described.[10] The cohort consisted of randomly selected community dwelling men aged at least 40 years residing in Adelaide, who were recruited between 2000–2002. The study was approved by the North West Adelaide Health Service and the Royal Adelaide HREC.

Measures

For both cohorts, height, weight and BMI were recorded. Subjects underwent home multichannel polysomnography (PSG), using an Embletta X100 (Embla Systems, Broomfield, CO) or a Somte (Compumedics, Abbotsford, VIC) portable sleep recorder in the schizophrenia cohort and the Embletta X100 in the control group. A sleep technician performed manual

scoring according to the American Academy of Sleep Medicine 2007 alternate criteria to derive an apnoea–hypopnoea index (AHI).[11]

The primary outcome was a diagnosis of severe sleep apnoea defined as an AHI of ≥ 30. The prevalence of severe OSA in the ASSET and MAILES groups was determined. ASSET and MAILES subjects were then matched for age and BMI, and the prevalence in the two groups was compared, controlling for these factors.

Statistical methods

Relative risks were estimated directly using Poisson regression with sandwich estimated covariance matrix,[12] and using propensity score matched conditional logistic regression. In both models, severe OSA was considered an event. Age, separately and with BMI, was adjusted for in the Poisson regression and propensity score matching. Due to the imbalance in age distribution between the two cohorts, the Poisson regression was repeated in the subgroup of individuals with ages between 41 and 61 that spans the age range of both cohorts. The propensity score matching attempted to match 25 controls for each case. Analyses were performed in R (version 3.3.1) using statistical, survival, non-random and splines packages.

Results

The ASSET group consisted of 24 men with schizophrenia who had undertaken home PSG recording. Six (25%) participants had severe OSA (AHI > 30). The MAILES sample consisted of 837 men who had been randomly selected for home PSG. The MAILES cohort was older ($p < 0.001$) and less obese ($p < 0.001$) than the ASSET subjects. The median age of the MAILES subjects was 59 years (range 41–88), median BMI was 28 (range 27–47) and median AHI was 11 (range 1–109). One-hundred and three (12.3%) MAILES participants had severe OSA (AHI

> 30). The unadjusted comparison of the prevalence of severe OSA indicates a significantly higher rate in the ASSET population ($p = 0.05$).

When adjusting for age alone in the unrestricted sample, the relative risk of severe OSA was 2.9 (95% CI 1.0–8.1, $p = 0.05$). When adjusting for age and BMI in the unrestricted sample, the relative risk of severe OSA was reduced to 1.7 (95% CI 0.8–3.7) and became non-significant $p = 0.17$.

Restrictions and matching were performed to test the statistical robustness of the results. When restricting for age, there were 15 participants included in the ASSET and 569 participants included in the MAILES, and when using the propensity scoring matching there were 13 participants included in the ASSET and 325 participants included in the MAILES (see Table 1). The sample composition for each analysis is outlined in Figure 1.

Discussion

This study demonstrates that severe OSA is highly prevalent in men with schizophrenia, occurring at a rate of approximately 25%. However, we were unable to demonstrate an increased risk of OSA in men with schizophrenia compared to general population controls when adjusting for age and BMI. This finding refutes our hypothesis of an independent OSA risk factor intrinsic to schizophrenia and indicates that high rates of severe OSA in men with schizophrenia are driven primarily by obesity.

The high rates of OSA in men with schizophrenia reported here add to substantial literature reporting a link between major mental illness, disproportionate cardiometabolic risk and death related to premature cardiovascular dis- ease.[13] OSA is likely to play an additive role in driving cardiovascular risk in a significant number of men with schizophrenia. OSA is associated with hypertension, insulin resistance and increased cardiovascular mortality, and treatment with

nocturnal continuous positive airway pressure improves these risk factors and quality of life, and reduces direct and indirect healthcare costs.[14] Men with schizophrenia should be considered at high risk of OSA with early identification and treatment a clinical priority.

The non-significant odds of OSA in men with schizophrenia compared to the general population cohort when matching for age and BMI argues against a psychiatric disease-specific or antipsychotic medication-associated risk factor. This finding is unsurprising given that obesity and increased neck circumference are known to be directly causative of OSA, but does contrast with previous literature describing an association between second-generation antipsychotics and OSA independent of BMI.[7] Whilst we can provide no evidence to support such an association, the link between psychotic illness, antipsychotic medications and OSA is likely to be complex. Antipsychotic medications do confer a predictable risk of weight gain,[15] ostensibly contributing to an increased risk of OSA in some patients. However, the impact of neurobiological changes affecting sleep architecture described in schizophrenia,[16] how these are modified by antipsychotic drugs and how this influences sleep disordered breathing remain to be defined.

Although our dataset is limited by not addressing the prevalence of OSA in women with schizophrenia, previously published epidemiological data suggest that they have similar rates of obesity and smoking[1] and, as such, it is likely that women are similarly predisposed to developing OSA. A further limitation was insufficient power to perform multivariate regression analysis to identify other factors associated with the increased prevalence of OSA. Additionally, all subjects included in our analysis were taking clozapine, which may influence the generalisability of our results. It is possible that non-clozapine antipsychotics influence OSA risk through other factors, which may account for our finding that contradicts previous literature reporting on people exposed to a variety of different antipsychotic drugs.

Conclusion

Our data suggest that OSA is highly prevalent in men with schizophrenia. Given that up to one-quarter of men with schizophrenia may have severe OSA and that effective treatment exists, it is imperative that OSA be incorporated into cardiometabolic monitoring for people with schizophrenia. Future research should be directed towards determining the relative prevalence in women with schizophrenia and investigating the role of disease-specific factors in driving OSA risk.

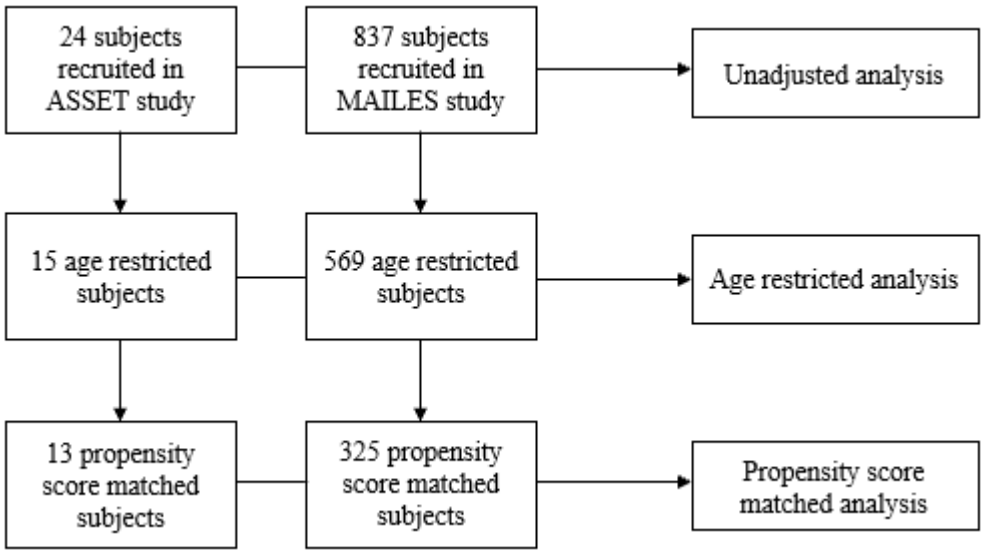

Figure 1: Sample composition of each analysis

Table 1: Relative risk estimates

	Cohort	E (N)	Prevalence	Unadjusted		Age adjusted		Age & BMI adjusted	
				RR [95% CI]	p-value	RR [95% CI]	p-value	RR [95% CI]	p-value
All	S	6 (24)	25% [9.8, 46.7]	2.0 [1.0, 4.2]	0.05	2.9 [1.0, 8.1]	0.05	1.7 [0.8, 3.7]	0.17
	M	103 (837)	12.3% [10.2, 14.7]						
Age restricted	S	4 (15)	26.7% [7.8, 55.1]	2.5 [1, 5.9]	0.04	4.5 [1.6, 12.7]	0.004	2.6 [1.3, 5.4]	0.008
	M	61 (569)	10.7% [8.3, 13.6]						
PS matched	S	4 (13)	30.8% [9.1, 61.4][1]			4.0 [1.2, 13.8]	0.03	2.2 [0.6, 8.6]	0.25
	M	32 (325)	9.8% [6.8, 13.6] [1]						

Event and prevalence rate reported for age matched cohorts. For the age and BMI matched schizophrenia and MAILES cohorts the prevalence rates were 23.1% [5, 53.8] & 11.5% [8.2, 15.6] respectively. Abbreviations: S (schizophrenia cohort), M (general population cohort), E (event), RR (relative risk), PS (propensity score).

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Chapter 5: Paper 4

Pilot cohort study of obstructive sleep apnoea in community dwelling people with schizophrenia

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Abstract

Objectives: We aimed to assess the incidence of Obstructive Sleep Apnoea (OSA) in people with schizophrenia, to explore clinical associates with OSA and how well OSA screening tools perform in this population.

Methods: All patients registered in a community outpatient Clozapine clinic, between January 2014 and March 2016 were consecutively approached to participate. Participants were screened for OSA using at home multichannel polysomnography (PSG) and were diagnosed with OSA if the apnoea-hypopneoa index (AHI) was >10 events/hr. Univariate comparison of participants to determine whether AHI >10 events/hr was associated with demographic factors, anthropometric measures and psychiatric symptoms and cognition, were performed. The sensitivity, specificity, positive predictive value and negative predictive value of the commonly used sleep symptoms scales and OSA screening tools were also determined.

Results: Thirty participants were recruited, 24 (80%) men and six (20%) women. Mean age was 38.8 (range: 25-60), mean BMI was 35.7 (range 19.9-62.1). The proportion of participants with OSA (AHI >10 events/hr) was 40%; 18 (60%) had no OSA, four (13%) had mild OSA (AHI 10.1-20) and eight (27%) had severe OSA (AHI>30). Diagnosis of OSA was significantly associated with increased weight, BMI, neck circumference and systolic blood pressure. Diagnosis of OSA was not significantly associated with PANSS, MADRS, PSP or BACS scores. All OSA screening tools demonstrated poor sensitivity and specificity for a diagnosis of OSA.

Conclusion: OSA was highly prevalent in this cohort of people with schizophrenia and occurred at a high severity based on AHI. Diagnosis of OSA was associated with increased weight, BMI, neck circumference and systolic blood pressure.

Introduction

Obstructive sleep apnoea (OSA) is a reversible breathing disorder characterised by obstruction of the airway during sleep resulting in intermittent hypoxia and repeated arousals. The major risk factor for OSA is obesity and OSA can be contributed to by use of sedating medications. Untreated OSA results in non-restorative sleep and is associated with increased cardiometabolic risk, decrements in cognitive capacity, poorer occupational performance, daytime somnolence and depressive symptoms (Patil et al., 2007).

OSA is likely to be highly prevalent in people with schizophrenia given the high rates of obesity in this population (Galletly et al., 2012). We conducted a systematic review of existing literature examining rates of OSA in cohorts of people with schizophrenia and identified four previous studies that reported OSA prevalence of between 19-57% (Myles et al., 2016), which is substantially higher than that seen in general population studies including a landmark 2015 study that reported rates of severe OSA of 15% in men aged 40-60 years, and 1% in women aged 40-60. (Heinzer et al., 2015). However, no previous literature reports the prevalence of OSA in unselected cohorts of people with schizophrenia using gold-standard diagnostic methods. Similarly, only one previous study examined the diagnostic performance of general population OSA screening tools in this cohort and this study was confounded by a heterogeneity of diagnoses with a cohort with "mental illness", 48% of which had a diagnosis of schizophrenia or schizoaffective disorder (Anderson et al., 2012). The result of this study suggests that OSA screening tools perform poorly in people with schizophrenia and comorbid OSA. Optimal identification of OSA in people with schizophrenia is an unmet clinical need and requires further clarification given the availability of effective treatment that may modify cardiovascular risk, which remains the main determinant of premature mortality in people with schizophrenia (Laursen et al., 2012).

The impact of untreated OSA on cognitive performance and psychiatric disease symptoms in people with schizophrenia also requires further clarification. People with schizophrenia consistently perform 1.5 standard deviations below population means in standardized cognitive assessments (Keefe et al., 2008). Disease-related cognitive decrements are generally treatment-resistant to antipsychotic medications and are associated with poorer functional and social recovery (Fett et al., 2011). Untreated OSA has a well-established association with impaired cognitive function and poorer occupational performance (Patil et al., 2007) which is reversible with continuous positive airway pressure (CPAP) treatment (Matthews and Aloia, 2011). As such it is possible that co-morbid OSA may worsen negative and cognitive symptoms in people with schizophrenia. This association has not been previously investigated and if demonstrated may offer a novel means to modify treatment-resistant symptoms and improve functional recovery.

We conducted a prospective pilot cohort study to determine the prevalence of OSA in an unselected group of community patients with schizophrenia prescribed clozapine. Our aims were to determine whether diagnosis of OSA was associated with anthropometric measures, psychiatric symptoms, medication use and cognitive performance. Further, we aimed to ascertain whether the existing OSA screening tools were useful in predicting OSA in people with schizophrenia.

Methods

Population

Subjects were recruited from a clozapine outpatient clinic with 104 registered patients in Adelaide, South Australia. The “clozapine clinic” provides weekly and monthly reviews of people with treatment resistant schizophrenia or schizoaffective disorder taking clozapine. Inclusion criteria included males and females aged 18-64 years, a current clinical diagnosis of

schizophrenia or schizoaffective disorder and currently prescribed clozapine. Exclusion criteria included inability to provide informed consent and a diagnosis of sleep disordered breathing, as defined by a partial or complete cessation of breathing occurring many times throughout the night, resulting in daytime sleepiness or fatigue that interferes with a person's ability to function. Every patient registered in the clinic between January 2014 and March 2016 was approached to participate in the study. Ethics approval was provided by The Central Adelaide Local Health Network Human Research Ethics Committee. All participants gave written informed consent.

Measures

Baseline demographic and anthropometric data were recorded including age, sex, medical history, prescribed medications, height, weight, waist and neck circumference, body mass index (BMI) and blood pressure. Abdominal obesity was defined as a waist circumference ≥ 94 cm for men and ≥ 80 cm for women. Hypertension was diagnosed if the person had a systolic blood pressure ≥ 130 mmHg and/or a diastolic pressure ≥ 85 mmHg. Psychopathological measures included the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987), Montgomery Asperger's Depression Rating Scale (MADRS) (Williams and Kobak, 2008) and Personal and Social Performance scale (PSP) (Morosini et al., 2000). Standardised cognitive assessment was undertaken using the Brief Assessment of Cognition for Schizophrenia (BACS) (Keefe et al., 2008). Subjective sleep quality was assessed with the Pittsburg Sleep Quality Inventory (PSQI) (Buysse et al., 1989), subjective daytime sleepiness with the Epworth Sleepiness Scale (ESS), severity of insomnia with Insomnia Severity Index (ISI) (Morin et al., 2011) and sleep related quality of life with Functional Outcomes of Sleep Questionnaire (FOSQ) (Weaver et al., 1997). Patients were assessed with standard OSA screening questionnaires including the OSA50 (Chai-Coetzer et al., 2011), and the STOP-BANG questionnaire (Ong et al., 2010).

Following recruitment and baseline measures subjects underwent at-home multichannel polysomnography (PSG) using an Embletta X100 (Natus Medical Inc, USA) or Somte (Compumedics, Australia) portable sleep recorder administered in the participants home. PSG data were manually scored using the 2007 AASM alternate criteria to obtain an apnoea-hypopnoea index (AHI) (Iber et al., 2007). A diagnosis of OSA was determined as an AHI >10 events/hr and categorised as moderate if AHI was 20.1-30 or severe if AHI was >30 (Ruehland et al., 2009).

Statistical Methods

Statistical analyses were performed using SPSS 24 (IBM, New York). Univariate analysis was performed using chi-squared tests, independent samples t-tests for parametric data, Mann-Whitney U tests for non-parametric data and Pearson's test for linear correlation. Logistic regression was performed to determine the predictive value of diagnostic screening tests and diagnosis of severe OSA (AHI >30). A p-value of <0.05 was considered the threshold for statistical significance.

Results

104 patients enrolled in the clozapine clinic were approached for inclusion. 30 patients undertook study measures (see diagram 1). The other 74 patients satisfied inclusion criteria but did not give their consent to participate in the research project. No participants had previously been assessed for OSA using PSG. All patients tolerated PSG and provided diagnostic quality sleep studies, one patient repeated the study due to an equipment error. The demographic and anthropometric data of the 30 patients are presented in table 1. The majority of the sample was overweight (27% BMI 25-30) or obese (63% BMI>30). 90% of subjects either lived alone or had no bed partner to corroborate the presence or absence of snoring or apnoeas. 77% of participants were prescribed clozapine as their only antipsychotic medication, 20% one

additional antipsychotic medication and 3% two additional antipsychotic medications. 27% of participants were prescribed clozapine as their only psychotropic medication, 43% were prescribed one additional psychotropic medication and 30% were prescribed two or more additional psychotropic medications.

Table 1: Demographic and anthropometric data

	All: N=30	Men: N=24 (80%)	Women N=6 (20%)
Mean age (range)	38.8 (25-60)	39.5 (25-60)	36.0 (30-42)
Mean BMI (range)	35.7 (19.9-62.1)	34.4 (19.9-62)	40.6 (25.8-48.5)
BMI categories			
Normal (BMI 18.5-25)	10% (n=3)	12.5% (n=3)	-
Overweight (BMI 25.1-30)	27% (n=8)	29% (n=7)	17% (n=1)
Obese (BMI >30)	63% (19)	58% (n=14)	83% (n=5)
Mean neck circumference cm (range)		43.15 (35-53)	41.2 (39-43)
Mean waist circumference cm (range)		117.3 (85-162)	125.9 (100-140)

OSA defined as an AHI >10 was present in 12 patients or 40% (95%CI = [23, 59]) of the cohort. The cohort mean AHI was 21.1 (SD 35) with a range of 0-134 (see table 2).

Table 2: PSG data

OSA categories	Total (n=30)	Men (n=24)	Women (n=6)
AHI 0-10 (normal)	60% (n=18)	58% (n=14)	67% (n=4)
AHI 10.1-20 (mild)	13% (n=4)	17% (n=4)	-
AHI 20.1-30 (moderate)	-	-	-
AHI >30 (severe)	27% (n=8)	25% (n=6)	33% (n=2)

*The DSM-V and AASM classifies mild OSA from an AHI>5, however Australian guidelines use AHI>10. If we had used the international standard of AHI>5 there may have been greater 'mild OSA' diagnoses.

Diagnosis of OSA (AHI >10) was significantly associated with higher weight, BMI, waist circumference, neck circumference and systolic blood pressure. Diagnosis of OSA was not significantly associated with age or heart rate (see table 3). Dose of clozapine was not

significantly associated with diagnosis of OSA (mean dose AHI <10 406mg, mean dose AHI ≥10 399mg, p=0.91).

Table 3: AHI associations with mean anthropometric measures

	AHI <10 (n=18)	AHI ≥10 (n=12)	Mean difference [95%CI]	p-value*
Age years (SD)	37.9 (7.4)	40.2 (12.0)	2.4 [-10.6, 5.9]	0.92
Weight kg (SD)	95.5 (27.3)	128.5 (34.8)	-33.0 [-56.3, -9.8]	<0.01
BMI kg/m^2 (SD)	32.0 (9.0)	41.2 (8.9)	-9.2 [-16.1, -2.3]	0.01
Waist circumference cm (SD)	109.8 (18.2)	132.8 (14.8)	-23.0 [-35.9, -10]	<0.01
Neck circumference cm (SD)	40.0 (2.7)	46.6 (4.2)	-6.6 [-9.4, -4]	<0.01
Systolic BP mm/Hg (SD)	121.8 (12.9)	132.7 (14.2)	-10.8 [-21.1, -0.25]	0.04
Heart rate b/min (SD)	97.7 (11.7)	99.1 (10.2)	-1.4 [-9.9, 7.1]	0.73

*Independent sample t-test

Mean ESS, PSQI and ISI scores for the entire cohort were 4.4 (SD=3.3), 5.0 (SD=2.0) and 7.9 (SD=6.1) respectively. There was no detectable difference between mean ESS, PSQI and ISI scores in those with AHI ≥10 and those with AHI <10 (see table 4). 93% of the cohort (28 subjects) had ESS scores within the normal range (score <10) and of the two subjects with elevated ESS (score ≥10) one was diagnosed with OSA. 63% of the cohort (19 subjects) had PSQI scores within the normal range (score <5), of the 11 subjects with an elevated PSQI (score ≥5) two (18%) were diagnosed with OSA. 83% of the cohort (25 subjects) had ISI scores within the normal range (score <15) and of the five subjects with an elevated ISI (score ≥15) one (20%) was diagnosed with OSA. There was no association found between sleep quality measures and AHI scores. Total ESS did not correlate with total AHI (r=0.07, p=0.73), global PSQI did not correlate with total AHI (r=0.27, p=0.15), nor did total ISI scores (r=0.19, p=0.32).

Table 4: Associations between OSA and mean symptom severity scores

	AHI <10 (n=18)	AHI ≥10 (n=12)	p-value *
Mean ESS (SD)	4.0 (3.5)	5.2 (3.1)	0.34
Mean PSQI (SD)	5.4 (2.2)	4.3 (1.8)	0.16
Mean ISI (SD)	9.1 (6.7)	6.0 (3.5)	0.15

*Mann-Whitney U test

The OSA50 score (using a cut-off score of ≥5) correctly classified six subjects with OSA and eleven subjects without OSA. Sensitivity of OSA50 was 50%, specificity was 61%, (positive predictive value) PPV was 46% and negative predictive value (NPV) was 64%. The STOP-BANG score (using a cut-off score of ≥3) correctly classified eleven subjects with OSA and five subjects without OSA. Sensitivity of STOP-BANG was 92%, specificity 28%, PPV was 46% and NPV was 83%. In a logistic regression for predicting severe OSA (AHI >30) there was no detectable association with OSA50 total score and outcome (p=0.26) and only a low discriminatory ability (ROC-AUC=0.62). In contrast the association with STOP-BANG total score was weakly detectable (p=0.02) and had moderately higher discriminatory value (ROC-AUC=0.77) (see figure 1, supplementary appendix).

There were no significant associations between diagnosis of OSA and measures of psychopathology using the total PANSS, MADRS and PSP, nor was there a significant association between diagnosis of OSA and mean BACS z-score (see table 5).

Table 5: Associations between OSA and mean psychopathology and cognitive scores

	AHI <10 (n=18)	AHI ≥10 (n=12)	Mean difference (95% CI)	p-value*
Total PANSS (SD)	61.8 (15.8)	66.4 (21.3)	- 4.6 [-18.7, 9.5]	0.51
MADRS (SD)	5.9 (4.1)	4.8 (2.9)	1.1[-1.7, 3.9]	0.43
Total PSP (SD)	56.4 (13.9)	49.5 (14.0)	6.9 [-4.1, 17.9]	0.21
BACS total z-score (SD)	-1.53 (0.74)	-1.95 (1.3)	0.42 [-0.47, 1.3]	0.68

*Mann-Whitney U test.

Discussion

This pilot study indicates that OSA is highly prevalent in stable community dwelling people with schizophrenia, occurring at a rate of approximately 40%. These rates are substantially higher than those seen in the general population (Heinzer et al., 2015) reflecting the excess of obesity seen in our cohort and populations with major mental illness more generally (Galletly et al., 2012). Diagnosis of OSA was significantly associated with weight, BMI and neck circumference indicating these are clinically relevant predictors of OSA similar to general populations. Our results align with estimates reported in previous literature of between 19-57% (Myles et al., 2016), however are comparatively more robust due to our use of an unselected cohort, a cohort that contains only people with schizophrenia and diagnostic methods that have not been used in prior studies.

Despite the high incidence of OSA in our pilot, sleep symptom scores were not substantially increased. The ESS and PSQI, which are validated in general populations as measures of sleep symptom severity (Buysse et al., 1989; Johns, 1991), were within the normal range in the majority of people diagnosed with OSA, were not significantly higher in people with OSA and did not correlate with AHI. These findings are similar to previous literature (Anderson et al., 2012) and suggest that the ESS and PSQI should not be used as a means of identifying patients with schizophrenia at high risk of sleep-disordered breathing. The current Australian assessment for rebatable PSGs requires an above threshold score on the ESS. Given the high prevalence of OSA in this population, we suggest that this should not be a restriction for people with Schizophrenia.

Similarly, population screening tools performed poorly for the identification of OSA in our cohort. The STOP-BANG and OSA-50 scores have reasonable sensitivity and specificity in primary care populations (Ong et al., 2010;Chai-Coetzer et al., 2011) and are useful as a means

of identifying patients at risk of OSA requiring further diagnostic assessment. However, neither have been validated in people with major mental illness. In our cohort, the OSA-50 demonstrated a sensitivity of 50% and specificity of 61% whilst the STOP-BANG demonstrated a sensitivity of 92% and specificity of 28%, which is lower than that demonstrated in a general population validation cohort (Ong et al., 2010). This lack of diagnostic accuracy may reflect the scores' reliance on observed sleep symptoms, which are likely to be under-recognised in our cohort given 90% of subjects lacked a bed partner. The superior sensitivity of the STOP-BANG questionnaire reflects this scores' reliance on anthropometric measurements such as weight, waist circumference, neck circumference and blood pressure. As such the STOP-BANG is a preferable tool for the identification of OSA in people with schizophrenia at the expense of a high false positive rate given the ubiquitous burden of obesity in this population that make the majority of patients high risk.

We were unable to demonstrate a significant association between OSA and psychopathology scores or standardized measures of cognition in our cohort. OSA is known to be associated with poorer occupational performance, cognitive decrements and depression in general populations (Patil et al., 2007), which are reversible with CPAP treatment (Sánchez et al., 2009;Pan et al., 2015). It is plausible, due to the high prevalence of sleep disordered breathing in this population, that co-morbid OSA could contribute to or worsen negative symptoms of schizophrenia in some people. Unfortunately, our study is insufficiently powered to detect a difference in psychopathology or cognitive measures. Future research in larger samples are required to definitively explore this possible association given treatment of OSA may potentially modify overlapping cognitive decrements which tend to be treatment resistant, and correlate with functional outcomes.

Whilst our study is the first to report prevalence of OSA in an unselected community cohort of people with schizophrenia using gold-standard diagnostic measures, there are a number of limitations to our analysis that warrant discussion. Firstly, our data is derived from a pilot cohort study and the sample size was underpowered to detect a significant association for a number of outcomes. This is a limitation of the literature more broadly, with the largest previous cohort reporting OSA prevalence in people with schizophrenia having a sample size of 24 (Anderson et al., 2012). Further research is required in larger cohorts to examine whether OSA is associated with poorer psychopathological and cognitive outcomes. Similarly, due to our sample size we were unable to perform meaningful multivariable analysis. Further evaluation of factors predictive of OSA in people with schizophrenia would be valuable to develop specific screening tools given the poor performance of existing tools we report here. Secondly, our cohort existed entirely of people exposed to clozapine which is associated with the highest risk of obesity compared to other antipsychotic agents. Given OSA in people with schizophrenia is primarily driven by obesity (Myles et al., 2018) and that clozapine use has previously been demonstrated to be associated with risk of OSA (Alam et al., 2012), our results may be biased to a higher prevalence of OSA compared to people with schizophrenia more generally. Thirdly, our data is observational and does not determine whether treatment of OSA co-morbid with schizophrenia improves cognitive measures, psychopathological outcomes, quality of life outcomes or cardiovascular risk factors. However, in an extension of this pilot study we monitored the response to CPAP and found CPAP improved obesity and cognition when used in people with schizophrenia and severe OSA (Myles et al., 2019). Given the high prevalence of OSA in our pilot and because CPAP treatment modifies these outcomes in general populations further intervention studies are required to determine whether OSA treatment has any role in improving outcomes in this population.

This study indicates that OSA is highly prevalent in people with schizophrenia and is likely to be substantially under-recognised given that no subject diagnosed with OSA in our cohort had previously undergone diagnostic assessment for OSA. These results suggest OSA screening and diagnostic assessment should form part of routine metabolic evaluation in people with schizophrenia given subjects are able to tolerate PSG assessment and effective treatment exists. Our results also suggest general population sleep symptom tools and diagnostic screening questionnaires are unlikely to reliably identify people at risk and that obesity and increased neck circumference remain the best predictors of OSA in this population. Further research in larger samples is required to determine more accurate predictors of OSA in this population and the impact of co-morbid OSA on cognitive and psychopathological outcomes in people with schizophrenia.

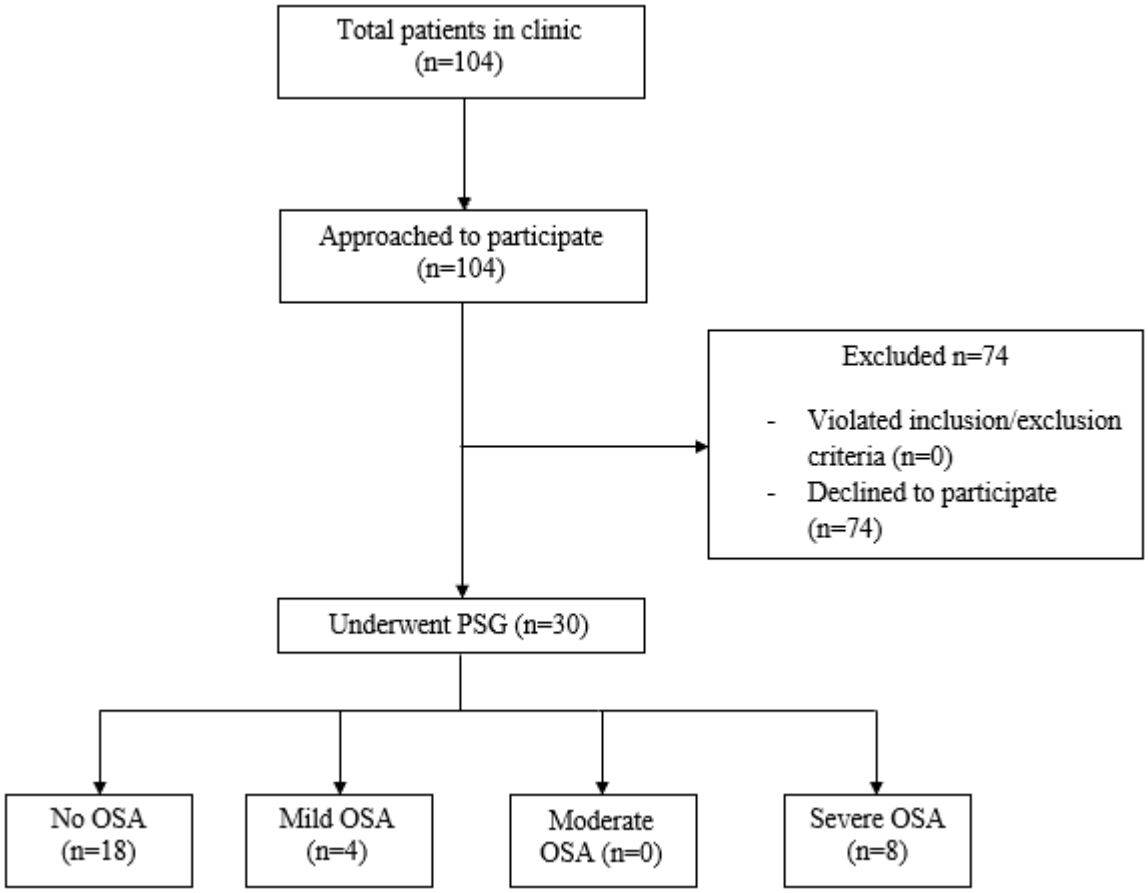

Figure 1: Consort diagram

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Chapter 6: Paper 5

Cognition in schizophrenia improves with treatment of severe obstructive sleep apnoea: A pilot study

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Abstract

Previous studies have shown that people with schizophrenia have high rates of Obstructive Sleep Apnoea (OSA). Despite this, intervention studies to treat OSA in this population have not been undertaken. The ASSET (Assessing Sleep in Schizophrenia and Evaluating Treatment) pilot study investigated Continuous Positive Airway Pressure (CPAP) treatment of severe OSA in participants recruited from a clozapine clinic in Adelaide. Participants with severe untreated OSA (Apnoea-Hypopnoea Index (AHI) > 30), were provided with CPAP treatment, and assessed at baseline and six months across the following domains: physical health, quality of sleep, sleepiness, cognition, psychiatric symptoms and CPAP adherence. Six of the eight ASSET participants with severe OSA accepted CPAP. At baseline, half of the cohort had hypertension, all were obese with a mean BMI of 45, and they scored on average 1.47 standard deviations below the normal population in cognitive testing. The mean AHI was 76.8 and sleep architecture was markedly impaired with mean rapid eye movement (REM) sleep 4.1% and mean slow wave sleep (SWS) 4.8%. After six months of treatment there were improvements in cognition (BACS Z score improved by an average of 0.59) and weight loss (mean weight loss 7.3 ± 9 kg). Half of the participants no longer had hypertension and sleep architecture improved with mean REM sleep 31.4% of the night and mean SWS 24% of the night. Our data suggests CPAP may offer novel benefits to address cognitive impairment and sleep disturbance in people with schizophrenia.

1. Introduction

Obstructive sleep apnoea (OSA) is a nocturnal breathing disorder caused by repeated collapse of the upper airway during sleep, resulting in repetitive arousal. OSA is associated with poor cardiovascular health due to physiological changes related to intermittent hypoxia, and reduced quality of life due to sleep disturbance (Al Lawati et al., 2009). Continuous positive airway pressure (CPAP) reverses these pathophysiological changes and improves quality of life. (Jing et al., 2008). OSA is prevalent in people with schizophrenia due to high rates of obesity (Galletly et al., 2012) and men with schizophrenia are 2.9 times more likely to have OSA than age matched general population controls (Myles et al., 2018). A recent systematic review estimated that 19–57% of people with schizophrenia suffer comorbid OSA (Myles et al., 2016); these rates are much higher than that seen in the general population (Heinzer et al., 2015). Despite this, there is minimal literature reporting outcomes following treatment of OSA in this population.

The standard treatment for OSA is nocturnal CPAP which involves wearing a face or nasal mask that applies a continuous pressure to splint the upper airway during sleep. Effective CPAP treatment prevents obstructive events that cause repetitive hypoxia and arousals; and restores normal sleep architecture. In general population studies, not all people with OSA can tolerate CPAP, and the duration of CPAP use per night impacts on the clinical efficacy (Weaver et al., 2007). Mean CPAP adherence of four hours per night is considered the minimum required for efficacy. Treatment outcomes and adherence rates for CPAP in people with schizophrenia have not been reported previously and would be valuable in determining whether treatment of OSA in this population is efficacious.

In the general population CPAP reverses morbidity associated with OSA including impaired cognition and vigilance, insulin resistance, and hypertension (Al Lawati et al., 2009; Jing et

al., 2008; Patel et al., 2003). Ratings of quality of life, daytime sleepiness, depression and anxiety also improve with CPAP. Thus, treatment of OSA in people with schizophrenia could potentially improve not only cardiometabolic risk factors, but also neurocognitive and functional outcomes. OSA and schizophrenia (Afonso et al., 2011) are associated with disruptions to sleep architecture, as such it is also important to determine whether sleep architecture is normalized to the same extent in people with schizophrenia compared to the general population.

This pilot study examined subjects diagnosed with schizophrenia and comorbid OSA. Subjects undertook psychiatric, cardiometabolic, cognitive and quality of life assessments prior to undergoing treatment with CPAP. The participants were then followed longitudinally during 6 months of CPAP treatment to determine adherence, efficacy and acceptability of treatment, and changes in baseline measures. To our knowledge this is the first prospective assessment of CPAP usage in people with schizophrenia and comorbid OSA.

Specifically, we aimed to determine:

1. The efficacy of and adherence to CPAP treatment in people with schizophrenia and comorbid OSA.
2. Changes in anthropometric measurements before and following six months of CPAP treatment
3. Changes in psychiatric symptoms, quality of life measures, sleep quality measures and cognitive measures before and during CPAP treatment.

2. Materials and methods

2.1. Population

Subjects were recruited from a psychiatric outpatient clinic in Adelaide, South Australia. Inclusion criteria included males and females aged 18–64 years, a current clinical diagnosis of schizophrenia or schizoaffective disorder, currently prescribed clozapine and a diagnosis of severe OSA made during assessment in the ASSET study. Exclusion criteria included inability to provide informed consent and a diagnosis of sleep disordered breathing made prior to enrolment in the ASSET study. Subjects were recruited between January 2015 and March 2016. Ethics approval was provided by The Queen Elizabeth Hospital Ethics Committee. All participants gave written informed consent.

2.2. Measures

A trained research nurse collected data on each participant at baseline at the Lyell McEwin Hospital Research Department, South Australia. Demographic and anthropometric data was recorded on the day prior to or the day following at-home diagnostic polysomnography (PSG) and included age, sex, medical history, prescribed medications, height, weight, waist and neck circumference, body mass index (BMI) and blood pressure. Waist circumference was measured to the nearest 0.5cm at the level of the iliac crest following two normal breaths. Abdominal obesity was defined as a waist circumference ≥ 94 cm for men and ≥80 cm for women. Hypertension was diagnosed if the person had a systolic blood pressure ≥ 130 mm Hg and/or a diastolic pressure ≥ 85 mm Hg. Psychopathological measures included the Positive and Negative Symptoms Scale (PANSS) (Kay et al., 1987), Montgomery Asperger's Depression Rating Scale (MADRS) (Williams and Kobak, 2008) and Personal and Social Performance Scale (PSP) (Morosini et al., 2000). Cognition was assessed using the Brief Assessment of Cognition for Schizophrenia (BACS) (Keefe et al., 2008). The results of the BACS were

recorded as Z scores across individual domains and as a total score for Verbal Memory (VM), Digit Sequencing (DIGI), Token Motor Task (TMT), Verbal Fluency (Fluency), Symbol Coding (SC), the Tower of London (TL) and Total z score (Total). A score of zero indicates that the participant is on par with the general population mean. Scores in the negative range indicate cognitive decrements and are presented as standard deviations below the normal population means. Validation studies in people with schizophrenia score 1.5 standard deviations below the normal population mean. Subjective sleep quality was assessed with the Pittsburg Sleep Quality Inventory (PSQI) (Buysse et al., 1989), severity of insomnia with Insomnia Se- verity Index (ISI) (Morin et al., 2011), Restless Legs Scale (RLS) (Group, 2003), and sleep related quality of life with Functional Outcomes of Sleep Questionnaire (FOSQ) (Weaver et al., 1997).

Following recruitment and baseline measures subjects underwent at-home eight channel PSG performed using an Embletta ×100 (Natus Medical Inc., USA) or Somte (Compumedics, Australia) portable sleep recorder administered in the participants home by a trained psychiatric registrar. PSG data were manually staged by a BRPT registered Sleep Technician supervised by a board registered sleep physician at the Adelaide Institute for Sleep Health (ASIH) using the 2007 AASM al- ternate criteria to obtain an Apnoea-Hypopnoea Index (AHI) (Iber et al., 2007).

Eight subjects had an AHI > 30 events/h and were considered to have severe OSA, all were offered and accepted CPAP titration. We targeted an AHI > 30 events/h because this severity of OSA has been associated with a higher risk of cardiovascular events. Five of the participants then underwent laboratory-based CPAP titration overnight with additional PSG recording and one underwent at-home APAP titration using a Respironics REMstar Auto System (Philips, Netherlands). One subject underwent at-home APAP titration at their request. One subject

failed CPAP titration due to discomfort in the laboratory setting and one developed nausea when using the mask. Both of these subjects declined at-home titration. The remaining six formed the cohort reported in this paper. These six subjects were provided with CPAP machines from the Adelaide Institute for Sleep Health and received routine clinical care from this service consisting of an initial physician review and a one-hour education session with a trained CPAP nurse. Ongoing care included physician follow up with an associated nurse review every three months and phone contact from the nurse between reviews.

The PSG data provided a range of sleep measures including AHI, mean apnoea/hypopnea duration, longest apnoea duration, number of desaturations < 90%, total sleep duration, sleep latency, duration of each stage of sleep, duration of slow wave sleep (SWS), total sleep time, duration of non-rapid eye movement (non-REM) and rapid eye movement (REM) sleep, sleep efficiency, number of arousals and REM latency.

Participants were followed up after six months of CPAP use using the same anthropometric, psychopathological, cognitive and sleep quality measures as at baseline.

CPAP usage was determined by analyzing subject specific CPAP telemetry recorded using Encore Anywhere (Philips, Netherlands) software. Recorded CPAP adherence data included mean daily CPAP usage, percentage usage of > 4 h, mean hourly usage on days used, average usage across all days, percentage of night with large leaks, average AHI and average snoring index.

2.3. Outcomes

The primary outcome was efficacy of CPAP treatment determined by changes in sleep architecture and AHI, and adherence to CPAP. Secondary outcomes were changes in

anthropometric measures, psychopathological measures, sleep quality measures and cognition at six-month follow-up.

2.4. Statistical methods

Statistical analyses were performed using SPSS 24 (IBM, New York). We present descriptive statistics including frequencies, means and standard deviations. No inferential statistics were performed due to the small sample size.

3. Results

104 subjects were approached for at-home PSG screening as part of the ASSET pilot study. 30 subjects were recruited and underwent baseline study measures of whom 8 were diagnosed with severe OSA. Reasons for declining participation in at-home PSG screening were not collected in these non-consenting patients. Eight subjects from the ASSET study with severe OSA (AHI > 30 events/h) were offered CPAP, six (5 male, 1 female) of whom successfully underwent CPAP titration and completed six months of treatment (see Fig. 1).

The sample was young and had high rates of obesity and hypertension. Mean age of the sample was 37.4 years (SD 12.3years), mean BMI was 45 (SD 9.6 range: 36.4–62.1), mean waist circumference was 137.4cm (SD 9.8cm range: 126cm–154cm), mean neck circumference was 47.7 cm (SD 4.5 cm, range: 44 cm–53 cm), and mean AHI was 76.8 (SD 45, range: 40.2–134.5).

3.1. CPAP acceptability and sleep architecture pre and post-CPAP introduction

Five CPAP titrations occurred in the laboratory setting, allowing PSG to be recorded throughout CPAP initiation. PSG measures of sleep architecture at baseline and after CPAP of the five subjects are presented in Table 1. At baseline the sample had extremely severe OSA with AHIs that ranged from 37.6–134.5 (mean 83.3), and associated disruption of normal sleep

architecture. The proportion of restorative SWS and REM sleep were reduced across the sample with mean time in SWS at baseline of 4.8% and mean time in REM of 4.1%. There was consistent improvement across these sleep domains with treatment, with REM sleep rebounding to 31.4% of the night and SWS 24% of the night.

3.2. CPAP adherence

CPAP usage was assessed using Philips Encore Anywhere software. This allowed determination of residual AHI with treatment, mask leakage, snoring, and percentage of the night CPAP was being used. Usage data for the first month is presented in Table 2, and usage data for the first six months of treatment is presented in Table 3. CPAP use of > 4 h per night is considered adequate adherence and is sufficient to substantially reverse levels of sleepiness (Weaver et al., 2007). In the six months of treatment the mean proportion of nights when CPAP was used for ≥4 h was 60%, and mean usage was 7.6 h/night, indicating adequate adherence. Mask leak and residual AHI are indicators of the effectiveness and proficiency with using CPAP. The average residual AHI across the first six months of treatment was 3.6events/h and percentage of the night in large leak 9.7%, indicating adequate treatment effect.

3.3. Physical health

Height, weight, body mass index (BMI), waist circumference (WC), and neck circumference (NC) before and during treatment are presented in Table 4, blood pressure and heart rate before and during treatment are presented in Table 5. The participants had high rates of obesity and hypertension (100%) for such a young sample after six months of CPAP treatment, with no other interventions, five participants lost weight and three no longer had hypertension.

3.4. Psychiatric symptom scales

Psychiatric symptom measures were recorded at baseline and after six months of CPAP therapy and are presented in Table 6. Higher scores on the PANSS indicates more severe psychosis, higher scores on the MADRS indicates more severe depression and higher scores on the PSP indicate better overall functioning. There were no observable changes in psychopathology scales in these participants. The baseline scores were below diagnostic and clinically significant ranges.

3.5. Sleep quality scales

Sleep quality measures were recorded at baseline and after six months of CPAP therapy and are presented in Table 7. Higher scores on the PSQI, FOSQ, ESS, ISI and RLS indicate worse sleep quality in those domains. Sleep quality and functional consequences of poor sleep did not consistently change with CPAP. Insomnia severity reduced consistently, but the threshold for clinical insomnia is a score of 15, and as such the baseline results were not within the diagnostic range for most participants.

3.6. Cognition

Cognition was recorded at baseline and after six months of CPAP therapy using the BACS, the results are presented in Table 8. At baseline the mean BACS total Z score was −1.47 and Verbal memory (short term memory) −1.89. CPAP demonstrated improvements across several domains including Verbal memory 0.55 and the overall change was 0.59 (SD 0.25).

4. Discussion

This pilot study demonstrates CPAP treatment is effective at normalizing sleep architecture disturbances in subjects with schizophrenia and comorbid severe OSA. Average measures of

CPAP use were adequate at one month and were sustained over a six-month follow-up period. Average daily usage stabilized between 5 and 6 h on average whilst percentage of days with usage > 4 h a night was maintained at or above 60% for the duration of follow-up. This latter criterion is the threshold for adequate CPAP adherence for clinical efficacy. CPAP adherence has not been investigated previously in schizophrenia, and our results indicate that this treatment is acceptable, and usage is sustained in the long term. After six months treatment, the AHI remained sup- pressed, indicating effective reversal of obstructive apnoea, and there was a reduction in time spent with mask leakage, indicating that subjects became more proficient at fitting their masks correctly.

Treatment with CPAP normalized sleep architecture with a rebound in REM sleep from an average of 4.1% to 31.4%, and a tripling of slow wave sleep. This may be important clinically as slow wave sleep is associated with rejuvenation and neuroendocrine homeostasis. Interestingly at follow-up after CPAP and in spite of substantial improvement in sleep architecture, there was little change in patient reported subjective sleep quality scales. There was a slight improvement in ISI scores, no change in FOSQ scores and a trend towards worsening of PSQI scores. A disconnect between objective functional outcomes and subjective impairment indicators have been previously noted in people with schizophrenia (Strassnig et al., 2018), our data similarly suggests subjective self-ratings are not an accurate reflection of objective sleep quality in people with schizophrenia.

Participants treated with CPAP had an average 7.3 kg weight loss at 6 months with an average 2.5 point reduction in BMI and an average 4.5 cm reduction in waist circumference. This is a novel finding that warrants further evaluation. Obesity is highly prevalent in people with schizophrenia and weight loss is difficult to achieve and maintain. All of our participants were taking clozapine, the most obesogenic anti- psychotic drug. In the general population, treatment

with CPAP is not associated with weight loss (Redenius et al., 2008). The loss of weight in our subjects may reflect improved vitality and an increase in physical activity; future studies should include objective measures of activity such as actigraphy to explore this possibility. In addition, restoration of normal oxygenation during sleep may be associated with a normalization of insulin resistance, which might advantageously influence macronutrient metabolism.

Hypertension also improved, with a mean reduction of 12.1 mm Hg in systolic blood pressure and 4.8 mm Hg in diastolic blood pressure. All six participants met criteria for hypertension at baseline, but only three met these criteria at six months. These changes are consistent with general population studies of CPAP treatment in OSA (Martínez-García et al., 2013). At baseline all of our participants met criteria for obesity, all had at-risk waist circumference, and all had hypertension. People with schizophrenia have much higher rates of metabolic syndrome than the general population (Galletly et al., 2012), and our findings indicate improvement in some of the components of metabolic syndrome.

Our subjects were relatively young (mean age 37.4 years, range 26 to 57). The early onset of obesity and metabolic disturbances in people with schizophrenia has been documented previously (Foley et al., 2013; Galletly et al., 2012). Our findings emphasize that OSA, like obesity and metabolic syndrome, can occur early in this population. Young people with the risk factors for OSA (obesity, elevated waist and neck circumference, smoking, alcohol abuse, sedating medications) should be screened using an objective measure such as home PSG, as they may well have undiagnosed OSA.

OSA is associated with cognitive deficits, particularly: attention, vigilance, short term/working memory, executive functioning and motor functioning. People with normal or low baseline cognitive function are more vulnerable to the cognitive deficits of OSA, and these deficits have been found to normalize with CPAP treatment (Barnes et al., 2004; Matthews and Aloia, 2011;

Pan et al., 2015). The mechanisms underlying the cognitive deficits caused by OSA are poorly understood but may be explained to some degree by sleep fragmentation, sleep deprivation, hypoxia, chronic inflammation and cerebellar vascular damage. CPAP treatment improves performance across multiple cognitive domains (Pan et al., 2015) resulting in improved functional and occupational outcomes in the general population (Tregear et al., 2010). Translation of this benefit to people with schizophrenia and comorbid OSA would be an innovative means of modifying cognitive symptoms and real-world functional outcomes: currently an area of unmet clinical need. Our pilot results indicate that treatment of severe OSA with CPAP improves cognition in people with schizophrenia. Cognitive function improved with an average overall Z score improvement on the BACS of 0.59. Cognitive impairment is a major determinant of functional outcome in Schizophrenia (Green et al., 2000) and has been identified as a crucial target for treatment (MATRICS) (Green et al., 2004) but, as with obesity, achieving meaningful change has been difficult.

This study provides proof of concept that treatment of OSA with CPAP is feasible in people with schizophrenia and offers insight into the novel benefits treatment may have on sleep quality, cardiometabolic outcomes and cognition in this population. The diagnostic measures and treatment interventions undertaken in this study are standard practice, not investigational and importantly are broadly available and easily accessible in most public health services. We have demonstrated that the investigation and treatment of OSA is well tolerated and acceptable in a population of subjects with serious mental illness, thus indicating that stable schizophrenia itself is neither a barrier to effective treatment nor an excuse for clinical apathy when a sleep disorder is suspected. Furthermore, highly powered randomized trials should be performed in the future to determine whether CPAP treatment of OSA comorbid with schizophrenia has a clinically relevant effect on cognitive and psychopathological symptoms.

4.1. Limitations

Whilst our results are important and encouraging, several limitations to our study should be acknowledged. Firstly, the small numbers and observational nature of the study do not allow causal inferences to be made from the follow-up data presented and are hypothesis generating only. Similarly, the absence of a control group makes it difficult to determine whether changes in cognition are independently associated with CPAP treatment, further controlled studies are required to validate our results. Measures of fasting blood sugar, cholesterol and triglycerides, and insulin resistance were not recorded and should be included in future studies of CPAP treatment of OSA in schizophrenia. Secondly, whilst our data does support the acceptability of PSG and CPAP these results may not be broadly generalisable to typical populations of people with psychotic ill- ness. Whilst consecutive recruitment was undertaken, subjects refusing to participate in screening for OSA may have introduced selection bias where those less likely to adhere to CPAP were self-excluded from screening. Recruitment was also from a clozapine clinic, potentially representing a population where psychotic symptoms may be better controlled and thus adherence to treatment more likely. Similarly, universal clozapine exposure may have biased results in our cohort as the effect of clozapine on sleep architecture is poorly understood. Clozapine is highly sedating and may confound interpretation of objective daytime sleepiness measures that have been validated in general populations. Thirdly, the study interventions and follow-up may have introduced bias in that subjects may have felt more encouraged to participate and adhere to treatment. We consider this unlikely however as the majority of the study was undertaken using pre-existing sleep services and standard follow-up.

5. Conclusion

People with schizophrenia commonly suffer lifetime disability due to severe, chronic functional impairment. Our pilot data indicates that effective treatment of OSA with CPAP

therapy is achievable and well tolerated in people with schizophrenia and may improve cognition, sleep architecture and cardiometabolic measures, including blood pressure and weight. There is no previous published literature on the cognitive and physical outcomes before and after CPAP. Further re- search such as a randomized controlled trial of CPAP in people with schizophrenia and OSA, to determine whether CPAP leads to cognitive enhancement, improves functional outcomes and reduces cardiovascular disease (CVD) risk factors would be beneficial.

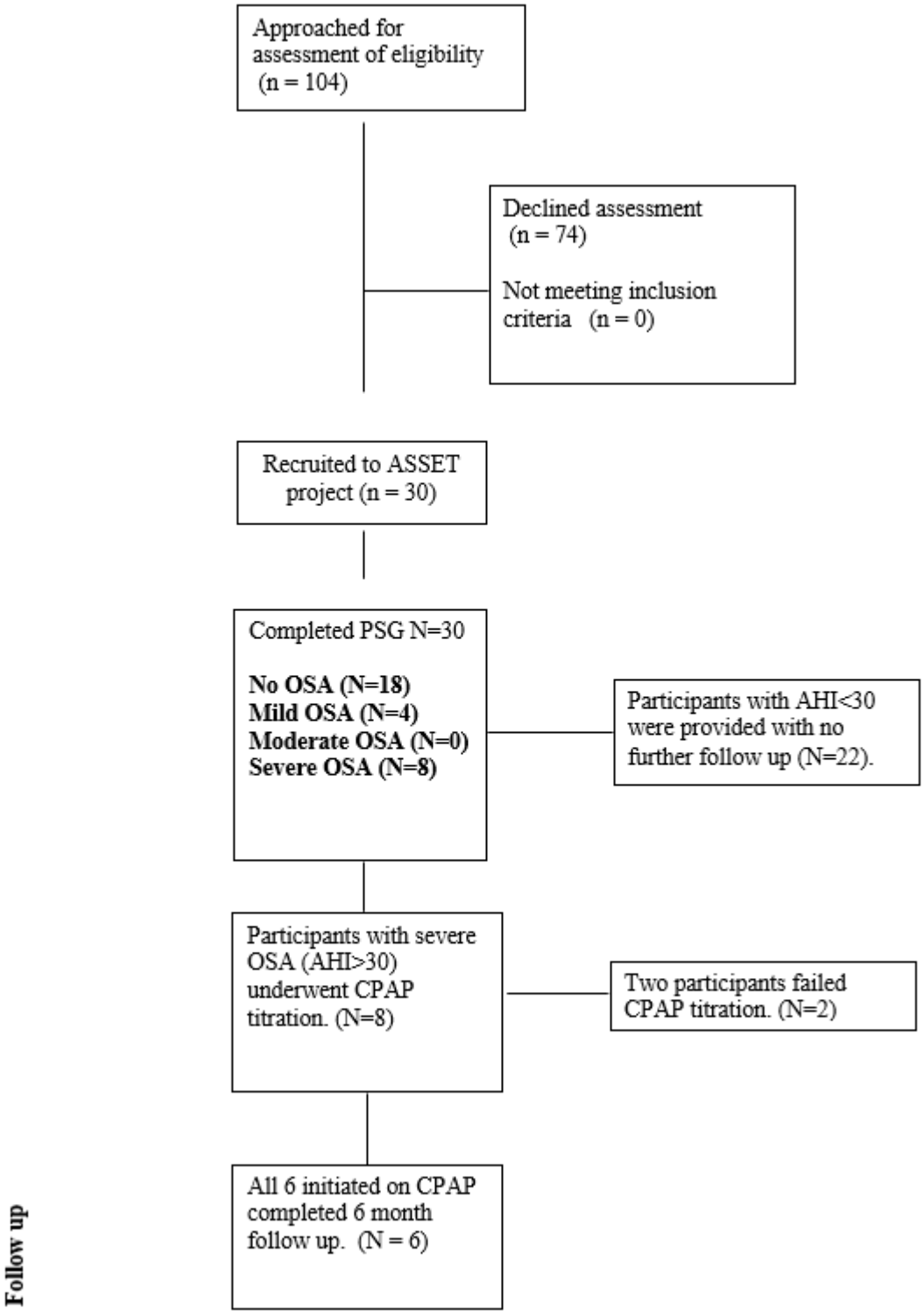

Figure 1: Consort diagram

Table 1: Sleep Architecture at baseline and immediately after CPAP initiation

	AHI		% Non-REM (stage 1&2 plus SWS)		% Slow wave sleep (SWS)		% REM sleep	
ID	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP
1	73.4	1.1	97.6	84.6	4	20.4	2.4	15.4
2	130.7	7.9	98.8	66.5	.2	21.6	1.2	33.5
3	134.5	3.7	98.9	54.7	7.9	32.8	1.1	45.3
4	37.6	4.4	84.4	76.6	12.1	17.5	15.6	23.4
5	40.2	10.7	100	60.7	0	28.1	0	39.3
Mean (SD)	83.3 (47.2)	5.5 (3.7)	95.94 (6.5)	68.62 (12)	4.8 (5.2)	24 (6.2)	4.1 (6.5)	31.4 (12)

Table 2: CPAP usage during the first month of treatment

	Days used	Percentage of days ≥4 hr	Average usage in hours on days used	Average usage in hours on all days	Average % of the night in large leak	Average AHI
1	24	61.3	6.1	4.7	.3	2.2
2	19	35.5	4.4	2.8	1.4	8.5
3	30	96.8	9.2	8.9	4.4	4.8
4	29	84.4	7.75	7	21.7	1.7
5	14	37.5	9.5	4	6.7	4.4
6	29	80.6	8.75	8.15	35.2	7.3
Mean (SD)	24 days (6.5 days)	66% (25%)	7.6hrs (2hrs)	5.9hrs (2.4hrs)	11.6% (14%)	4.8 (2.7)

Abbreviations: Apnoea-Hypopnoea Index (AHI).

Table 3: CPAP usage during the first six months of treatment

	Days used	Percentage of days ≥4 hr	Average usage in hours on days used	Average usage in hours on all days	Average % of the night in large leak	Average AHI
1	148	67	6.85	5.5	1.7	1.6
2	115	39.6	5.2	3.3	3.9	6.8
3	177	89	8.7	8.5	6.8	1.9
4	109	53.5	7.5	4.5	11.8	1.5
5	72	34.6	8.8	3.5	8.4	2.7
6	158	78.3	8.75	7.5	26	7.3
Mean (SD)	130days (38days)	60.3% (21.5%)	7.6hrs (1.4hrs)	5.4hrs (2.1hrs)	9.7% (8.7%)	3.6 (2.7)

Abbreviations: Apnoea-Hypopnoea Index (AHI).

Table 4: Weight, BMI, WC and NC changes after 6 months treatment with CPAP

ID	Age	Height	Weight		BMI		WC		NC	
			Baseline	CPAP	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP
1	26	176	192.5	183.3	62.14	59.79	154	151	53	missing
2	40	170	136	125.3	47	43.01	135	133	53	46
3	30	175	142.4	121.3	46.5	39.61	139.5	134	43	missing
4	45	181	133.2	126	40.69	38	140	124	45	43
5	26	186	125.8	131	36.4	37.86	130	134	44	44
6	57	158	92.6	92	36.86	36	126	120	48	46
Mean (SD)			137.1(32.3)	129.8 (29.7)	44.9 (9.5)	42.4 (8.9)	137.4 (9.7)	137.2 (10.7)	47.5 (4)	44.6 (1.5)
Mean Change (SD)			-7.3 (8.9)		-2.55 (2.8)		-4.7 (6.5) N=5		-2.75 (3.0) N=4	

Abbreviations: Continuous Positive Airway Pressure (CPAP), Body Mass Index (BMI), Waist Circumference (WC), Neck Circumference (NC).

Table 5: Blood pressure and HR changes after 6 months treatment with CPAP

ID	Systolic BP		Diastolic BP		Hypertension* Y v N		Heart rate	
	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP
1	139	145	75	88	Y	Y	95	106
2	127	121	88	87	Y	Y	88	93
3	134	109	79	74	Y	N	102	82
4	153	120	92	84	Y	N	90	92
5	133	143	92	80	Y	Y	116	102
6	154	129	97	81	Y	N	112	90
Mean (SD)	140 (11.1)	127.8 (14.1)	87.2 (8.5)	82.3 (5.2)	50% reduction in hypertension		100.5 (11.6)	94.2 (8.6)
Mean change (SD)	-12.1 (18)		-4.8 (10.2)				-6.3 (14)	

* Hypertension was diagnosed if the person had a systolic blood pressure ≥ 130 mmHg and/or a diastolic pressure ≥ 85 mmHg.

Table 6: Psychiatric symptom scales before and after 6 months treatment with CPAP

	PANSS		MADRS		PSP	
ID	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP
1	73	62	4	Missing	49	60
2	42	54	2	2	72	60
3	86	92	12	4	33	37
4	43	57	0	3	60	61
5	63	67	6	10	60	60
6	54	52	4	0	60	50
Mean	60.2 (17.4)	64 (14.8)	4.8 (4.6)	3.8 (3.8)	55.6 (13.3)	54.7 (9.6)
Mean change (SD)	3.8 (9.3)		-1.0 (5.0)		-1.0 (8.7)	

Abbreviations: Positive and Negative Symptom Scale (PANSS), Montgomery Aspergers Depression Rating Scale (MADRS), Personal and Social Performance Scale (PSP), Continuous Positive Airway Pressure (CPAP).

Table 7: Sleep Quality measures before and after six months of CPAP

ID	PSQI		FOSQ		ISI		RLS		ESS	
	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP
1	7	11	30	35	11	6	7	0	4	4
2	7	8	39	31	7	1	0	0	9	10
3	4	4	19	27	16	7	11	14	11	3
4	5	4	36	39	5	1	8	5	2	5
5	8	6	31	32	12	8	0	12	3	5
6	3	2	35	31	7	1	0	0	-	-
Mean	5.7	5.8	31.7	32.5	9.7	4	4.3	5.2	5.8 (4)	5.4 (2.7)
Mean Change (SD)	0.16 (2.1)		0.83 (5.91)		-5.6 (1.86)		0.83 (6.43)		-0.4 (3.5)	

Abbreviations: Pittsburgh Sleep Quality Index (PSQI), Functional Outcomes of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), Restless Leg Scale (RLS), Epworth Sleepiness Scale (ESS).

Table 8: Brief Assessment of Cognition for Schizophrenia (BACS)

	VM		DIGI		TMT		Fluency		SC		TL		Total	
	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP	Baseline	CPAP
1	-2.35	-1.63	-0.81	-2.08	-2.24	-0.52	1.05	0.55	0.03	0.34	0.07	0.07	-1.06	-0.81
2	-1.31	-0.38	0.46	1.22	-0.52	-0.38	-0.35	0.22	0.74	0.34	0.35	0.62	-0.16	0.41
3	-3.50	-2.46	-3.59	-2.58	-1.57	-0.38	-2.16	-2.33	-2.52	-2.2	-1.31	-1.03	-3.64	-2.73
4	-0.69	0.66	-0.56	0.71	-1.18	-1.18	-0.19	0.22	-0.45	-0.29	1.17	1.45	-0.47	0.39
5	-2.25	-2.35	-1.57	-0.05	-0.12	-0.38	-1.83	-1.5	-1.33	-0.69	-0.48	-0.75	-1.88	-1.43
6	-1.21	-1.83	-1.82	-0.81	0.01	1.2	-0.52	-0.68	-1.4	-0.85	-1.58	-1.58	-1.62	-1.13
Mean	-1.89	-1.33	-1.32	-0.6	-0.93	-0.27	-0.67	-0.59	-0.82	-0.56	-0.3	-0.2	-1.47	-0.88
Mean change (SD)	0.55 (0.75)		0.71 (1)		0.66 (0.8)		0.085 (0.41)		0.15(0.37)		0.09 (0.23)		0.59 (0.25)	

Abbreviations: verbal memory (VM), digit sequencing (DIGI), token motor task (TMT), verbal fluency (fluency), symbol coding (SC), Tower of London (TL).

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Chapter 7: Summary of research findings, discussion and concluding remarks

Overview of thesis aims

The aim of this thesis is to explore the relationship between schizophrenia and OSA to develop a translatable evidence base for improved clinical detection and treatment. This broad objective aligns with contemporary research efforts to improve the management of modifiable physical ill-health in people with major mental illness but is novel in the sense that prior to this thesis there was a dearth of evidence reporting on OSA comorbid with schizophrenia. This thesis was led by the following research questions:

1. How prevalent is OSA in schizophrenia and is prevalence higher than in the general population?
2. Is OSA comorbid with schizophrenia associated with poorer psychiatric, physical health and quality of life outcomes, compared to people with schizophrenia who do not have OSA?
3. What risk factors or diagnostic tools are reliable for the clinical detection of OSA in people with schizophrenia?
4. Is treatment for OSA tolerable and does it improve physical health and psychiatric outcomes in people with schizophrenia?

The narrative arc of this thesis was firstly to report observational data on prevalence and clinical predictors of OSA in a cohort of people with schizophrenia and subsequently to prospectively determine whether CPAP treatment of diagnosed OSA is undertaken as prescribed and results in improvement in physical health, psychiatric and cognitive outcomes. The specific aims were to:

1. Determine the prevalence of OSA using diagnostic PSG in an unselected psychiatrically stable, community dwelling cohort of people with treatment resistant schizophrenia, who were prescribed clozapine.
2. Determine whether prevalence of OSA in this cohort is higher than a general population matched control cohort.
3. Undertake exploratory analysis to determine whether or not OSA in people with schizophrenia is associated with physical health outcomes, psychiatric symptom severity, cognitive function, medication use and quality of life measures.
4. Prospectively determine whether common sleep symptom scores and diagnostic screening tools developed for detection of OSA in general populations are accurate in people with schizophrenia.
5. Determine if treatment of OSA comorbid with schizophrenia is undertaken as prescribed and whether it is associated with improvement in physical health, psychiatric disease and cognitive outcomes.

Summary of research findings

Paper 1

Beginning this thesis with a systematic review allowed me to examine existing literature to determine what is already known in regard to my aims and to highlight clinically important deficiencies in the literature to explore in subsequent chapters. The review included studies that reported the prevalence of OSA in cohorts of people with schizophrenia and related disorders. Examining these studies allowed me to establish a putative baseline prevalence estimate of OSA in cohorts with schizophrenia and, in those studies reporting applicable clinical data, to determine whether specific physical health or psychiatric measures might assist as a means of clinical identification.

Unfortunately the included literature was heterogeneous and included samples that varied substantially in age, degree of obesity, psychiatric disease stability and diagnostic measures of OSA such that no single study was broadly generalizable. Importantly some studies were likely to have bias towards a higher prevalence of OSA because of convenience sampling of older patients or those referred for PSG because of clinical suspicion of OSA; whilst other studies may have been biased to lower rates because of low rates of obesity in the cohort which is not typical of people with schizophrenia generally. Regardless, this review found rates of OSA between 13.5 – 57.1%, which indicates that OSA is likely to be highly prevalent in people with schizophrenia. Only one study reported OSA prevalence in comparison to a general population control group and did not demonstrate a significant excess of OSA, however this result was likely to have been influenced by non-standard diagnostic measures and a very low BMI in the schizophrenia and control cohort.

Increased age, BMI >25, male sex and neck circumference were the factors reported to be associated with a diagnosis of OSA across the studies. However, there was a lack of data reporting other clinical predictors or whether OSA diagnostic screening tools were valid in these cohorts. Importantly mean ESS and PSQI scores were low in people with schizophrenia and comorbid OSA in one study, indicating that sleep symptoms and daytime somnolence are less likely to be reported in this population. As such the clinical recommendations made in this paper emphasised the importance of anthropometric parameters and age and de-emphasised sleep symptom severity in identifying those patients suitable for further evaluation with PSG. At the time, this paper was the only published paper to report clinical guidelines for detection of OSA in people with schizophrenia. Outside of these findings, this paper did not provide any information on the physical health and psychiatric associations with a diagnosis of OSA nor did it provide information on treatment of OSA in schizophrenia. These deficits in knowledge provided justification for the subsequent chapters of this thesis.

Paper 2

This paper addressed whether symptoms of OSA were associated with physical health, psychiatric and quality of life outcomes in a large representative sample of people with schizophrenia. Whilst prior studies have reported prevalence of general sleep disturbance in schizophrenia (Serretti et al., 2004; Sweetwood et al., 1976), this paper is the first to report on sleep disturbances characteristic of OSA, and how these disturbances correlated with other clinical outcomes. In this sample sleep disturbance was common with 41.9% of people reporting snoring and 17.4% of people reporting respiratory pausing during sleep, making it likely that undiagnosed OSA was highly prevalent in this cohort, especially in those that reported pausing. This finding is perhaps unsurprising given that approximately 47% of the cohort were overweight or obese, putting them at especially high risk of OSA.

Univariate exploratory analysis indicated that a number of adverse outcomes were associated with snoring and pausing. Salient positive findings included reduced odds of employment or study, increased odds of diagnosed cardiovascular disease, reduced odds of engaging in physical activity and, lower mean quality of life, independent living and psychological wellbeing scores. A multivariate logistic regression model adjusting for male sex, age and BMI indicated that history of cardiovascular disease and excessive alcohol consumption remained predictive of snoring and pausing. These findings support the hypothesis that OSA is a potentially modifiable cardiovascular risk factor in people with schizophrenia. Furthermore, the higher rate of unemployment and significant impairments in independent living and psychological wellbeing suggest that sleep disturbance may drive decrements in social participation and engagement in people with schizophrenia. As such these outcomes may also be modifiable with treatment of underlying co-morbid OSA. The caveat to these inferences is that this paper does not provide evidence of causal association; any presumed benefit from treatment of OSA requires prospective validation. Interestingly this paper was unable to

demonstrate an association between OSA symptoms and prescription of atypical antipsychotic drugs on univariate analysis. Comparative literature has not consistently reported an association between antipsychotic use and diagnosis of OSA (Rishi et al., 2010; Shirani et al., 2011) and unfortunately this paper does not provide any definitive evidence as to whether an association exists. The obesogenic potential of some of these drugs may plausibly increase the risk of OSA in people with schizophrenia, however further evidence using multivariate analysis controlling for BMI and other traditional risk factors is required to more definitively evaluate this possible association.

Overall this paper indicates that sleep disturbances typical of OSA are prevalent in schizophrenia and are associated with increased risk of cardiovascular disease and adverse socio-occupational and lifestyle outcomes. Whilst not demonstrating causality these findings further support the hypothesis that treatment of co-morbid OSA in schizophrenia may improve these outcomes.

Paper 3

The matched cohort study reported in this paper investigated whether the prevalence of OSA in people with schizophrenia is significantly higher than in the general population. The design allowed for multivariate analysis of factors predictive of a diagnosis of OSA. The cohorts were comprised of unselected groups screened for OSA using PSG: the first dataset (ASSET study) reported on a cohort of people with schizophrenia and the second dataset (MAILES study) a general population control group. The control group was comprised entirely of males and as such analyses were restricted to males only.

This paper demonstrated that men with schizophrenia had significantly higher rates of OSA than the general population, with an approximately two-fold increase in risk. On multivariate analysis this relative risk became non-significant when adjusting for age and BMI. These

results confirmed my hypotheses that OSA is more prevalent in people with schizophrenia and that this risk is primarily driven by obesity (given the significantly lower mean age of the schizophrenia cohort). This is the first study to demonstrate an increased relative risk of OSA in people with schizophrenia and foregrounds the importance of improving detection in this population. Furthermore, the adjusted analysis provides robust evidence that this increase in risk is largely drive by obesity and as such argues against a specific antipsychotic medication associated risk factor beyond their obesogenic potential.

Paper 4

This paper reported the main results of the ASSET study which consecutively screened people with schizophrenia for OSA using PSG. It reported on 30 subjects with schizophrenia prescribed clozapine and is the first study in the literature to report the prevalence of OSA in an otherwise unselected psychiatrically stable cohort. The methods of this paper allowed for reporting of the prevalence of OSA, exploratory univariate analysis of factors associated with diagnosis of OSA and prospective evaluation of sleep symptom scores and OSA diagnostic tools.

This paper indicated that OSA was highly prevalent in the cohort, occurring at a rate of 40% for any severity (AHI >10) and 27% for severe OSA (AHI >30). Similar to the results of paper 3 anthropometric measures of elevated BMI, waist circumference and neck circumference were all significantly associated with diagnosis of OSA. Salient negative findings included no significant difference in mean dose of clozapine, mean scores on PANSS and MADRS, total Personal and Social Performance (PSP) scores and BACS total scores between those with and without a diagnosis of OSA. Analysis of sleep symptom scales indicated that there was no mean difference in mean ESS, PSQI or Insomnia Severity Index (ISI) between those with and without OSA. As a corollary a large proportion of the entire cohort had ESS (93%), PSQI

(63%) and ISI (83%) scores within the normal population range and none of the three symptom scales had a significant correlation with AHI. Similarly, the two diagnostic scoring tools assessed in this paper (OSA50 and STOP-BANG) were poorly discriminative for diagnosis of OSA in this cohort. Sensitivity and specificity for OSA50 was 50% and 61% respectively and for STOP-BANG 92% and 28% respectively. ROC curves also demonstrated low to moderate discriminatory value for the OSA50 (AUC=0.62) and STOP-BANG (AUC=0.77).

In sum these findings confirm a high rate of OSA in people with schizophrenia and indicate that diagnosis is strongly associated with anthropometric factors. We were unable to detect an association with psychosis symptom severity (PANSS), depressive symptomatology (MADRS), social functioning (PSP) and cognitive decrements (BACS), which refutes the hypothesis that OSA compounds these negative outcomes of schizophrenia. Importantly, this paper demonstrates that sleep symptom scores are unreliable in people with schizophrenia and should not be used for identification of at-risk patients at the clinical level. It is interesting to note that the majority of people diagnosed with OSA in this cohort had ESS and PSQI scores within the normal population range which is indicative of how unreliable these tools are at identifying self-reported sleep pathology in people with schizophrenia. Similarly, this study indicates that general population OSA screening tools perform poorly in people with schizophrenia. Whilst the STOP-BANG was marginally superior to the OSA50 because of a better sensitivity, neither tool was sufficiently accurate to be recommended for clinical use in this population.

Paper 5

The final paper of this thesis was an extension of paper 4 reporting a small prospective single-arm intervention trial of CPAP treatment in subjects of the ASSET trial who were diagnosed with severe OSA (AHI >30). This paper addressed the final aim the thesis, namely whether

CPAP treatment was effective at treating OSA and to prospectively determine whether treatment was associated with improvement in physical health, psychiatric and cognitive outcomes. Eight subjects of the ASSET trial were eligible for inclusion. Six underwent successful CPAP titration and completed six months of treatment and had follow-up measures performed. To our knowledge this is the first CPAP intervention trial in people with schizophrenia co-morbid with OSA.

This paper indicated that CPAP treatment was effective at normalising AHI in all participants and improving sleep architecture with substantial rebound REM sleep and tripling of SWS observed across the cohort. Importantly, adherence to CPAP treatment was good with four of the six participants utilising CPAP for >4 hours per night. Mean usage per night across the entire group of 5.9 hours which is consistent with adequate usage for treatment effect (Weaver et al., 2007). Interestingly we did not observe change in subjective sleep quality scores (as measured by ESS and PSQI), despite objective improvements in AHI and sleep architecture. This observation confirms that for people with schizophrenia, subjective self-ratings are not useful in measuring or monitoring symptoms of sleep disturbance.

In regard to physical health outcomes CPAP treatment at six months was associated with mean weight loss of 7.3kg which was an unexpected finding given that OSA treatment in general populations is usually associated with modest weight increase (Redenius et al., 2008). CPAP treatment was also associated with modest improvement in mean systolic blood pressure and effectively reversed a diagnosis of hypertension in three participants. This finding is consistent with CPAP treatment effect in general populations (Martinez-Garcia et al., 2013). Consistent with the results of paper 4, we were unable to detect change in PANSS, MADRS or PSP scores with CPAP treatment which was probably a reflection of these scores being below the diagnostic range at baseline in all participants. Importantly, we were able to demonstrate an

improvement in cognition at follow-up with mean change in BACS total Z-score of 0.59, which supports our hypothesis that comorbid OSA is a modifiable cause of cognitive decrements in people with schizophrenia. Despite the small sample size, this paper provides a proof-of-concept that CPAP treatment is feasible and effective in people with schizophrenia and is likely to have novel benefits in terms of cardiometabolic and cognitive outcomes.

Theoretical implications of main findings and future directions

The five papers presented in this thesis substantially expand and improve on literature describing the relationship between, outcomes of and treatment for OSA comorbid with schizophrenia. More broadly this thesis also contributes incremental evidence to improve the physical health and cognitive outcomes of people with schizophrenia, which is the overarching aim of this work. Taken together the data in this thesis demonstrates clearly that OSA is highly prevalent in schizophrenia, is likely to be poorly recognised using general population screening/symptom tools and is associated with adverse physical health outcomes. Perhaps of more importance and novelty, however, is that this thesis provides preliminary evidence that people with schizophrenia undertook CPAP when it was prescribed, and that CPAP was effective at normalising objective measures of sleep disturbance and architecture and is associated with positive physical health and cognitive outcomes. The implications of these findings are services should consider incorporating OSA screening into routine physical health assessments in people with schizophrenia; further research is required to develop robust clinical tools for accurate identification of OSA; and treatment with CPAP should be undertaken in people with OSA comorbid with schizophrenia because it may result in positive clinical outcomes.

In regard to the first two aims of this thesis, the results presented here confirm that OSA is highly prevalent in schizophrenia occurring at a rate of approximately 40% which is double

that seen in general male populations. This result falls within the higher range of estimated prevalence in the systematic review presented in chapter 2. Furthermore, this result is likely to be more robust and generalisable to typical populations of people with schizophrenia than previous literature, because of the unselected recruitment method that avoids the demographic biases inherent in previous studies. The high risk of OSA in people with schizophrenia, the fact that no subjects in the ASSET trial had been previously assessed for OSA and the poor correlation of sleep symptoms with diagnosis confirm that OSA is under-diagnosed in schizophrenia. One important implication is that screening for OSA should be incorporated into routine physical health assessment for people with schizophrenia. Importantly, the results of this thesis have been incorporated into updated clinical practice guidelines for schizophrenia that have been published during my doctoral candidature (Galletly et al., 2016) which indicates the impact my research has had.

Because OSA is prevalent in schizophrenia the elucidation of clinical associations is important to identify predictors to enhance diagnosis of OSA at the clinical level. This thesis demonstrates that obesity is the main contributing factor to risk of OSA which is perhaps unsurprising given the excess rates of obesity in people with schizophrenia compared to the general population and because obesity is the strongest predictor of OSA generally. Of potentially more importance, however, are the negative findings of this thesis. Paper 2 indicated that prescription of atypical antipsychotic drugs was not associated with symptoms of OSA; paper 3 found that relative risk of OSA in people with schizophrenia became non-significant when controlling for age and BMI arguing against atypical antipsychotic medications (as a drug class) as an independent predictor of OSA; and paper 4 did not demonstrate an association between mean dose of clozapine and diagnosis of OSA. These results indicate that antipsychotic drugs are unlikely to play an aetiological role in OSA independent of their obesogenic effect. This thesis also demonstrates that common sleep symptom scores (ESS and

PSQI) and OSA diagnostic tools (OSA50 and STOP-BANG) perform poorly in people with schizophrenia. This may be because people with schizophrenia are unaware of subjective sleep disturbance, do not participate in activities queried in these questionnaires and lack a partner to report observed snoring during the night or tiredness during the day. As such, an important finding of this thesis is that these general population tools should generally be avoided for stratifying risk of OSA at the clinical level. Future research is required in larger cohorts to develop and validate population-specific tools which reliably identify those at risk of OSA in whom further diagnostic testing is warranted.

Clinical outcomes associated with OSA were also explored in this thesis to identify adverse outcomes that may be amenable to treatment. Paper 2 indicated that symptoms of OSA were associated with reduced odds of employment, lower mean quality of life and psychological wellbeing scores and increased odds of cardiovascular disease. Although self-reported sleep symptoms and daytime somnolence are low in people with schizophrenia, it is possible that these adverse psychosocial outcomes are driven by sleep disruption intrinsic to OSA that may go unrecognised by patients or clinicians. The significance of increased odds of cardiovascular disease is difficult to interpret because of the shared risk factor of obesity. It is plausible however, that OSA may exacerbate insulin resistance and hypertension in some people and exacerbate the risk of developing cardiovascular disease. This thesis was not able to validate the hypothesis that OSA is associated with adverse psychiatric outcomes in schizophrenia. Paper 4 did not demonstrate any significant difference in mean PANSS, MADRS or PSP scores in people diagnosed with OSA and those who were not. These findings suggest that OSA does not directly exacerbate psychopathology intrinsic to schizophrenia, however further research in larger cohorts is required to definitively explore this possibility.

The final and perhaps most important part of this thesis was demonstrating that CPAP treatment of OSA is effective in people with schizophrenia. The single arm intervention trial presented in paper 5 demonstrated that CPAP titrations were achievable and that adherence to CPAP treatment was adequate to achieve therapeutic efficacy in the majority of participants. Effects of CPAP treatment at six-month follow-up included significant weight loss, improvement in systolic blood pressure and improvement in cognitive scores. These findings suggest treatment of OSA comorbid with schizophrenia should be a priority in improving both physical health and cognitive outcomes in people with schizophrenia. Due to the small sample size these results can only be considered hypothesis generating and as such further randomised trials with larger numbers are required to definitively confirm these exciting early findings.

Limitations

Whilst this thesis fills substantial gaps in existing research, there are a number of limitations inherent to the experiments reported here that warrant consideration. Firstly, although the dataset reported in paper 2 was large, it utilised OSA specific sleep symptoms as the dependent variable to explore possible associations with putative diagnosis of OSA. As previously discussed and as shown by our prospective validation of the PSQI and ESS, self-reported sleep symptom scores are likely to perform poorly in people with schizophrenia. This is particularly true for witnessed apnoeas during sleep as most people in this cohort lacked a bed partner who could have observed this symptom. As such this experiment may have misclassified a proportion of subjects as not having OSA because of unrecognised symptoms and biased the reported associations. Furthermore, whilst this paper did identify significant associations between OSA symptoms and adverse outcomes, these may have been confounded by other co-occurring factors such as obesity, physical health comorbidity and smoking which may explain part of these findings.

In regard to paper 3, the main limitation of our findings is that the results are only applicable to men due to the lack of female general population controls. There is evidence of substantial difference in sex-specific risk factors for OSA [9] and as such it is possible that the association we observed for men does not hold true for women. More generally this experiment is also limited by the small sample size of the schizophrenia cohort which precluded powered analysis of other OSA risk factors.

Whilst the experiment reported in paper 4 is the first to report OSA prevalence using diagnostic measures in a psychiatrically stable cohort of people with schizophrenia, it is limited by recruitment factors that may impact on the generalisability of our results. Firstly, all subjects included in this experiment were prescribed clozapine. Because clozapine is the most obesogenic antipsychotic drug it is plausible that our estimate of prevalence is an overestimate in comparison to non-clozapine populations who may be less obese. In addition it is possible that clozapine may be an independent risk factor for OSA because of its sedative qualities or possible effect on reducing sensitivity to hypoxaemic drive during sleep. Whilst we were not able to demonstrate any significant difference in mean dose of clozapine in people with OSA, this does not preclude clozapine as confounding factor in our prevalence estimate. Clozapine is also the most effective agent for treatment refractory schizophrenia and it is possible the cohort analysed in this experiment are more psychiatrically stable than more general populations of people with schizophrenia. As such our reported success with PSG and CPAP compliance may not be generalizable to less psychiatrically stable populations.

Finally, the main limitation of paper 5 is the small sample size of participants undertaking CPAP and the single arm nature of the intervention. Whilst this case series does report exciting results it can only be considered hypothesis generating. Further randomised intervention trials with larger cohorts are required to definitively confirm our findings.

Conclusion

This thesis expands broadly on previous literate and provides novel insights into the relationship between OSA and schizophrenia. Our results indicate that OSA is highly prevalent in schizophrenia, is driven mainly by excess rates of obesity in this population and is associated with poor physical health outcomes, reduced quality of life and poorer psychological wellbeing. Detection and treatment of OSA should be incorporated into the routine physical healthcare of people with schizophrenia and our results go some way to providing practical evidence to develop screening tools. Importantly this thesis indicates that CPAP treatment of OSA in people with schizophrenia may be beneficial in facilitating weight loss, improving blood pressure control and ameliorating cognitive impairment in this population.

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Appendix 1: Original systematic review submission

Obstructive sleep apnoea and schizophrenia; a systematic review to inform clinical practice

Obstructive sleep apnoea and schizophrenia; a systematic review to inform clinical practice

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Abstract

Background: Many risk factors for obstructive sleep apnoea (OSA) are commonly found in people with schizophrenia. Identification and treatment of OSA may improve physical health in this population; however there are no guidelines to inform screening and management.

Objectives: Systematic review to determine, in people with schizophrenia and related disorders, (1) the prevalence of OSA; (2) the physical and psychiatric correlates of OSA; (3) the health impact of treatment of OSA in terms of measures of psychiatric and physical health, and quality of life; (4) the diagnostic validity of standard OSA screening tools.

Data Sources: Medline, EMBASE, ISI Web of Science and PsycINFO electronic databases were searched. Cohort, case-control or cross-sectional studies or RCTs reporting on prevalence of OSA in subjects with schizophrenia and related disorders were reviewed.

Results: The prevalence of OSA varied between 13.5% and 52%. Diagnosis of OSA was associated with larger neck circumference, BMI >25, male sex and older age. There were no data on physical or psychiatric outcomes following treatment of OSA. Diagnostic applicability of screening tools for OSA was not investigated.

Conclusion: OSA is prevalent in people with schizophrenia and related disorders, and is potentially under-recognised. Further research is required to determine utility of OSA screening tools, the relationships between antipsychotic medications and OSA and the benefits of treating OSA. We propose a strategy for the identification of OSA in people with schizophrenia and related disorders.

Keywords: schizophrenia, psychosis, obstructive sleep apnoea, and systematic review

1. Introduction

Schizophrenia is a chronic psychotic disease with peak onset in adolescence and early adulthood. Whilst negative symptoms, psychotic relapses and chronic socio-occupational impairment are common, cardiovascular disease is recognised as the primary cause of morbidity and mortality in this population and is responsible for a 16-18 year reduction in life-expectancy (Laursen, 2011). Obstructive sleep apnoea (OSA) is independently associated with heightened risk of hypertension, diabetes, stroke, heart failure and cardiovascular disease, thus comorbid OSA may be an additive and modifiable risk factor for cardiovascular disease in people with schizophrenia (Epstein et al., 2009).

OSA is likely to be prevalent in people with schizophrenia given the high rates of obesity, metabolic syndrome (Galletly et al., 2012; Mitchell et al., 2013), tobacco smoking (Myles et al., 2012), alcohol consumption (Moore et al., 2012), and sedative medication use, all of which are recognised risk factors in the general population (Al Lawati et al., 2009; Galletly et al., 2012). Whilst recent reviews have reported on OSA in schizophrenia (Alam and Chengappa, 2011; Gupta and Simpson, 2015; Kalucy et al., 2013) and in general psychiatric populations (Gupta and Simpson, 2015) they do not provide guidance regarding screening strategies for OSA in people with schizophrenia. A clinically focussed review of available literature could provide evidence for cost-effective application of OSA screening in this population.

Currently, screening for OSA is not recommended in any current physical health guidelines for schizophrenia. OSA may be less easily recognised among people with schizophrenia, where sleep disturbance, daytime somnolence and cognitive impairment are potentially mistaken for negative symptoms of schizophrenia or medication side effects. It is also unclear whether current screening tools for OSA, validated in the general population, are applicable to people with schizophrenia.

We performed a systematic review to determine, in cohorts of people with a current diagnosis of schizophrenia or schizoaffective disorder: (1) the prevalence of OSA; (2) the physical and psychiatric correlates of OSA; (3) the health impact of treatment of OSA in terms of psychiatric, physical health and quality of life measures and; (4) the diagnostic validity of standard OSA screening tools and standardised measures of daytime sleepiness.

2. Materials and methods

The methods are based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (Moher et al., 2009).

2.1 Searches

Online searches of the electronic databases Medline (1966 to April 2015), EMBASE (1988 to April 2015), ISI Web of Science (1900 to April 2015) and PsycINFO (1967 to April 2015) were undertaken using the search terms (psychosis OR schizophrenia OR OR psychotic OR schizoaffective disorder) AND (sleep apnoea OR sleep apnea OR sleep disordered breathing OR parasomnia* OR hypersomnia* OR circadian rhythm sleep disorder*) IN (title AND abstract AND keyword). The search was limited to English language publications. Studies not published in peer-reviewed journals were not considered for inclusion. Study methodologies acceptable for inclusion were retrospective or prospective cohort studies, cross-sectional studies, case-control studies or randomised-controlled trials. Case series and reports were not considered for inclusion. HM performed the electronic searches. The abstracts of all identified papers were reviewed, and HM and NM reviewed in full-text any article appearing to report on schizophrenia and OSA in the title or abstract.

2.2. Inclusion criteria

Papers were considered for inclusion if they reported on:

1. Subjects with current diagnosis of a schizophrenia, schizoaffective disorder, or schizophreniform disorder;
2. Prevalence of OSA based on formal overnight diagnostic testing, not specifically limited to multichannel polysomnography (PSG).

Papers were considered for assessment for each objective if they individually reported on either:

1. The prevalence of OSA in the cohort
2. Psychiatric disease, physical health or anthropometric measures and quantitative assessment of how these related to a current diagnosis of OSA including;
    a. Quantitative measures of sedative, hypnotic or antipsychotic medication use
    b. Positive or negative symptom scores
    c. Body mass index (BMI), neck circumference, sex, age, weight, blood pressure (BP)
    d. Cognitive function
    e. Quality of life
    f. Social and occupational function
3. Prospective assessment of any OSA or daytime sleepiness screening tools used for the identification of subjects subsequently diagnosed with OSA
4. Physical health or psychiatric disease measures before and after treatment of OSA

2.3. Definition of psychiatric disease and OSA measures

A diagnosis of each psychotic illness was defined according to the primary research. We included studies that specified the proportion of participants within the cohort with a diagnosis of either: schizophrenia, schizoaffective disorder, or schizophreniform disorders. Studies generally defined these diagnoses according to DSM or ICD criteria with or without validation

according to specified diagnostic interviews. No study included people diagnosed with schizophreniform disorder.

The gold standard for diagnosis of OSA is overnight multichannel PSG (Epstein et al., 2009). However we included broader definitions of diagnosis including at-home PSG, and overnight oximetry monitoring. This was used as the measure of defining a case, due to the paucity of literature. We felt that an inclusive strategy would be beneficial despite the trade-off of reduced accuracy. The diagnostic measures specific to each study were identified in the results.

2.4. Outcome and data reporting

Two authors, HM and NM, examined the full text of each paper to identify aims, methodology and outcomes (see table 1). The following data relevant to each study was extracted:

1. Study name, date of data collection and population demographics
2. Study design
3. Diagnostic tool and criteria used to define a diagnosis of OSA
4. Number of subjects enrolled in each study
5. Outcome measures specific to the four analyses listed above

Narrative review of the data is outlined in the results and discussion. No further statistical analyses were undertaken.

3. Results

The details of the search strategy are outline in figure 1. Electronic searches identified 817 articles excluding duplicates. Review of title or abstract yielded 129 articles, which were reviewed in full text. Four original articles reporting applicable data were identified (see table

1). (Poulin et al., 2003)(Poulin et al., 2003)(Poulin et al., 2003)(Poulin et al., 2003)(Poulin et al., 2003)The specific results for each objective are outlined below.

3.2. Prevalence of OSA

Four studies determined the prevalence of OSA in cohorts of subjects with schizophrenia using overnight multichannel PSG (Anderson et al., 2012; Winkelman, 2001) modified PSG (Ancoli-Israel et al., 1999) or overnight oximetry (Takahashi et al., 1998). The prevalence of diagnosed OSA varied between 13.5% and 57.1% across the four studies (see table 1).

The available studies varied in subject demographics. Winkelman (Winkelman, 2001) recruited subjects based on suspicion of OSA, which may underlie the higher prevalence in that cohort. Anderson (Anderson et al., 2012) included a proportion of patients who did not have schizophrenia or a related disorder and excluded subjects with previously diagnosed OSA, thereby reducing the reported prevalence. Ancoli-Israel (Ancoli-Israel et al., 1999) studied an older age group (mean age 59.6 years). The low rates reported by Takahashi (Takahashi et al., 1998) may be as a result of the low mean BMI (of 23.9) in this Japanese cohort, which is not typical of people with schizophrenia generally.

The diagnostic criteria for OSA differed significantly across the studies. Overnight multichannel PSG is considered to be the gold standard for diagnosis of OSA with the Apnoea Hypopnea Index (AHI) from PSG being the most reproducible diagnostic measure. Anderson et al (2012) was the only study to conduct multichannel PSG and report an AHI, whilst Winkelman (2001) reported Respiratory Disturbance Index (RDI) and Ancoli-Israel et al (1999) reported RDI with modified polysomnography. Whilst RDI is recognised as a measure of sleep disordered breathing it is considered to underestimate severity of disease because it measures events across total recording time rather than more specifically across sleep time, potentially reducing the accuracy of these studies (Epstein et al., 2009). Takahashi (1998)

reported Oxygen Desaturation Index (ODI) and therefore it could not be determined whether unstable breathing events were obstructive or central in nature. The distinction is important given the possibility that antipsychotic medications may induce central apnoea (Rishi et al., 2010).(Sharafkhaneh et al., 2005)

One study (Takahashi et al., 1998) reported prevalence of OSA based on ODI in a group of inpatients with schizophrenia matched with a group of healthy control recruited from staff at the same hospitals. The prevalence was 18.1% in the schizophrenia group and 22.9% in the control group, a difference that was not statistically significant. The absence of a difference in this case-control study is possibly attributable to the low mean BMI across the two groups and may reflect shared risk factors between the groups.

3.3. Physical and psychiatric correlates of OSA

Two studies (Anderson et al., 2012; Winkelman, 2001) report data on physical health and demographic predictors of OSA and three studies report data on the associations between antipsychotic medication use and OSA (Anderson et al., 2012; Takahashi et al., 1998; Winkelman, 2001). No studies report on measures of quality of life, psychiatric symptoms, cognitive function, or social and occupational function, and how these correlate with OSA diagnosis.

Anderson et al. (2012) reported correlations between diagnosis of OSA (based on AHI) and age, sex, weight, BMI, neck circumference and blood pressure. Age ($r=0.47$, $p=0.001$) and neck circumference ($r=0.311$, $p=0.028$) were positively correlated with AHI whilst the other measures were not correlated with AHI in univariate analyses. Binary logistic regression revealed male sex (OR=21.9, 95%CI 1.3-370.3) and BMI >25 (OR 36.1 95%CI 1.3-990.1) as significant predictors of OSA using AHI >5 as the dependent variable. Winkelman (2001) employed stepwise multiple logistic regression relating age, BMI and sex to OSA, using an

RDI >10 as the dependent variable. This analysis demonstrated significant associations for male sex (OR=5.76 95%CI 2.08-15.27), age (OR=1.03 95%CI 1.00-1.06) and BMI (OR=1.14 95%CI 1.08-1.21).

The three studies reporting on antipsychotic medications (Anderson et al., 2012; Takahashi et al., 1998; Winkelman, 2001) demonstrated conflicting results, likely as a result of methodological differences in assessment of antipsychotic use. Takahashi et al (1998) reported no significant correlation between dose of antipsychotic medication (expressed as mg equivalent dose of haloperidol) and ODI. Winkelman (2001) demonstrated no significant association between antipsychotic use (defined categorically as present or absent) and an RDI >10 using multiple logistic regression., However, the association was significant at a higher RDI cut-off of >20 (OR=5.02, 95%CI 1.44-17.56). Anderson et al (2012) reported a negative correlation between quantitative measures of antipsychotic use (expressed as percentage of maximum dose) and AHI> 5 (r=-0.382, p=0.014), however no significant association was demonstrated between the number of prescribed antipsychotic medications and AHI >5 as the dependent variable on binary logistic regression.

Benzodiazepine use was examined in two studies (Takahashi et al., 1998; Anderson et al., 2012) with conflicting results. Takahashi (1998) reported a positive correlation between hypnotic medications (expressed as number of pills per day) and DI in women included in that study, whilst Anderson (2012) reported no significant interaction between categorical benzodiazepine use and AHI on binary logistic regression.

3.4. Diagnostic utility of OSA screening tools or measures of daytime sleepiness

No study examined the utility of available OSA screening tools in predicting a diagnosis of OSA in this population. Anderson et al (2012), in a cohort that included people with diagnoses other than schizophrenia or schizoaffective disorder, examined measures of daytime sleepiness

and sleep disturbance by prospectively recording Epworth Sleepiness Score (ESS) (Johns, 1991) and Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) scores in subjects who subsequently underwent PSG. This study defined diagnosis of OSA as an AHI >5. An abnormal ESS was defined as a score ≥10 whilst an abnormal PSQI was defined as a score >5. The prevalence of OSA was 52% in this study. The mean ESS was 5.6 (SD=5.04) and the mean PSQI was 6.5 (SD=3.5) across the cohort. 15% of subjects had an ESS >9 whilst 56% of patients had a PSQI >5. ESS and PSQI scores were moderately correlated (r=0.38, p=0.007).

3.5. Physical health and psychopathological measures following OSA treatment

No study reported treatment of OSA in people with schizophrenia or schizoaffective disorder, thus no primary evidence exists evaluating the acceptability of CPAP treatment or its efficacy on measures of physical health, psychopathology or functioning.

4. Discussion

This review suggests that OSA is common in people with schizophrenia and schizoaffective disorder with rates reported between 13.5% and 57.1%. The disparity in prevalence estimates across the included studies reflects variations in patient populations including age, selection bias, degree of obesity and the diagnostic measures used. It is likely that acute changes in mental state in inpatient studies negatively affect compliance with PSG, whilst increased use of sedating medications could exaggerate the severity of OSA. The prevalence of OSA in stable community patients with schizophrenia and schizoaffective disorder and the influences of obesity, sedative medication use, alcohol abuse, smoking and antipsychotic medication remain to be determined.

The prevalence of OSA reported in the included studies is substantially higher than general population prevalence estimates of between 3-4% in men and around 2% in women (Young et

al., 2008). However, only one included study (Takahashi et al., 1998)examined the relative prevalence of OSA in people with schizophrenia compared to general population controls using a case-control methodology. This study reported no difference in relative prevalence, but was potentially confounded by the low mean BMI in both groups. Interestingly the general prevalence of OSA in the control group was 22.9%, which is substantially higher than would be expected in the general population. Another study, not included in this review, examining case records in a large cohort of US veterans (Sharafkhaneh et al., 2005) reported a significant odds ratio of OSA in a psychosis cohort of 1.49 compared to other patients without psychosis. However, this study did not base a diagnosis of OSA on PSG, utilised opportunistic screening and did not include information on non-Veteran's Health Administration healthcare contact, potentially reducing the observed prevalence of OSA (1.6% in that study) given that up to 80% of OSA remains undiagnosed despite adequate access to healthcare (Kapur et al., 2002; Young et al., 1997). Further evaluation of the relative prevalence of OSA in future research would be valuable as a means of clarifying the extent to which OSA is driven by shared risk factors between people with schizophrenia and the general population.

Age, BMI >25 and male sex were significantly associated with OSA in people with schizophrenia or schizoaffective disorder in two studies (Anderson et al., 2012; Winkelman, 2001) and an association with neck circumference was reported in one study (Anderson et al., 2012).These findings are consistent with American Academy of Sleep Medicine general population guidelines,(Epstein et al., 2009) that identify BMI and increased neck circumference as primary predictors of OSA. Similarly the STOP-BANG questionnaire (Chung et al., 2008) utilises criteria of BMI >35, age >50 years, neck circumference >40cm and male sex, along with observed apnoeas, hypertension, snoring, and symptoms of daytime sleepiness, with a reported sensitivity of 70.9% for OSA in the general population. This provides indirect evidence that general screening tools and guidelines would be useful in

identifying at-risk patients at the clinical level, with the caveat that as yet such screening tools have not yet been specifically validated in this population. The literature reviewed here also suggests BMI at a lower cut-off of >25 constitutes a risk factor in comparison to the general population where BMI >35 is considered to confer increased risk.

Interestingly the one study (Anderson et al., 2012) that examined measures of daytime sleepiness using the ESS and PSQI reported lower levels of daytime sleepiness in people with schizophrenia compared with general population controls (Johns, 1991). This observation is supported by other literature (Rishi et al., 2010) reporting that a minority of patients with schizophrenia and comorbid OSA reported sleeping difficulties or snoring prior to diagnosis. These findings lend weight to the suggestion that OSA may be particularly under-recognised in schizophrenia. People with schizophrenia are less likely to have an intimate partner observing nocturnal symptoms (given just 10.9% of community patients are in de-facto or married relationships, (Morgan et al., 2011)). Partner reports of snoring, pausing and daytime somnolence may therefore be less useful for developing a risk profile for OSA in people with schizophrenia, compared to the general population. People with schizophrenia and related disorders have high rates of unemployment, which may limit witnessed daytime somnolence (Waghorn et al., 2012). Furthermore clinicians or patients may discount sleep symptoms as a side effect of antipsychotic medication. The evidence suggests an emphasis be placed on physical risk factors rather than symptoms such as daytime sleepiness for identification of OSA in people with schizophrenia.

The literature reports an inconsistent association between antipsychotic and hypnotic use, and OSA, which is likely confounded by variability in measures of medication use across the available studies. Antipsychotic medications possess sedative and hypnotic properties that may superficially improve insomnia in some patients but could potentially contribute to daytime

somnolence and negatively impact sleep-wake cycle regulation. Previous literature demonstrating patients taking antipsychotic medications have higher prevalence (Shirani et al., 2011) and severity of OSA (Rishi et al., 2010) suggests antipsychotic medications could play an aggravating role in people with schizophrenia and comorbid OSA. Similarly no clear association was reported between hypnotic use and OSA in the included studies potentially as a result of inconsistent and clinically non-relevant measures of medication use. However there is a recognised association between benzodiazepine use and OSA in the general population (Dolly and Block, 1982; Hanly and Powles, 1993). Prescription of hypnotic medication is common in schizophrenia however the degree to which this increases risk or severity of OSA is yet to be determined. Whilst physiological sleep changes are recognised in schizophrenia (Cohrs, 2008; Keshaven et al., 1995; Monti and Monti, 2004; Wilson and Argyropoulos, 2012), the aetiological role of neurobiological determinants and antipsychotic or hypnotic treatment effects on the development of OSA are as yet unclear and require further evaluation.

No study was identified that assessed patients before and after treatment of OSA to determine impact on physical health, psychopathology or other domains of function in people with schizophrenia. In the general population OSA is associated with depression, anxiety, reduced quality of life and decrements in daytime work performance owing to fatigue or sleepiness (Lal et al., 2012; Patil et al., 2007); whilst treatment of OSA with CPAP has demonstrated efficacy in improving quality of life (Rizzi et al., 2014). OSA could potentially compound the negative symptoms of amotivation, apathy and social withdrawal in schizophrenia and could contribute to poorer prognostic outcomes. In people with OSA, treatment with CPAP might therefore improve negative symptoms, mood, cognition, and functional capacity. Investigating this hypothesis, and the acceptability of, and adherence to CPAP treatment in this population should also be a research priority.

We suggest that OSA screening be considered as part of the physical health assessment of people with schizophrenia. OSA is potentially under-recognised, may be an additive risk factor for poor physical health in this population and treatment has the potential to improve cardiovascular risk and quality of life. Based on the available literature OSA screening should be conducted with emphasis on neck circumference >40cm, obesity, male sex, age >50, loud snoring, and apnoeas. The OSA50 (Chai-Coetzer et al., 2011) is an appropriate tool for this purpose and has been validated in the general population in a primary care setting. An OSA50 score ≥5 should prompt referral for PSG as the preferred diagnostic test. We propose sleep symptoms as a subordinate criterion for consideration for referral for PSG, given patients with schizophrenia are unlikely to report symptoms of daytime sleepiness, these symptoms may be confounded by medication side effects or psychiatric symptoms, and most lack partners to report snoring or nocturnal apnoeas.

The available evidence suggests that OSA is more prevalent in people with schizophrenia than in the general community, but may be under-recognised. Screening for OSA should be included in the physical health assessment of people with schizophrenia. It is possible that treatment is a means of modifying cardiovascular risk and improving symptoms and psychosocial functioning. Further research should be directed towards estimates of OSA prevalence in community samples with stable schizophrenia, validation of OSA screening tools in this population and investigation of OSA treatment outcomes specifically focussing on whether OSA treatment improves negative symptoms of schizophrenia.

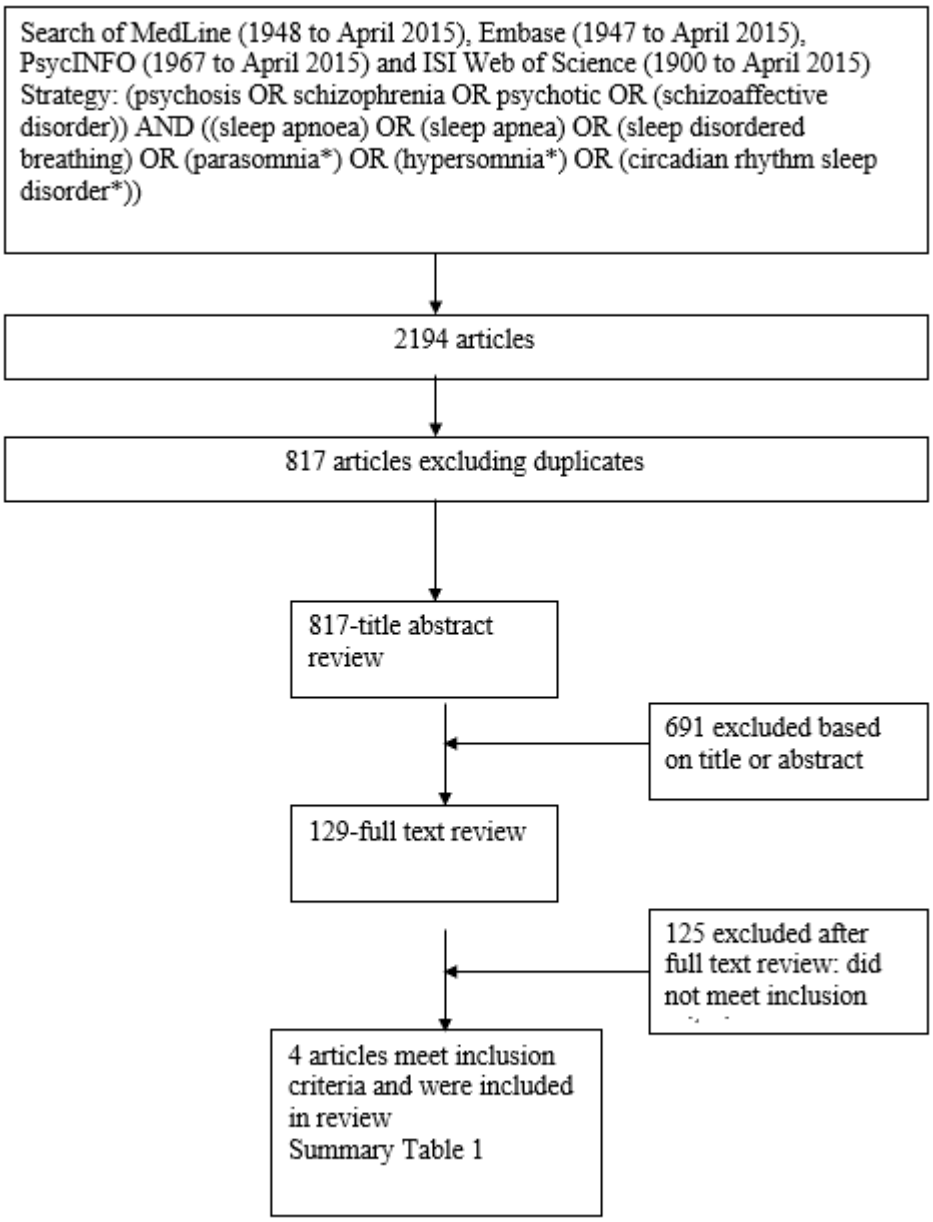

Figure 1: Flow chart of search strategy and results

Table 1: Studies reporting prevalence of OSA in populations of patients with schizophrenia

Study	Population	Diagnostic measure	OSA criteria	Prevalence
Anderson et al. 2012	52 outpatients with major mental illness, of which 25 (48%) had a diagnosis of schizophrenia or schizoaffective disorder	Polysomnography	Severity based on AHI Mild – AHI 5-15 Moderate – AHI 15-30 Severe - >30	52% prevalence 32% mild 14% moderate 6% severe
Winkelman et al. 2001	46 inpatients with schizophrenia or schizoaffective disorder considered at high risk of OSA referred to sleep disorders clinic	Polysomnography	RDI >10	57.1% in males 46.2% in females
Ancoli-Israel et al. 1999	52 geriatric outpatients (mean age 59.6 years) with schizophrenia or schizoaffective disorder	Modified polysomnography	RDI >10	48% prevalence
Takahashi et al. 1998	101 inpatients with schizophrenia	Overnight oximetry	DI	21.9% in males 13.5% in females

Abbreviations: AHI apnoea-hypopnoea index as defined by AASM (Kushida et al., 2005); RDI respiratory desaturation index defined as defined by ASDA criteria (ASDA, 1992) (Timms RM, 1988), DI desaturation index as defined by >4% oxygen desaturations at least 5 times per hour.

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