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# Self-reported health outcomes in patients with obstructive sleep apnoea

Unraveling the role of bio-psycho-social factors

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# Self-reported health outcomes in patients with obstructive sleep apnoea

## Unraveling the role of bio-psycho-social factors

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# Contents

# List of abbrevations

| | |
|---|---|
| AHI | Apnoea-Hypopnoea Index |
| BAI | Beck Anxiety Inventory |
| CMHo | Cook Medley Hostility Scale |
| CPAP | Continuous Positive Airway Pressure |
| CSE | Coping Self-Efficacy |
| ESS | Epworth Sleepiness Scale |
| FOSQ | Functional Outcomes of Sleep Questionnaire |
| GHQ-28 | General Health Questionnaire |
| MFI | Multidimensional Fatigue Inventory |
| MLR | Multiple linear regression analyses |
| MSPSS | Multidimensional Scale of Perceived Social Support |
| OSA | Obstructive Sleep Apnoea |
| PMS | Pearlin Mastery Scale |
| PROMs' | Patients' reported outcome measures |
| PSG | Polysomnography |
| PSQI | Pittsburgh Sleep Quality Index |
| QoL | Quality of Life |
| RCTs | Randomised Controlled Trials |
| WRFQ 2.0 | Work Role Functioning Questionnaire 2.0 |

# Introduction

1

"Sleep is the most
innocent creature there
is and a sleepless man
the most guilty."

Franz KAFKA

Obstructive sleep apnoea (OSA) is a common chronic disorder that often requires lifelong care (Force AOSAT and American Academy of Sleep Medicine, 2009). We aimed to extend current knowledge on the factors which may be closely related to the management of this chronic disease. Therefore, this study on OSA focuses on the bio-psycho-social factors that have been identified as key determinants of health outcomes in various chronic diseases, but for which less is known about their role in OSA. This chapter covers the theoretical background of the study, describes the theoretical model used for the study, presents the aims and the specific research questions, and concludes with the outline of the thesis.

## 1.1 Obstructive sleep apnoea: definition, symptoms and epidemiology

OSA is defined as a repetitive, intermittent cessation of air flow at the nose and mouth during sleep. The clinical syndrome is characterized by repeated episodes of upper-airway occlusion during sleep, which can be complete (apnoea) or incomplete (hypopnoea) and of varying duration (Leung, 2019). Patients with OSA often snore and report daytime sleepiness (Manarino et al., 2012; Peppard et al., 2013) and fatigue (Manarino et al., 2012).

OSA concerns 2–10% of the adult population (Leger et al., 2012); it is more prevalent in men compared with women and extremely rare in premenopausal women (Krystal et al., 1998). Most population-based studies have identified a gender-specificity in OSA prevalence, i.e. a 2- to 3-fold greater risk for males compared to females (Strohl and Redline, 1996; Quintana-Gallego et al., 2004). OSA prevalence and severity have also been found to rise linearly with age (Bixler et al., 1998; Gabbay and Lavie, 2012). Depending on age, the prevalence of moderate and severe OSA (apnoea-hypopnoea index; AHI ≥15) among men is 10–17% and among women 3–9% (Peppard et al., 2013). These estimated prevalence rates represent substantial increases over the last two decades, with relative increases of between 14% and 55% (Peppard et al., 2013).

Furthermore, the majority of people with OSA are typically unaware of apnoea/hypopnoea episodes. Although long-term consequences, such as fatigue, excessive daytime sleepiness, and increased cardiovascular and cerebrovascular risk, may be severe, symptoms often begin subtly and gradually and may remain underestimated for many years, noticed by bed partners only (Schmaling and Afari, 2000). Previous studies have concluded that OSA affects approximately 20% of US adults (Young et al., 2002; Finkel et al., 2009), about 90% of whom may be undiagnosed (Finkel et al., 2009). Thus, OSA remains a largely underdiagnosed and undertreated problem, although its impact on both morbidity (Macey et al., 2010; Rottapel et al., 2019) and socio-economic costs (Leger et al., 1994; Wittmann and Rodenstein, 2004; Mulgrew et al., 2007; Leger et al., 2012) is enormous.

Sleep-disordered breathing has major socioeconomic consequences for patients and their spouses both years before and after diagnosis (Jennum et al., 2014). Compared to healthy people, individuals suffering from OSA are less productive,

have increased health care utilization, an increased likelihood of accidents (Karimi et al., 2015), reduced work capacity, and work participation (Mulgrew et al., 2007; Leger et al., 2012). Sleep loss among partners of OSA patients also results in frustration, exhaustion, interference with work, and strained relationships (Luyster et al., 2016). It has been shown that untreated OSA patients have up to two-times greater health care costs when compared with controls without OSA (Wittmann and Rodenstein, 2004). Costs of undiagnosed people with OSA include direct costs due to possible consequences, such as driving accidents, as well as the development of comorbidities such as cardiovascular diseases, diabetes, metabolic syndrome, and an increased overall mortality rate (Tkacova and Dorkova, 2010; Leger et al., 2012; Pack et al., 2012; Ayas et al., 2014). Although the exact costs are difficult to calculate, data from 106 countries showed that increased healthcare spending to treat undiagnosed OSA varies between 1,950 and 3,899 dollars per patient per year, which represents approximately a total of 3.4 billion dollars per year (Knauert et al., 2015). These costs are usually caused by more frequent practitioner visits, increased hospitalizations, and the development of comorbidities (Wittmann and Rodenstein, 2004).

OSA-related symptoms such as sleep disruption, snoring, sleep-related choking, insomnia, nocturia, disruption of bedpartner's sleep, morning headaches, impairments in productivity, poor-quality relationships, and daytime fatigue have been shown to have a negative impact on patients' psychological well-being, quality of life (QoL), and functional status (Young et al., 2002; Sharafkhaneh et al., 2005; Mulgrew et al., 2007; Tsara et al., 2009; Antic et al., 2011; Weaver, 2013; Rezaeitalab et al., 2014; Patil et al., 2019). Besides physical impacts, OSA is associated with a higher prevalence of neuropsychiatric comorbidities or symptoms (Sharafkhaneh et al., 2005; Tkacova and Dorkova, 2010; Lin and Winkelman 2012; Kang et al., 2012), such as anxiety (Sharafkhaneh et al., 2005; Krakow et al., 2015), depression, posttraumatic stress disorder, psychosis, or dementia (Sharafkhaneh et al., 2005). Choi et al. (2015) reported an increased prevalence of suicidal ideation in OSA patients when compared to the general population. Moreover, psychological distress may reversely influence the progress of OSA-related physical symptoms (e.g. Hall et al., 2004; Krakow et al., 2015).

Another source of concern is that diagnosing OSA may often represent a difficult task for health care professionals because of the patient's unawareness and the variations in presentation (Lurie, 2011; Peppard et al., 2013). Moreover, patients presenting with fatigue or daytime sleepiness may be misdiagnosed with depression or other illness (Lin et al., 2008).

## 1.2 Measuring self-reported health outcomes in obstructive sleep apnoea

In many areas of medicine, patient-reported outcome measures (PROMs) are gaining substantial attention as priority components to assess when gauging the effect of treatment for all manner of diseases (Tam et al., 2014; Pang et al., 2016; Appleby

et al., 2016). OSA disabling symptoms pose multiple challenges on patients' health outcomes, such as well-being, QoL, and functional status (Antic et al., 2011; Weaver, 2013; Jackson et al., 2018). Therefore, along with an increase of OSA, the assessment of self-reported health outcomes has gained attention and become an important construct in this chronic disease (Kushida et al., 2012; Tam et al., 2014).

The gold standard diagnostic test for OSA is the overnight polysomnography (PSG) (Epstein et al., 2009). During an overnight polysomnogram, the frequency of obstructive events is reported as the apnoea-hypopnoea index (AHI). The severity of OSA is based on the number of apnoea and hypopnoea events per hour (American Academy of Sleep Medicine, 2005). However, there is a discrepancy between the AHI levels used to denote outcomes of therapy and real-world outcomes, such as QoL, functional status, patient perception of disease, cardiovascular measures, or survival (Tam et al., 2014). Some previous studies on continuous positive airway pressure (CPAP) treatment effectiveness (Weaver et al., 2005; Kushida et al., 2012; Tam et al., 2014) also favour the usage of QoL and functional status measures together with AHI; yet in the case of OSA, the AHI remains persistent as the primary, and frequently the only, outcome measure reported in the vast majority of research and clinical practice (Pang et al., 2016).

Therefore, screening PROMs based on self-reported symptoms of OSA is important for gaining information on the prevalence and comorbid conditions of OSA or on CPAP treatment effectiveness (Weaver et al. 2005; Sivertsen et al., 2008; Kushida et al., 2012). Moreover, patients' self-reported outcomes represent any assement coming directly from patients, without interperetation by a health care professional or others, about how they function or feel in relation to their health condition. Thus, identifying issues faced by patients and their families about living with an illness can generate knowledge that may consequently impact treatment decisions and adherence. In general, the use of PROMs may enhance the understanding of how health-practitioners can affect health outcomes (Krabbe et al., 2017).

### 1.2.1 Functional status

Recent studies have emphasized the importance of studying patients' functional status in sleep medicine research, because of its ability to provide insights that may go beyond the pathophysiology of commonly investigated OSA-related symptoms (Boccabella and Malouf, 2017). Functional status is defined as an individual's ability to perform normal daily activities or tasks that are essential to meet basic needs and fulfill usual roles (Wilson and Cleary, 1995). The concept of functional status consists of two main domains: capacity and performance. Functional capacity can be defined as a person's maximum ability to perform daily activities in the physical, psychological, and social domains of life, whereas functional performance refers to what people actually do in the course of their daily living (Leidy, 1994). Both domains can be influenced by biological or physiological impairment, symptoms, and mood impairments but also by health perceptions (Krabbe, 2017). There is general consensus that physical function, social function, role function, and psychological

function represent the minimum required to define and measure functional status (Sherbourne et al., 1992).

Previous research has shown an impairment of functional status (Reishtein et al., 2006; Perimenis et al., 2007; Weaver et al., 2007; Tippin et al., 2016), including impairment of work functioning, in OSA patients (Wittmann and Rodenstein, 2004; Mulgrew et al., 2007; Reuveni et al., 2008; Sivertsen et al., 2008; Leger et al., 2012). Furthermore, the current studies show that the treatment response is inadequate to return OSA patients to the functional level of healthy individuals who are asymptomatic of sleep-disordered breathing, and that CPAP treatment may not improve function in a dose-response manner (Weaver, 2013; Tippin et al., 2016; Jackson et al., 2018).

### 1.2.2 Work functioning

The prevalence of OSA is high; the disease affects 9% of the female and 24% of the male working-age population (Young et al., 2009). While OSA is a non-occupational disease, given its frequency, comorbidities, and potential to impair work functioning, it is inevitable that it may manifest as an important health and safety issue in the workplace (Kales and Czeisler, 2016). Sleep disturbances, excessive daytime sleepiness and frequent awakeness showed to be a risk factors with respect to occupational accidents (Cappuccio et al., 2010). Moreover, the economic costs of OSA on health care systems, as well as on individuals and their households, have also substantial relevance. Previous studies have focused mainly on the economic impact of OSA on public health systems (Wittmann and Rodenstein, 2004; Reuveni et al., 2008) and occupational accidents (e.g. Garbarino et al. 2016), while the assessement of work functioning was not prominent. Some studies have evaluated work performance in patients with OSA, but results have been disputed (Jurado-Gámez et al., 2015). Few previous studies showed a significant impairment of work functioning in patients with OSA (Mulgrew et al., 2007; Sivertsen et al., 2008; Omachi et al., 2009). According to Reishtein, OSA patients have difficulties to complete a task at work, feel a lack of trust from coworkers and report subsequent embarrassment (Reishtein et al., 2006). Working OSA patients were also found to have low productivity levels and a high rate of psychological distress (Jurado-Gámez et al., 2015).

### 1.2.3 Health related quality of life

The main goal for the treatment of OSA is to prevent complications and comorbidities, while preserving a good quality of life (QoL). Knowledge about the role of bio-psycho-social factors and their associations with patients' health outcomes is therefore of great importance (Haslam et al., 2018). The World Health Organisation Quality of Life (WHOQoL) group defined QoL as ´*an individual's perception of their position in life, in context of the culture and values in which they live and in relation to their goals, expectations, standards and concerns*´ (WHOQoL Group,

1994). QoL has several domains, like functional competence, health-related complaints and psychological and social functioning. Health-related quality of life (HRQoL) is considered to be an integral domain of QoL. When QoL is discussed in relation to health or diseases, it almost always means HRQoL, unless specified otherwise (Dutt et al., 2016). HRQoL is increasingly used as an outcome of treatment effectiveness. In broad terms, HRQoL serves as a restricted definition of QoL in the sense that it was designed to exclude externalities, such as housing, financial situation, living conditions, or spirituality. HRQoL is associated with an expanded concept of health status, one embracing social interaction as well as emotional and psychological well-being (Krabbe, 2017). According to Schipper (1992) QoL in clinical medicine represents the functional effects of illness and its consequent treatment upon patient, as perceived by the patient. Because the concepts of QoL and HRQoL are closely tied to each other (Dutt et al., 2016), we will use them in this paper interchangeably, with omission of external domains such as spirituality, or living conditions.

### 1.2.4 Psychological distress

Psychological distress is understood as the opposite continuum to psychological well-being (Goldberg and Hillier, 1979; Spiteri et al., 2013). The World Health Organisation (WHO, 2012) states that ´well-being exists in two dimensions, subjective and objective. It comprises an individual's experience of their life as well as a comparison of life circumstances with social norms and values´. Health is projected as an integral component of well-being, while good health represents a necessary condition for attaining the highest possible levels in all other aspects of well-being (Salomon et al., 2003). The relationship between health and well-being is interdependent; health influences well-being and well-being itself influences health. There are a number of associations between psychological well-being and physical health outcomes, such as improved immune system response, higher pain tolerance, increased longevity, improved cardiovascular health, or slower disease progression (Howell et al., 2007; Steptoe et al., 2015).

### 1.2.4.1 Suicidal ideation

Suicide and attempted suicide are major public health concerns with complex aetiologies which encompass a multifaceted array of risk and protective factors (O'Connor, 2017). Suicide is an important cause of death worldwide. Globally, more than 800,000 people take their life every year, and there are many more suicide attempts (World Health Organization, 2016). Suicidal ideation and suicidal behaviours have been conceptualised to lie on a continuum, whereby those who experience suicidal ideation may progress to make suicide plans and then, subsequently, make an attempt or die by suicide (Tarrier et al., 2013). Indeed, data from a cross-national study of 17 countries estimated that 33.6% of individuals who experience suicidal ideation will subsequently develop a suicide plan, and 56% of those with a plan will make a suicide attempt (Nock et al., 2008). Therefore, identifying

and intervening at the start of this trajectory is imperative for developing effective suicide prevention strategies. Recent approaches have defined suicide as a health behaviour, in the sense that a person makes a decision to take his/her own life, so an appreciation of the psychology of the suicidal mind is crucial to suicide prevention (O'Connor, 2017). One of the key developments in the field of suicide theory and research is the ideation-to-action framework, which stipulates that the development of suicidal ideation and the progression from suicidal ideation to suicidal behaviour are distinct phenomena with distinct explanations and predictors (Klonsky, 2016). Moreover, there is growing recognition that we need to move beyond psychiatric categories to further understand the pathways leading from suicidal ideation to suicidal behaviour (O'Connor, 2017).

Suicidal ideation is a common health concern in primary care (Rückert-Eheberget al., 2019). The findings of previous studies support the need to screen for suicidality in general medical settings, over and above the use of general depression instruments (Druss and Pincus, 2000; Krakow et al., 2011). A significant association was found between chronic medical conditions and suicidality, and it persisted after adjusting for depressive disorder or alcohol abuse (Druss and Pincus, 2000). A total of 25.2% of individuals with a general medical condition and 35.0% of those with two or more medical illnesses reported lifetime suicidal ideation (Tang and Crane, 2006). The lifetime prevalence of suicide attempts was between 5 and 14% in individuals with chronic pain, and the prevalence of suicidal ideation was 20% (Tang and Crane, 2006).

A growing body of research indicates that sleep disturbances are associated with suicidal ideation and suicidal behaviors. To date, however, the majority of the research has focused on insomnia. Sleep disorders differentially affect functioning, and the relationship between OSA and suicide has yet to be established. OSA, in contrast to insomnia, is characterized by frequent awakenings that disrupt the natural progression of sleep cycles and sleep architecture. Thus, patient with OSA may in fact obtain more total sleep time than the typical insomnia patient; however, the sleep of the OSA patient may be less restorative. Because of this etiologic difference, it is unclear what aspect of generalized sleep disturbance contributes to suicide risk. For example, if the association between sleep and suicide only represents a function of the loss of total sleep time, then sleep disorders such as OSA, that do not significantly reduce total sleep time, should not be associated with increased suicide risk. However, if the association between sleep and suicide is related to other aspects of sleep disturbances (e.g. hypersomnolence, fatigue, or neurophysiologic changes), then OSA and other sleep disorders may emerge as being associated with increased suicide risk (Bishop, et al., 2018).

Recently, an increased suicidal ideation has been observed in patients treated in medical sleep centres (Krakow et al., 2011), including patients with OSA (Choi et al., 2015). Sleep-related problems were found to pose multiple challenges for mental and physical functioning. Poor night-time sleep quality was found to be associated with an increased risk of committing suicide in one decade even when adjusted for depressive symptomatology (Bernert et al., 2014). Krakow et al. (2011)

found an association between sleep-related problems and suicidal ideation in patients treated in medical sleep centres, which remained significant after controlling for depression. In 2015, Choi et al. reported a suicidal ideation prevalence of 20.5% in a Korean population among OSA patients, but information about the prevalence of suicidal ideation in OSA patients in other countries is lacking. Consequently, it is important to understand the associations between sleep-related problems, suicidal ideation, and suicidal behaviour. Another source of concern is that people with sleep problems suffering from psychological distress rarely seek formal mental health care (Weissman et al., 1997; Wojnar et al., 2009). Therefore, the idea of depending solely on the available psychological and psychiatric care to detect individuals at risk of suicidal ideation may be insufficient for early suicide prevention efforts, especially for people with chronic diseases such as OSA.

## 1.3  Biomedical factors and their associations with self-reported health outcomes

Of all approaches to health, the biomedical approach is unquestionably considered to be the most influential. This approach understands health primarily through the lens of disease, and it attributes the cause of ill health to breakdown in normal biological and physiological functioning. In so doing, it gives a clear direction in how best to manage health – and this is to focus on treating the source of breakdown in the body (Haslam et al., 2018). Relevant and potentially modifiable biological factors in the prediction of health in this study concerned OSA severity (assessed by AHI) and sleep-related problems (including night-time sleep quality, daytime sleepiness, and fatigue). Another biomedical factor in this study concerned CPAP treatment.

### 1.3.1  OSA severity and sleep-related problems

Since OSA is diagnosed according to a cut-off in the Apnoea-Hypopnoea Index (AHI), a logical assumption is that higher AHI is associated with higher OSA-related symptoms, including sleep-related problems. However, previous research has shown that AHI may not correlate well with the presence or degree of daytime sleepiness (e.g. Bixler et al., 2005; Roure et al., 2008; Macey et al., 2010; Dündar et al., 2015), sleep quality (Macey et al., 2010), anxiety, or depressive symptomatology (Macey et al., 2010; Asghari et al., 2012; Rezaeitalab et al., 2014).

Although excessive daytime sleepiness is considered a cardinal symptom of OSA, the association between daytime sleepiness and OSA severity is unclear (Adams et al., 2016). In the Sleep Heart Health Study and the Wisconsin Sleep Cohort Study, daytime sleepiness was found to be associated with OSA severity (Kapur et al., 2005; Young et al., 2009). On the contrary, some recent studies showed that the presence of daytime sleepiness may represent an unreliable indicator of OSA (Adams et al., 2016; Al Houqani and Arora, 2019). Furthermore, approximately 50% of OSA patients deny daytime sleepiness (Roure et al., 2008). The subjective evaluation of daytime sleepiness is also often complicated by the

fact that patients may report complaints regarding lack of energy or depressive symptomatology (Lin et al., 2008) rather than sleepiness itself (Chervin, 2000). Moreover, the phenomenon of residual sleepiness, e.g. excessive daytime sleepiness in OSA patients treated effectively with CPAP, implies that the underlying pathology of daytime sleepiness may be different from that of OSA per se (More et al., 2019). As this particular area of the associations between OSA severity, sleep-related problems and health-outcomes remains unclear, our studies may be useful in enhancing our understanding of these relationships.

### 1.3.2  Continuous positive airway pressure treatment

In terms of treatment, CPAP represents the first treatment of choice in most patients with OSA (American Academy of Sleep Medicine, 2008; Patil, 2019). To date, CPAP represents the most effective intervention for managing OSA; however, adherence may be poor (Aloia et al., 2004; Weaver and Grunstein, 2008; Rakel, 2009; Weaver and Sawyer, 2010; Barrata et al., 2018), with rates ranging from 29% to 81% (Weaver and Grunstein, 2008). Approximately, one fourth of all CPAP users discontinue its usage within the first year for reasons that range from discomfort and a feeling of claustrophobia from the mask, to inconvenience and its interference with travel (Aloia et al., 2004). The majority of OSA patients who continue using CPAP do not use it consistently or for the number of recommended hours each night (Aloia et al., 2004). Moreover, some interventions employed to improve CPAP adherence (e.g. education and telephone follow-up calls), were found to have only a limited success (Sawyer et al., 2011).

Some previous studies showed that patients' reports of improvement with CPAP treatment were often found to be discordant with PSG results. Thus, other clinically important health-related outcomes including QoL and functional status, are recommended to be used as complementary part in the evaluation of CPAP treatment response (Weaver et al., 2005). Some studies have concluded that OSA patients, even with a good CPAP compliance level, are not able to achieve their normal functional status and QoL when compared to general population levels of functioning (Perimenis et al., 2007; Weaver et al., 2007; Antic et al., 2011; Weaver, 2013; Tippin et al., 2016; Jackson et al., 2018). Poor CPAP treatment effects on health outcomes were especially profound in patients with psychological symptomatology (Kjelsberg et al. 2005; Hussain et al., 2014; Jackson et al., 2018). Moreover, results on CPAP treatment effectiveness were also found to be inconclusive regarding objective health outcomes, such as a decrease in blood pressure among OSA patients (e.g. Dimsdale et al., 2000; Pepperell et al., 2002; Bazzano et al., 2007; Bratton et al., 2014).

Nevertheless, CPAP therapy represents the gold standard treatment option and should be offered to OSA patients as a first choice treatment. Although improving CPAP treatment to maximize adherence is important, there is also a need for novel strategies which may be helpful in OSA management. Thus, present research and clinical practice should focus not only on the standard treatment of OSA, but

also on ensuring that symptoms such as poor sleep quality, daytime sleepiness, fatigue, or psychological symptoms are managed. To do that, we first need to understand how these biomedical and psycho-social factors relate to health outcomes in untreated OSA patients.

## 1.4 Psycho-social factors and their associations with self-reported health outcomes

About 40 years ago Engel (1978) authored the bio-psycho-social model and, in so doing, tried to reverse the dehumanization of health sciences and disempowerment of patients (Smith et al. 2013). The bio-psycho-social model considers the need to include not only the characteristics and normative functioning of biological systems (Haslam et al., 2018), but also the consideration of individuals' experience, daily functioning, productivity, emotional stability, performance of social roles, and social determinants (Fava and Sonino, 2007; Haslam et al., 2018).

The psychological and social factors assessed in this thesis have been studied for their positive association with health outcomes in various chronic illnesses, such as multiple sclerosis (Krokavcova et al., 2008a; Mikula et al., 2014; Mikula et al., 2016), chronic obstructive pulmonary disease (Tiemensma et al., 2016), cardiovascular diseases (Silarova et al., 2012; Silarova et al., 2014; Silarova et al., 2016), or insomnia (Troxel et al., 2010), but some of them are less known in OSA. Social factors related to external resources accessed from others were operationalized as perceived social support and coping self-efficacy for the ability to get support from family and friends. Psychological factors included anxiety and hostility together with intra-individual psychological resources such as coping self-efficacy for the ability to stop unpleasant emotions and thoughts, problem-focused coping-self-efficacy, and mastery over one's life and circumstances.

### 1.4.1 Anxiety

In addition to physical disorders, OSA patients may experience mental impairment. Many OSA patients suffer from anxiety symptoms (Yue et al., 2003; Shapiro et al., 2014; Krakow et al., 2015), but these are rarely systematically studied (Shapiro et al., 2014; Krakow et al., 2015). Anxiety includes a large spectrum of conditions varying from psychiatric diagnoses (e.g. generalised anxiety disorder, social phobia, or obsessive compulsive disorder) to threshold symptoms. Anxiety, especially at severe and panic levels, may have a major impact on sleep and breathing (Shapiro et al., 2014). Anxiety may contribute to poor treatment acceptance and adherence (Aloia et al., 2004) and, consequently, to an overall worsening of OSA symptoms and an increased risk of morbidity (Shapiro et al., 2014). Furthermore, comorbid anxiety in OSA patients has been found to have pathophysiological implications; i.e. permanent neurological alterations in brain areas regulating emotions were noted using magnetic resonance in anxious OSA patients compared to no significant change in non-axious OSA patients and controls (Kumar et al., 2009). A more nuanced theory suggests that OSA itself may represent a direct cause of anxiety,

because virtually anything that disrupts breathing (e.g. asthma, bronchitis, chronic obstructive pulmonary disease) easily causes or aggravates symptoms of anxiety (Krakow et al., 2015).

### 1.4.2 Hostility

Previous research has shown that various chronic diseases and an increased risk of illness were associated with hostility (Nabi et al., 2008), with strong evidence for cardiovascular diseases (Nabi et al., 2008; Silarova et al., 2014; Silarova et al., 2016). Affective consequences of OSA were also found to include elevated rates of hostility (Yue et al., 2003). Hostility is defined as a negative cynical attitude toward others, with a propensity for anger, aggression (Cook and Medley, 1954), mistrust, and cynicism (Barefoot et al., 1989). Previous research has identified hostility to be a risk factor for impaired psychological QoL in patients with cardiovascular diseases (Nabi et al., 2008; Silarova et al., 2014; Silarova et al., 2016). Hostility may be linked to increased negative emotionality (Brissette and Cohen, 2002) and psychological symptoms, such as sleep disruption (Brissette and Cohen, 2002; Tsuchiyama et al., 2013), depression (Heponiemi et al., 2006), suicidal ideation, and suicidal attempts (Brezo et al., 2006; Lemogne et al., 2011). In their review, Baglioni et al. (2010) concluded that hostility correlates with poor sleep quality, both in subclinical and clinical samples. Recently, Xiao et al. (2016) reported a strong association between hostility and decreased night-time sleep quality in patients with OSA. Moreover, hostility was found to be related to an attenuated decline in night-time blood pressure (Hall et al., 2004), which may potentiate the negative health consequences of OSA-related cardiovascular symptomatology. Individuals with high hostility may have a delayed onset of sleep due to rumination or elevated arousal following their daily interactions (Hall et al., 1997). Thus, negative experiences during the day may hinder physiological recovery at night, resulting in difficulties initiating sleep and a blunted decline in blood pressure (Hall et al., 2004).

However, evidence for a relationship between hostility and sleep-related problems is still scarce (Granö et al., 2008; Sadeh et al., 2011). Some studies and clinical observations hypothesize that sleep loss reduces affective stability and increases emotional reactivity (Anderson and Platten, 2011), aggression, and hostility (Kamphuis et al., 2012). Booth et al. (2006) found a correlation between daytime sleepiness and anger, as measured by the Bussy-Perry subscale, in sex-offenders with diagnosed OSA. Following CPAP treatment, OSA patients reported a lower level of hostility. Other authors define the role of hostility as the main cause of sleep problems; for example, Granö et al. (2008) in their longitudinal study concluded that transient, but not trait hostility may predispose for a shorter duration of sleep in the general population even when adjusted for psychiatric disorders.

### 1.4.3 Coping self-efficacy

Coping may be a determinant of both recovery and adaptation to disability (Lo Buono et al., 2017). Effective coping strategies may be beneficial in handling chronic

diseases, including OSA (Bardwell et al., 2001; Gassara et al., 2017). In general terms, coping can be defined as an effort to manage a situation and involves various cognitive and behavioural strategies to overcome external or internal demands which are appraised as either taxing or exceeding the person's resources (Folkman et al., 1986). The terms coping and coping self-efficacy are closely linked to each other (Park and Folkman, 1997; Bandura et al. 1999; Chesnay et al., 2006; Mikula et al., 2014; Mikula et al., 2016). The concept of coping self-efficacy is based on an integration of two well established theories within health research: the self-efficacy theory of Bandura (1999) and the coping theory of Lazarus and Folkman (1984). In the framework of these theories, coping-self efficacy addresses the second phase of coping, which represents how a person reacts to a stressful situation and most importantly which coping strategy he or she will apply based on the perceived self-efficacy. The choice and level of coping self-efficacy in a particular circumstance reflects prior relevant experiences (Bandura et al., 1977). During the process of secondary appraisal, the individual judges that an outcome is controllable through coping and addresses the question of whether person believes that he or she can carry out the requisite coping strategy (Lazarus and Folkman, 1984). Coping self-efficacy contributes to this judgment, which is an important prerequisite to coping behaviour (Park and Folkman, 1997). The ability to regulate emotions is crucial in diminishing psychological distress; however, healthy emotion-regulation may not merely be about using the "right" strategies (Haines et al. 2016).

According to the strategy-situation-fit hypothesis, emotion-regulation strategies are able to diminish psychological distress only when used in appropriate contexts (Bonanno and Burton, 2013; Haines et al. 2016). When dealing with their health conditions, patients use various coping strategies which may have different effects on their psychological well-being. When people obtain a 'fit' between stressful events and their coping strategies, they experience less psychological distress than when there is a lack of such a fit (Park et al., 2001). As such, greater levels of coping self-efficacy are associated with more effective regulation of emotional distress (Luberto et al., 2014). Previous research has focused on the effect of coping self-efficacy and coping behaviour on patients' self-reported health outcomes in various diseases, such as heart failure (Graven and Grant, 2013), multiple sclerosis (Mikula et al., 2016), or chronic obstructive pulmonary disease (Tiemensma et al., 2016). A higher level of coping self-efficacy was associated with a better adjustment to various chronic diseases (Chesney et al. 2006; Benka et al., 2014; Mikula et al., 2014; Mikula et al., 2016). Only a few studies have so far addressed this concept, but those that have showed that coping self-efficacy was associated with lower level of psychological distress (Chesney et al., 2006; Benka et al., 2014) and better QoL (Mikula et al., 2014; Mikula et al., 2016) in the context of chronic diseases. Overall, these results suggest that coping self-efficacy has direct effects on distress/well-being outcomes, beyond the impact of clinical and personality variables.

Some studies indicate that problem-focused coping was the most beneficial in handling disease (Scharloo et al., 2000; Graven and Grant, 2013; Tiemensma et al., 2016), especially in the mental health domain (Scharloo et al., 2000). In other studies, problem-focused coping was generally unrelated to illness adjustment (Bombardier et al., 1990). The emotion-focused coping triad, consisting of wishful thinking, self blame, and avoidance, was also found to be a maladaptive strategy when coping with chronic medical conditions (Bombardier et al., 1990). Nevertheless, in some studies, avoidance coping or more passive coping strategies, such as coping self-efficacy for stopping unpleasant emotions and thoughts, were defined as most effective (Mackay et al., 2012; Harmell et al., 2011; Mikula et al., 2016). Recent studies have concluded that the more active and less passive coping strategies reported by OSA patients, the lower the level of depressive symptoms experienced by patients (Bardwell et al., 2001; Gassara et al., 2017).

### 1.4.4 Mastery over one's life and circumstances

As patients with OSA have very little control over the symptoms of their disease and have to learn how to live with it, mastery may help them to reduce the stress that breathing difficulties and sleep-related symptoms bring about and may thus improve their health outcomes. Mastery is defined as a general sense of control over one's life and circumstances (Pearlin and Schooler, 1978). A higher level of mastery has been found to be associated with better health in people with chronic disease or disability (Cott et al., 1999). A diminished sense of mastery was associated with a decrease in physical, mental, and social functioning and with increased mortality rates in patients with chronic conditions (Surtees et al., 2006; Krokavcova et al., 2008a; Sloan et al., 2009). In OSA patients with comorbid insomnia, the positive associations between mastery and both physical and mental QoL remained significant even after adjustment for age, obesity, chronic diseases, erectile dysfunction, sleepiness, mood, and financial strain (Lang et al., 2016). Mastery as a part of patient empowerment (Aujoulat et al., 2008) was also found to be associated with individuals' capacity to make decisions about their health behaviour and to have or to take control over aspects of their lives that are related to health (McAllister et al., 2012). Research has also shown that people with a higher level of mastery are more likely to seek treatment at an early stage of disease, and to use health care services more efficiently (Menec and Chipperfield, 1997).

### 1.4.5 Social support

Social support is a very important aspect in the treatment of chronic and incapacitating diseases (Günbey and Karabulut, 2014). There is some evidence that having adequate psychosocial support may lead to an improvement of perceived QoL and reduced morbidity (Barefoot et al., 2005), while the absence of positive relationships was found to be a significant risk factor for morbidity and mortality (Cacioppo and Cacioppo, 2014). Lack of social support has a significant impact on health-related behaviour and risk for illness (Alemi et al., 2003); i.e. poor social support was associated with poorer self-rated health in patients with acute myocardial infarction (Bucholz et al., 2014), higher levels of blood pressure (Piferi et al., 2006), chronic arthritis pain (Lee et al., 2016), and multiple sclerosis (Krokavcova et al.,

2008b). Social support also had a positive influence on sleep in people with insomnia (Troxel et al., 2010).

Therefore, social support may be an important, though under-investigated, protective factor associated with healthier sleep, better QoL, and daytime functioning also in OSA patients. There are several plausible pathways that may link social support with sleep, including attenuating stress responses, encouraging healthy sleep behaviours, and entraining circadian rhythms (Troxel et al., 2010). OSA patients may experience lower levels of social support compared to other populations with chronic diseases. Some previous studies explained that OSA-related symptoms can negatively impact the partners' sleep and daytime functioning (Luyster, 2017) or engagement in social activities (Luyster et al. 2016). Recently, a significant negative impact of perceived OSA symptoms on marital satisfaction was described (Tramonti et al., 2017). Another indication for lower levels of social support in patients with OSA may be the association between poor social support and sleep disordered breathing symptoms (Glenn et al., 2015). Moreover, a low level of social support was independently associated with short sleep duration when controlled for sociodemographic variables (Glenn et al., 2015).

With a few exceptions (e.g. Troxel et al., 2010; Choi et al., 2015), previous research on sleep disorders has focused mainly on the association between social support and self-reported sleep disturbances (Troxel et al., 2010). Furthermore, very little is known about the role of social support in OSA. To our knowledge, only one study by Choi et al. (2015) focused on social support in OSA patients (i.e. in the association with suicidal ideation). Recently, supportive relationships were found to be associated with CPAP treatment adherence in female patients with OSA (Baron et al., 2017). Insufficient emotional (e.g., encouragement) and instrumental (e.g. help with putting on mask, verbal reminders) support from partners of OSA patients was further identified as a barrier for CPAP adherence (Broström et al., 2010; Luyster et al., 2016). There are two dimensions of social support, namely perceived social support and received social support (Dunkel-Schetter and Bennett, 1990). Perceived social support is defined as 'the perception of an individual about the amount and quality of support received from his/her social network', while received social support is defined as 'the objective quantification of the help and aid the person receives from his/her social network' (Kim et al., 2017). Perceived social support was identified as a stronger predictor of individual well-being than received social support. Furthermore, perceived social support was found to be more strongly associated with personality traits such as self-esteem (Goodwin et al., 2004).

## 1.5   Health model

In the context of the bio-psycho-social approach (Engel, 1978), our study design is partially based on the model proposed by Wilson and Cleary (1995) (Figure 1.1). The proposed model represents a taxonomy or classification scheme for different measures of health outcomes. These outcomes are divided into four levels:

symptoms, functional status, general health perceptions, and overall quality of life (QoL) (Wilson and Cleary 1995; Krabbe, 2017). In addition to classifying these outcome measures, the authors proposed specific causal relationships between them that link traditional clinical variables to measures of HRQoL. *"As one moves from left to the right in the model, one moves outward from the cell to the individual and to the interaction of the individual as a member of society"* (Wilson and Cleary, 1995). The model captures the factors affecting health as experienced by individuals (Wilson and Cleary, 1995; Krabbe, 2017). The main purpose of the proposed model was to distinguish between conceptually distinct measures of health-related QoL outcomes and to make the dominant relationships explicit. Therefore, the displayed direction of the arrows do not imply that reciprocal relationships are absent. Neither does the absence of arrows between non-adjacent levels imply that the associations are completely missing (Krabbe, 2017).

*Figure 1.1: Relationships among measures of patient outcome in a health-related quality of life. Conceptual model by Wilson and Cleary 1995. Linking clinical variables with health-related quality of life: a conceptual model of patient outcomes. The Journal of the American Medical Association 273 (1): 59-65.*
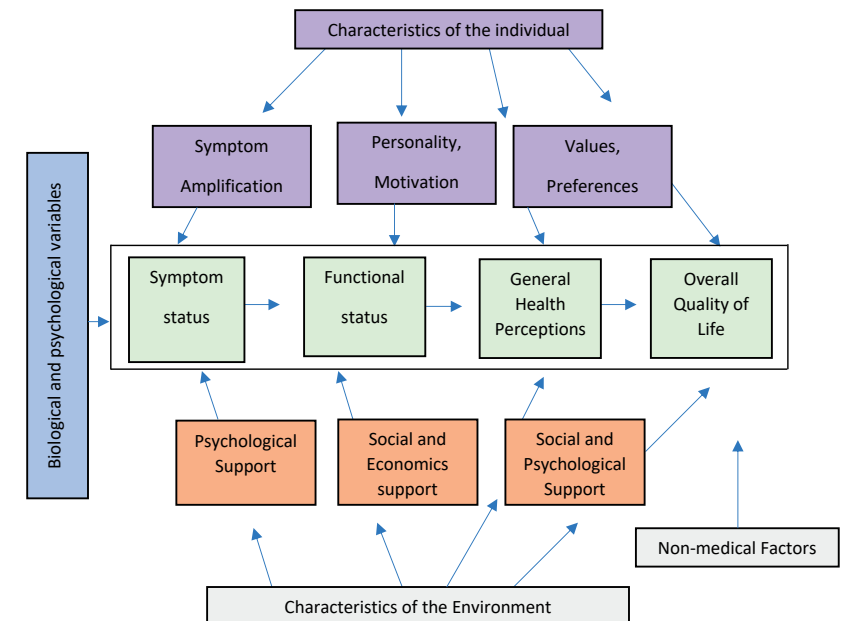
## 1.6 Aim of the thesis and research questions

This thesis aims to provide insights in the associations between biomedical, psychological, and social factors and self-reported health outcomes in patients with OSA. It builds on previous studies describing populations with various chronic diseases and adds knowledge to previous research by focusing on OSA patients. Figure 1.2 provides a visual overview of the associations examined in this thesis.

*Figure 1.2 Conceptual model of the associations examined in the thesis*



**OBSTRUCTIVE SLEEP APNOEA**

☐ biomedical factors; ☐ psychological factors; ☐ social factors; ☐ self-reported health outcomes; ☐ controlled variables
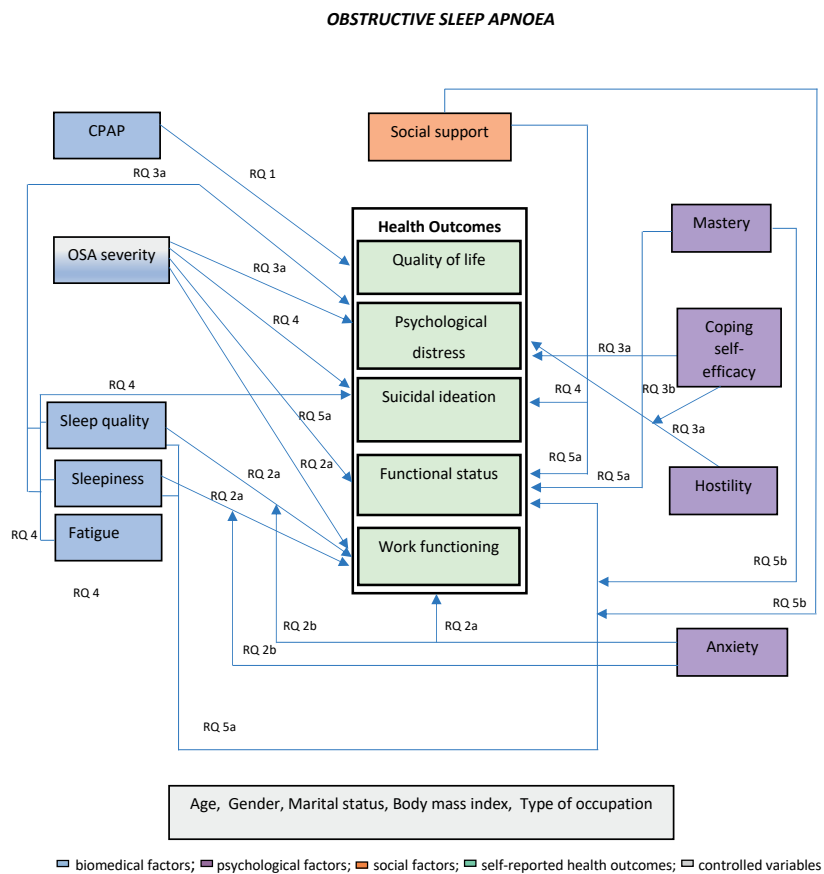
*Research question 1* (Chapter 3)
*Does Continuous Positive Airway Pressure (CPAP) treatment have a positive effect on quality of life in OSA patients when compared to sham CPAP, placebo pills, and conservative treatment?*

*Research question 2* (Chapter 4)
*Are OSA-severity, sleep-related problems, and anxiety associated with work functioning in OSA patients when controlled for age, gender, and type of occupation?*

*Research question 2a* (Chapter 4)
*Does anxiety moderate the association between sleep-related problems and work functioning?*

*Research question 3* (Chapter 5)
*Are hostility and coping self-efficacy dimensions associated with psychological distress in OSA patients when controlled for sociodemographic, clinical, and sleep-related variables?*

*Research question 3a* (Chapter 5)
*Do coping self-efficacy dimensions mediate the association between hostility and psychological distress?*

*Research question 4* (Chapter 6)
*What is the prevalence of suicidal ideation in OSA patients? Are OSA severity, sleep-related problems, and social support related to suicidal ideation in OSA patients?*

*Research question 5* (Chapter 7)
*Is there an association between social support, mastery, sleep-related problems and functional status in OSA patients when controlled for sociodemographic and clinical variables?*

*Research question 5a* (Chapter 7)
*Do social support and mastery mediate the association between sleep-related problems and functional status?*

## 1.7 Outline of the thesis

This thesis contains eight chapters.

Chapter 1: *"Introduction"* provides a general introduction into the associations between the key theoretical constucts of the thesis: OSA, CPAP treatment, self-reported health-related outcomes (functional status, work functioning, QoL and psychological distress, including suicidal ideation), sleep-related problems, anxiety,

hostility, coping self-efficacy, mastery, and social support. It also introduces the conceptual framework and research questions.

Chapter 2: *"Design of the study and data sources"* presents information about the study design. It describes the sample and procedure of the data collection and the study design and setting used in the thesis. It also provides a description of the measures and statistical analyses used.

Chapter 3: *"Quality of life of obstructive sleep apnoea patients receiving continuous positive airway pressure treatment: a systematic review and meta-analysis"* investigates the question of the effect of real CPAP treatment on QoL when compared to placebo pills, sham CPAP, and conservative treatment.

Chapter 4: *"Are disease severity, sleep-related problems and anxiety associated with work functioning in patients with obstructive sleep apnoea?"* examines whether OSA-severity, sleep-related problems, and anxiety are associated with work functioning in OSA patients. It also investigates whether anxiety moderates the associations between sleep-related problems and work functioning.

Chapter 5: *"Psychological distress in patients with obstructive sleep apnoea. The role of hostility and coping self-efficacy"* examines whether hostility and coping self-efficacy dimensions are associated with psychological distress in OSA patients. Additionally, it explores whether coping self-efficacy dimensions mediate the association between hostility and psychological distress.

Chapter 6: *"Suicidal ideation in patients with obstructive sleep apnoea and its relationship with disease severity, sleep-related problems and social support"* presents the prevalence of suicidal ideation in OSA patients and examines the relationships between OSA severity, sleep-related problems, social support and suicidal ideation in OSA patients.

Chapter 7: *"Social support, mastery, sleep-related problems and their association with functional status in untreated obstructive sleep apnoea patients"* examines the associations between social support, mastery, sleep-related problems and functional status in OSA patients. It also explores the mediating role of social support and mastery in the association between sleep-related problems and functional status.

Chapter 8: *"General discussion, implications, and conclusions"* summarizes and discusses the main findings of the thesis, its strengths, limitations and implications for practice and future research. At last, conclusions are drawn in the final section.

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A sun of rubber
was convulsed and set;
A blood black nothingness.
A system of cells.
Within cells interlinked.
Within one stem.
And dreadfully distinct.
Against the dark.
A tall white fountain played.

John Francis SHAD
and Vladimir NABOKOV

# Design of the study and data sources

This chapter provides a general overview of the study design, the origin of the data sources, and the statistical analyses used in this study.

## 2.1   Study design and setting

This cross-sectional study was conducted at the Department of Pneumology and Phtiseology, L. Pasteur University Hospital, and the Medical Faculty of PJ Safarik University in Kosice, Slovak Republic. All patients who visited the Department for a one-night polysomnography (PSG) between July 2013 and June 2016 and underwent PSG were eligible for the study. In line with ethical principles, we explained the purpose of the study to all participants and guaranteed confidentiality. We also explained that the collected data would only be used for the purposes of this study. All patients completed and signed an informed consent form prior to their participation in the study, which was fully voluntary and included no incentives for participation. The study was approved by the Ethics Committee of PJ Safarik University (approval no. 115/2011).

## 2.2   Sample and procedure

The Indication for a PSG was based on a general practitioner referral form. OSA was diagnosed based on an overnight sleep examination. Only OSA patients between 18 and 65 years of age were included due to possible functional changes, increased vulnerability and a decline in abilities and performance related to age. The study sample comprised patients with an Apnoea Hypopnoea Index (AHI; number of apnoeas+ hypopnoeas per hour of sleep) score of 5 or more, (American Academy of Sleep Medicine, 2005) who had no previous continuous positive airway pressure (CPAP) therapy or other OSA treatment, were Slovak-speaking and had no major comorbidities. Out of 263 eligible patients, 41 patients who underwent PSG refused to participate in the study, yielding a total response rate of 84.0%. Another 72 patients were excluded because of major comorbidities. The final study population comprised N=150 patients. The reasons for exclusion were major comorbidities related to sleep (a coexisting sleep disorder, such as insomnia, narcolepsy or circadian rhythm sleep disorder), major cardiovascular diseases (e.g. myocardial infarction, angina pectoris, primary pulmonary hypertension); pulmonary conditions (e.g. chronic obstructive pulmonary disease, Pickwick syndrome) and a history of cancer in the past twelve months. Neurological and psychological comorbidities included a neurological condition (e.g. stroke, epilepsy), a major psychiatric diagnosis (e.g. psychotic disorders, major depression) in the medical record, and/or current usage of psychiatric medications which may affect cognitive functions (e.g. benzodiazepines, antipsychotics, or antidepressants), drug abuse in the past six months and regular shift work in the past six months. Due to the assessment of health outcomes related to intimate relationships and sexual functioning, we excluded patients with diabetes and those using hypotensive medication, which may affect sexual function (following Hoekema et al., 2007). The screening for comorbidities was based on medical data and an initial clinical interview prior to data collection. The clinical diagnoses were established according to the standard International Classification of Diseases-10 revision Codes. Medical examinations of patients were conducted by a pulmonologist specialized in sleep-disordered breathing. Patients with non-respiratory sleep-related complaints (e.g. narcolepsy, insomnia) were routinely referred to another group of clinical specialists. The invitation letter, the informed consent and the questionnaire was sent to participants by postal mail three weeks before the medical examination. One week before the medical examination, patients were reminded about the questionnaire by a phone call. Patients completed the self-report questionnaire at home.

The final study sample comprised 150 OSA patients (AHI≥5). The sample had a mean age of 48.9±9.5 years and consisted of 68% men. More detailed information on each particular sample is described in the separate Chapters 3-7. The process of sample formation is depicted in Figure 2.1.

*Figure 2.1 Process of sample formation*
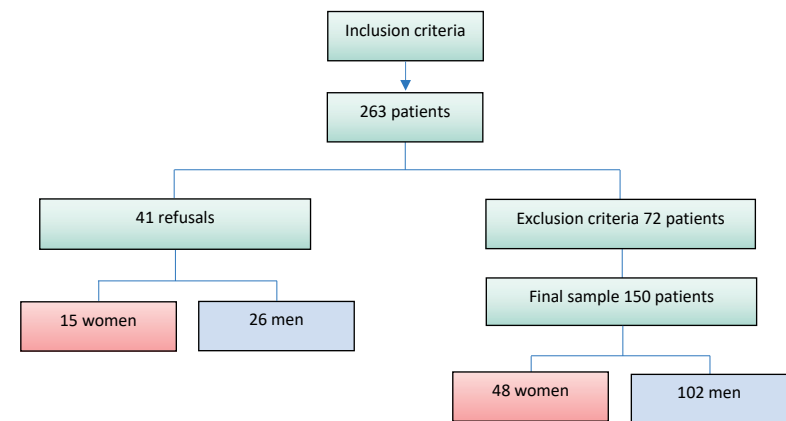
## 2.3 Measures

The Work Role Functioning Questionnaire (WRFQ 2.0) and the Functional Outcomes of Sleep Questionnaire (FOSQ) were systematically translated from the original language. A forward-backward translation was conducted to ensure that no original meaning was lost in the translation. Final changes in the translated versions were made accordingly. The measures used in the Chapters 3-7 are described below.

**Functional status**

Functional status was assessed using the Functional Outcomes of Sleep Questionnaire (FOSQ) (Weaver et al., 1997; Weaver et al., 2007). The FOSQ is a 30-item self-report, disease-specific measure designed to assess the impact of sleep disorders of excessive daytime sleepiness on multiple activities of functional outcomes relevant to daily behaviour and QoL. Functional status, as a measure of QoL, assesses those activities performed routinely in meeting basic needs and fulfilling essential roles (Leidy, 1994). The FOSQ has five subscales: activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcomes. Patients have to rate the difficulty of performing a given activity on a 4-point scale (no difficulty to extreme difficulty). Responses were averaged (excluding missing responses) to create a subscale score of 1 to 4, and then the subscale scores were summed for the total score (5-20), with higher scores indicating less effect of sleepiness on daily life (Billings et al., 2014). In our sample, the Cronbach's alphas were 0.90 for the total scale, 0.90 for the activity level, 0.84 for vigilance, 0.95 for intimacy and sexual relationships, 0.90 for the general productivity, and 0.82 for the social outcomes subscale, respectively.

**Work functioning**

Work functioning was assessed using the Work Role Functioning Questionnaire (WRFQ 2.0) (Abma et al., 2013). The WRFQ measures the perceived difficulties in performing work demands among workers, given their emotional or physical health problems. The WRFQ consists of 27 items divided into subscales: work scheduling demands and output demands, physical demands, mental and social demands, and flexibility demands. In addition, a total score can be calculated. Items are answered on a five-point scale: 0= difficult all the time (100%), 1= difficult most of the time (75%), 2= difficult half of the time (50%), 3= difficult some of the time (25%), 4= difficult none of the time (0%). The scores on 'Does not apply to my job' are transformed into missing values (Abma et al., 2013). The total score is calculated by adding all the answers and dividing by the number of items and then multiplying by 25 to obtain percentages between 0 and 100. Higher scores indicate better work functioning. To identify the prevalence of impaired work functioning, we used the cut-off value (<90) according Amick et al. (2004). In our sample, the Cronbach's alphas were 0.93 for the total scale, 0.97 for the work scheduling and output demands, 0.90 for the physical demands, 0.90 for the flexibility demands, and 0.94 for the mental and social demands subscale, respectively.

**Psychological distress**

Psychological distress was assessed using the General Health Questionnaire (GHQ-28) (Goldberg and Hillier, 1979). The GHQ-28 is a 28-item measure of psychological distress in the general population and within community or non-psychiatric clinical settings, such as among primary care or general medical out-patients. The GHQ-28 was developed as a screening tool to detect those likely to be at risk of developing psychiatric disorders. The questionnaire is divided into four subscales: somatic symptoms (items 1–7); anxiety/insomnia (items 8–14); social dysfunction (items 15–21) and severe depression (items 22–28) (Goldberg and Hillier, 1979). The items were assessed on a continuous scale (0-3), with the total score ranging from 0 to 84. Higher scores indicated a higher level of psychological distress. A total score of 23/24 represents the threshold for the presence of psychological distress (Goldberg and Hillier, 1979). In our sample the Cronbach's alpha for the total GHQ-28 scale was 0.83.

**Suicidal ideation**

Suicidal ideation was assessed using the General Health Questionnaire (GHQ-28) (Goldberg and Hillier, 1979). Four items directly dealing with suicidal ideation were used: "Have you thought about the possibility of killing yourself?"; "Do you wish to be dead and far away from everything? "; "Do you have continual thoughts about ending your life?"; and "Do you have the impression that life is not worth of living?" The validated four-item suicidal ideation subscale of the GHQ-28 has been previously used to assess suicidal ideation (Gili-Planas et al., 2001; Watson et al., 2001). In some previous studies the threshold of SI≥1 was used to assess the presence of suicidal ideation (Gili-Planas et al., 2001; Biddle et al., 2004). The GHQ threshold is partly determined by the prevalence of multiple diagnoses, with higher thresholds being associated by higher rates of both single and multiple diagnosis (Goldberg, et al. 1998). Thus, we assessed suicidal ideation in a binary manner to determine the prevalence of suicidal ideation, with a cut off of SI≥2, with the negative responses, given a score of zero, and the positive responses a score of one. The sum-score of the four items of suicidal ideation ranged from 0 to 4. Suicidal ideation was also used as continuous variable (1-4) in structural equation modelling, with a range from 4 to 16. Higher scores indicated a higher level of suicidal ideation. In our sample the Cronbach's alpha was 0.83.

**Anxiety**

Anxiety was measured using the 21-item Beck Anxiety Inventory (BAI), defining the most common anxiety symptoms (Beck and Steer, 1990). The BAI is a brief measure of anxiety with a focus on somatic symptoms. It was developed as an efficient measure to discriminate between anxiety and depression (Beck et al., 1988). Scores range from 0 to 63, with higher scores indicating a higher anxiety level. The following categories were defined: no anxiety symptoms (score 0-9), mild anxiety (score 10-18), severe anxiety (score 19-29), and very severe anxiety (score 30-63) (Beck and Steer, 1990). The Cronbach's alpha in our sample was 0.90.

## Hostility

Hostility was measured by the abbreviated 27-item version of the Cook-Medley Hostility Scale (CMHo) (Cook and Medley, 1954). The CMHo scale is a widely used self-report measure of the trait hostility. The scale primarily assesses the cognitive aspects of hostility, cynicism and mistrust. Cynicism items are defined as statements of belief; aggressive response items reflect behaviour, and hostile affect items reflect emotional experiences. Each item was rated on a dichotomised scale (1="true", 0="false"). The score ranges from 0 to 27, with a higher score indicating a higher level of symptoms (Cook and Medley, 1954). The Cronbach's alpha for the total scale in our sample was 0.85.

## Coping self-efficacy

Coping self-efficacy (CSE) was measured using the 26-item CSE Scale developed specifically for people suffering from chronic disease (Chesney et al., 2006). The CSE scale represents a measure of an individual's confidence in performing coping behaviours when faced with life challenges. The term CSE relates to the tendency to make certain attributions about control not in one context but many (Lazarus and Folkman, 1984). The CSE scale advances our ability to explore the theoretical links between the secondary appraisal of stress, which asks 'what can I do?', and the major coping functions postulated by stress and coping theory – the regulation of distress and the management of underlying problems (Chesney et al., 2006). Coping self-efficacy and coping behaviour are closely linked to each other (Park and Folkman, 1997; Bandura, 1999; Chesnay et al., 2006; Mikula et al., 2014; Mikula et al., 2018). The term coping self-efficacy is understood as a prerequisite for using actual coping strategies, as people need to be sure that they can perform coping actions before they act upon them (Chesney et al., 2006). Patients were asked to respond to the following question: 'When things are not going well for you, or when you are having problems, how confident or certain are you that you can do the following': 'sort out what can be changed, and what cannot be changed', 'break an upsetting problem down into smaller parts', 'look for something good in a negative situation', and 'get emotional support from friends and family', or 'take your mind off unpleasant thoughts'. The CSE consists of three subscales representing self-efficacy for the use of 'problem-focused coping' strategies (ranging from 0 to 120), 'ability to get support from friends and family' (ranging from 0 to 50) and the 'ability to stop unpleasant emotions and thoughts' (ranging from 0 to 90). Coping self-efficacy for the use of 'problem-focused coping' consists of items that measure an individual's self-efficacy with respect to overcoming problems by analysing the nature of the problem and employing cognitive strategies to make the respondent's perception of the problem less severe (e.g. 'break an upsetting problem down into smaller parts'). Coping self-efficacy for the 'ability to stop unpleasant emotions and thoughts' measures a respondent's self-efficacy with respect to trying not to dwell on negative feelings and altering the emotional response to an unsettling event or problem rather than addressing the characteristics of the problem itself (e.g. 'take your mind off negative thoughts'). The 'ability to get support from friends and family' represents a set of items that captures a social dimension by tapping the respondent's perception of their ability to seek help from friends and family to cope with problems (e.g. 'get emotional support from friends and family') (Chesney et al., 2006). The three factors in the CSE scale are consistent with the three major aspects of coping – problem-focused coping, emotion-focused coping, and social support. Although the scales are correlated, the results of the concurrent validity analyses indicate that the scales assess self-efficacy with respect to different types of coping and lend support to using the factors separately (Chesney et al., 2006). Respondents answered on an 11-point scale. A higher score indicates a higher ability to cope with a particular situation (Chesney et al., 2006). In our sample, the Cronbach's alphas were 0.94 for self-efficacy for the use of problem-focused coping strategies, 0.86 for coping self-efficacy focused on getting support, and 0.93 for stopping unpleasant emotions and thoughts, respectively.

## Mastery

Mastery was measured using the Pearlin Mastery Scale (PMS) (Pearlin and Schooler, 1978). The PMS measures an individual's level of mastery, a psychological resource that has been defined as "the extent to which one regards one's life-chances as being under one's own control in contrast to being fatalistically ruled" (Pearlin and Schooler, 1978). The scale includes 7 items (five negatively worded items and two positively worded items), e.g. "You have little control over the things that happen to you", and "What happens to you in the future mostly depends upon you". The negatively worded items require reverse coding prior to scoring, resulting in a score range of 7 to 35, with higher scores indicating higher levels of mastery (Pearlin and Schooler, 1978). The Cronbach's alpha of the scale was 0.85.

## Social support

The Multidimensional Scale of Perceived Social Support (MSPSS) is a 12-item self-report measure of social support (Zimet et al., 1988). It uses a seven-point Likert-type scale, with scores ranging from 'very strongly disagree' (1) to 'very strongly agree' (7), so the total score ranges from 12 to 84, with higher scores indicating greater social support (Zimet et al., 1988). The MSPSS has three subscales: significant others, family, and friends. In our sample, the Cronbach's alpha was 0.90 for all three separate subscales, and 0.94 for the total scale, respectively.

## Sleep-related problems

Sleep-related problems concerned night-time sleep quality, daytime sleepiness and fatigue. *Night-time sleep quality* was measured using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI is a self-rated questionnaire to assess sleep quality and disturbances over a one-month time interval. The PSQI consists of 19 self-report questions covering seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. The score ranges from 0 to 21, with higher scores reflecting poor night-time sleep quality. A cut-off score of 5 separates good from poor sleepers (Buysse et al., 1989). Results of some previous studies suggested that the seven PSQI domains are best represented by three latent factors (e.g.

Cole et al., 2006; Casement et al., 2012). The empirical examination of the factor structure of the PSQI identified distinct factors for perceived sleep quality, sleep efficiency, and daily disturbances (Cole et al., 2006). The PSQI subscales subjective sleep quality, sleep medications, and sleep latency loaded on the latent variable *perceived sleep quality*; the PSQI subscales sleep duration and habitual sleep efficiency loaded on the latent variable *sleep efficiency*; and the PSQI subscales sleep disturbances and daytime dysfunction loaded on the latent variable *daily disturbances* (Cole et al., 2006). *Sleep efficiency* is closely related to sleep quantity (Casement et al., 2012), while *daily disturbances* reflect sleep-related daytime impairment (i.e., trouble performing daytime activities) and interruptions in sleep due to physical or psychological symptoms (Casement et al., 2012). In our sample, the Cronbach's alpha was 0.85 for the total PSQI scale.

*Daytime sleepiness* was measured using the self-report Epworth Sleepiness Scale (ESS), an eight-item questionnaire assessing the tendency to fall asleep in various daytime scenarios (Miletin and Hanly, 2003). The score ranges from 0 to 24, with higher scores indicating greater daytime sleepiness. An ESS total score greater than 10 indicates excessive daytime sleepiness (Miletin and Hanly, 2003). The Cronbach's alpha in our sample was 0.86.

*Fatigue* was measured using the Multidimensional Fatigue Inventory (MFI-20) (Smets et al., 1995). It consists of 20 items that measure five dimensions of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. Each dimension contains four items with a five-point response format; the total score in each dimension ranges from 4 (no fatigue) to 20 (highest possible fatigue). The Cronbach's alphas were 0.80 for general fatigue, 0.89 for physical fatigue, 0.75 for reduced activity, 0.81 for reduced motivation, and 0.83 for mental fatigue, respectively.

**Sociodemographic and clinical data**
Information on age, gender, and marital status was obtained from patient records. Patients were asked to identify the one industry that best characterized their current employment (over the last 24 months) from a list of International Standard Classification of Occupations (International Labour Office, 1990). Patients were also asked to specify their occupation to reduce incorrect or inconsistent information. OSA patients in the following industries were classified as blue-collar workers: primary resource industry, construction industry, manufacturing industry, warehousing, transportation, and trade. Patients employed in public administration, armed forces, government and the service sector (including tourism, business services, education, healthcare, legislators, managerial occupations, professional and utilities) were classified as white-collar workers. Body Mass Index (BMI; height and weight) was assessed by a physician. BMI was categorized into: underweight (<18.50), normal (18.50-24.99), overweight (25.00-29.99) and obese (≥30.00). PSG was used to determine whether the diagnosis of OSA was present and to identify the severity of the disorder. OSA severity was determined based on the AHI (American Academy of Sleep Medicine, 2005) score, with three categories: mild OSA (AHI ≥5 and ≤15), moderate OSA (AHI >15 and ≤30) and severe OSA (AHI

>30). OSA severity was used as a continuous variable measured by AHI. OSA severity was determined using PSG and was based on an AHI (number of apnoeas + hypopnoeas per hour of sleep) score of 5 or more, according to standard criteria (American Academy of Sleep Medicine, 2005). An obstructive apnoea or hypopnoea can be defined as an event that lasts for ≥ 10 s and is characterized by an absence or a decrease from baseline in the amplitude of a valid measure of breathing during sleep that either reaches >50% with an oxygen desaturation of 3% or an arousal (alternatively a 30% reduction with 4% desaturation) (American Academy of Sleep Medicine, 2005). PSG consisted of the overnight recording of left and right electrooculograms, standard central and occipital electroencephalogram, submental electromyogram (EMG), bilateral tibialis EMG, nasal and oral airflow using a thermistor and thoracic, and abdominal excursions using respiratory inductive plethysmography, which directly monitor and quantify the number of respiratory events, related hypoxemia and arousals.

## 2.4  Statistical analyses

Several statistical methods were used for data analyses. The majority of the analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS 23), MedGraph, and ModGraph. Data management in the meta-analyses was conducted as proposed by Neyeloff et al. (2012). Additionally, Structural Equation Modelling (SEM) was performed (Chapter 6) with Mplus 7.1 (Muthén and Muthén, 2015). We described the background characteristics of the sample and calculated means and standard deviations (SD) for the total sample for continuous variables (Chapter 4-7) and stratified by variables under study, including gender (Chapter 7) and suicidal ideation (Chapter 6). Descriptive procedures included frequencies and percentages for categorical variables. T-tests were conducted to assess differences in the continuous variables. Differences in the categorical variables were analysed using Chi-square tests. Before we proceeded with more complex analyses, we investigated the bivariate correlations between the variables under study (Chapter 4, 5, 7). Partial correlations were used to control for sociodemographic variables (Chapter 6, Chapter 7). We applied an enter method in linear regression in Chapters 4, 5, and 7. We used G*Power 3 (Faul et al., 2009) to analyse different types of power in different statistical tests with medium effect size at α=0.05. Multicollinearity was assessed using the variance inflation factor (VIF<2.0). Missing data were expressed as percentage of total number of patients for each variable. A p-value of <0.05 was considered statistically significant. Finally, we performed mediation (Chapter 5 and Chapter 7) and moderation analyses (Chapter 4). The proportion of the effect which is mediated was calculated as the indirect effect divided by the total effect and multiplied by 100, while the as-advised standardized total effect was at least ±0.2 (Kenny, 2016). Sobel z-tests were used to examine the mediating effects in Chapters 5 and 7. To test the moderation effects (Chapter 4), the interaction terms between independent variables were added into the equation (Baron and Kenny, 1986). Detailed information about statistical analyses performed can be found in the "Statistical analyses" section of each chapter.

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# Quality of life of obstructive sleep apnoea patients receiving continuous positive airway pressure treatment: a systematic review and meta-analysis

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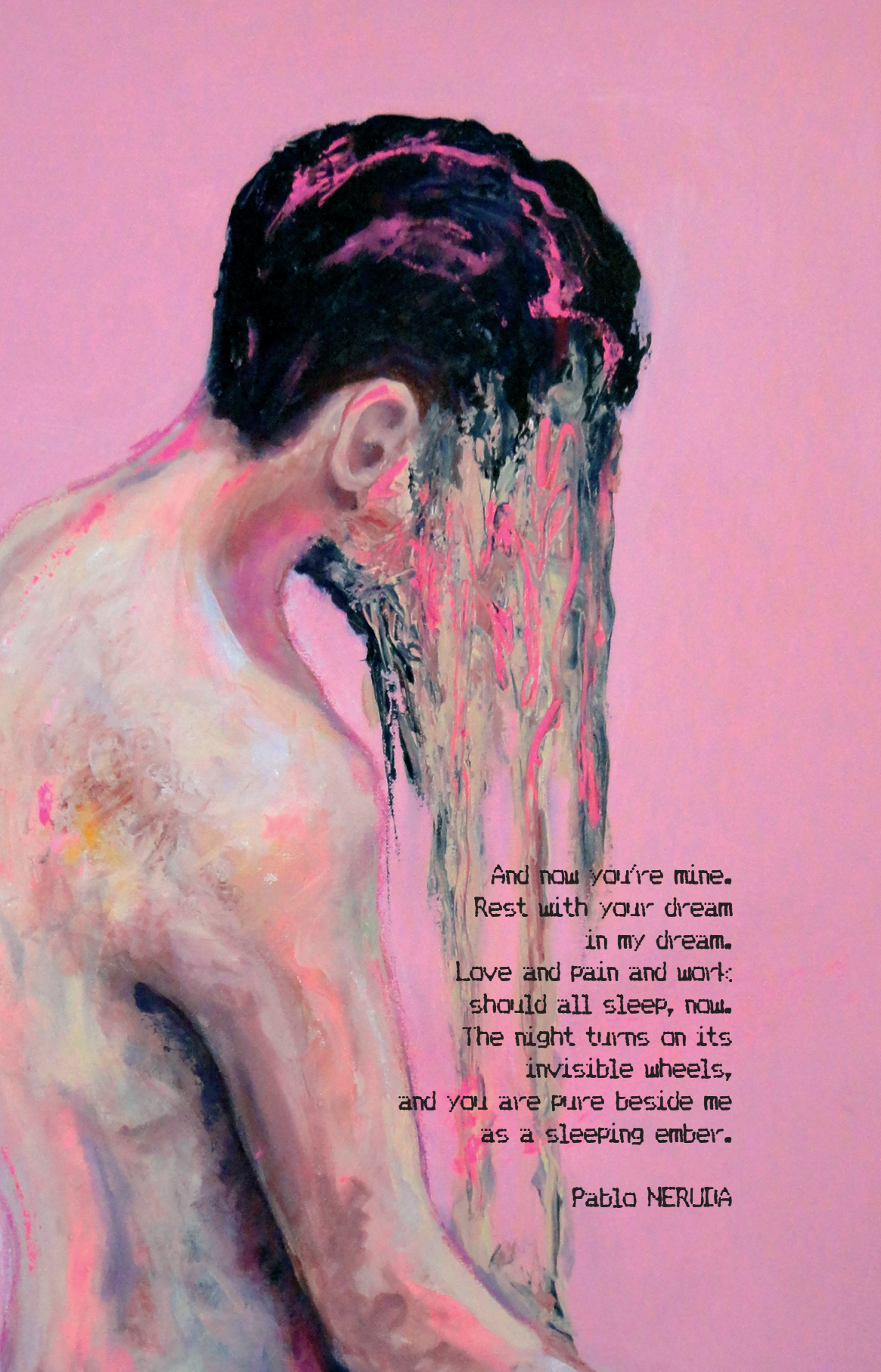
And now you're mine.
Rest with your dream
in my dream.
Love and pain and work
should all sleep, now.
The night turns on its
invisible wheels,
and you are pure beside me
as a sleeping ember.

Pablo NERUDA

## Abstract

### Background

Previous studies have shown conflicting results on the effect of continuous positive airway pressure (CPAP) on quality of life (QoL) in obstructive sleep apnoea (OSA) patients.

### Objectives

To systematically evaluate the effect of CPAP on QoL in OSA patients compared to sham CPAP, placebo pills, and conservative treatment.

### Methods

Studies were identified via Web of Knowledge, PubMed, PsychInfo, CINAHL, EMBASE, OpenGrey, and the Cochrane Library. Effect sizes and effect summaries were used for estimation of CPAP treatment effect. Subgroup analyses and sensitivity analyses were conducted to assess the robustness of the findings.

### Results

Meta-analysis of 13 randomised controlled trials showed no significant differences in overall and psychological QoL comparing values of CPAP treated patients with controls; however, physical QoL improved. CPAP significantly affected the overall QoL in studies with controls receiving sham CPAP, parallel design, low risk of bias, and mild OSA patients.

### Conclusion

Medical treatment of OSA may help to improve physical symptoms of OSA, whereas impaired psychological QoL still cannot be successfully alleviated with CPAP treatment.

## Introduction

Obstructive sleep apnoea (OSA) is an incapacitating chronic disease characterized by repetitive sleep-related episodes of complete (apnoea) or partial (hypopnoea) breathing pauses. It is a prevalent disorder associated with a multitude of adverse outcomes (Aurora et al., 2015). Symptoms of OSA include snoring, sleepiness, and fatigue (Manarino et al., 2012). Most studies have found that OSA concerns 2–10% of the adult population (Stradling and Davies, 2004; Leger et al., 2012). The prevalence of undiagnosed OSA syndrome in Western countries is up to 5% (Young et al., 2002). The impact of OSA on both morbidity and socioeconomic costs is enormous. Costs concern, in particular, health care expenditures and reduced work capacity and work participation (Stradling and Davies, 2004; Mulgrew et al, 2007). Although the exact costs are difficult to calculate, data from 106 countries showed that increased healthcare spending to treat undiagnosed OSA varies between 1,950 and 3,899 dollars per patient per year (Knauert et al., 2015).

OSA is associated with poor quality of life (QoL) (Sharafkhaneh et al., 2005; Mulgrew et al., 2007; Weaver, 2013) and has been linked to severe public health issues, such as obesity, diabetes, metabolic syndrome, cardio-vascular diseases (Stradling and Davies, 2004; Tkacova and Dorkova, 2010), and neuropsychiatric problems (Tkacova and Dorkova, 2010). The occurrence of an impairment in cognitive functioning, reduced vigilance (Kang et al., 2012), microsleeps or accidents is typical in people with OSA (Tregear et al., 2009). Sharafkhaneh et al. (2005) showed a significantly higher prevalence of mood disorders, posttraumatic stress disorder, psychosis and dementia among OSA patients. Some studies report an increased prevalence of suicidal ideation in OSA patients (Choi et al., 2015) when compared to the general population.

In terms of treatment, continuous positive airway pressure (CPAP) is the first treatment of choice in most OSA patients (American Academy of Sleep Medicine, 2008). CPAP has been reported to be effective in reducing OSA symptoms, cardiovascular morbidity and mortality, neurocognitive consequences and sleepiness, and in improving QoL (Moyer et al., 2001; Giles et al., 2006; Ye et al., 2009; Kuhn et al., 2017). Krahn et al. (2008) described a decrease in depression and suicidal ideation in untreated OSA patients immediately after the initiation of CPAP treatment. In recent years, increasing attention has been paid to the effectiveness of CPAP treatment on QoL improvement. The efficiency of OSA treatment has typically been judged based on polysomnography (PSG) outcomes. However, patients' reports of improvement were often found to be discordant with PSG results. Thus, other clinically important outcomes, including QoL and functional status, have been recommended as complementary outcomes in the evaluation of treatment response (Weaver et al., 2005).

Previous systematic reviews (Moyer et al., 2001; Merino et al., 2017) and meta-analyses (Jing et al., 2008; Kuhn et al., 2017; Patil et al., 2019) have shown conflicting results on the effect of CPAP treatment on QoL in OSA patients. The findings vary from improvement of QoL after receiving CPAP treatment (Moyer et al., 2001;

Merino et al., 2017) to improvement in the physical QoL domain only (Jing et al. 2008), or overall QoL improvement only when disease specific QoL measures (Patil et al., 2019), and also when all prospective studies, i.e. not only randomised controlled trials (RCTs) (Kuhn et al., 2017), were included.

Furthermore, earlier meta-analyses of RCTs included only one type of QoL measure (Kuhn et al., 2017); analysed studies focusing exclusively on elderly OSA patients (Jing et al., 2008; Kuhn et al., 2017; Merino et al., 2017) and included studies where the whole sample of OSA patients suffered from major comorbidities, such as stroke or heart failure (Jing et al., 2008; Kuhn et al., 2017; Patil et al., 2019), or studies of a combination of CPAP treatment with conservative treatment (Jing et al., 2008; Patil et al., 2019). We therefore aimed to systematically evaluate the effect of CPAP treatment on QoL in OSA patients compared to sham CPAP, placebo pills, and conservative treatment. Our systematic review and meta-analysis was restricted to RCTs only, with the exclusion of studies having a clear focus on major comorbidities, populations of children or elderly OSA patients, and studies that combined CPAP treatment with conservative treatment.

## Methods

A systematic literature review was conducted in accordance with the current guidelines for systematic reviews and meta-analyses (Higgins and Green, 2011). The multidisciplinary systematic review team consisted of six reviewers (VT, IN, SAR, RT, JPvD, and UB). Two authors had expertise in psychology (VT, IN), one in pulmonology, tuberculosis and respiratory diseases (RT), and three authors were trained in epidemiological methods and public health (SAR, JPvD, and UB).

### Formulation of the research question

The research question was formulated according to the PICO method (Higgins and Green, 2011), i.e.: 'In obstructive sleep apnoea patients, what is the effect of CPAP treatment on QoL compared to placebo pills, sham CPAP, and conservative treatment?' The anticipated *outcome* was improved overall QoL as well as the improvement in psychological and physical QoL after CPAP treatment.

### Search strategy and study identification

Studies were identified via Web of Knowledge, PubMed, PsychInfo, CINAHL, EMBASE, and the Cochrane Library from the inception date of the databases to March 2019. OpenGrey database was searched for any resources that might have been missed. Previous systematic reviews, meta-analyses, and guidelines were sought, and their reference lists were scanned. We did not include dissertations, economical evaluations, technical reports, conference abstracts, case studies, and letters. We did not use any language restrictions. Titles and abstracts were screened to identify potentially relevant studies. If the suitability of an article was uncertain, the full text was reviewed. We used keywords (Table 3.1) according to the PICO method (Higgings and Green, 2011). The detailed literature search strings for each

of the databases can be found in Supplement 3.1 (Table S3.2). Inclusion criteria were: RCTs examining the effect of CPAP treatment on QoL in OSA patients compared to controls using placebo pills, sham CPAP, or conservative treatment.

*Table 3.1 Description of used keywords according to the PICO method*

| P=population/patients/problem | 'sleep apnea', 'sleep apnoea', 'OSA' |
|---|---|
| I=intervention | 'continuous positive airway pressure', 'CPAP' |
| C= comparison/control | 'placebo pills', 'sham CPAP', 'conservative treatment' |
| O=outcome | 'quality of life', 'health status', 'self-rated health', 'self-perceived health', 'functional status' |

### Exclusion criteria

We excluded reviews, meta-analyses, studies focusing only on compliance with CPAP treatment or side effects of CPAP and different healthcare services, studies including only baseline comparison without a control group, and studies focusing on other types of treatment, or a combination of CPAP treatment with conservative treatment, such as lifestyle interventions. Studies including children, adolescents (<18), and elderly OSA patients (≥65 years of age) only were also excluded because of a possible increased vulnerability, functional changes, and a decline in abilities and/or performance related to age. Since major comorbidities may influence QoL, sleep, and affective symptomatology (Macey et al., 2010), studies including a primary study sample with an acute or severe comorbid medical illness, such as stroke, neurological disorders, heart failure, myocardial infarction, cognitive decline, or psychiatric diagnoses, were also excluded. The verification of the presence of major comorbidities in the full sample of OSA patients was based on Title, Abstract, and full-text screening.

We developed a form to standardize the first selection of relevant studies, based on the following criteria: 1) the study is an RCT, quantitative, and interventional; 2) the study population consists of adult OSA patients diagnosed by a medical professional; 3) the intervention is CPAP, and a control condition is present; and 4) generic or disease-specific QoL is measured. The title, abstract, and full-text screening were conducted independently by VT and IN. Disagreements were resolved by reaching a consensus of opinion. A third author (UB) was invited if consensus could not be achieved. Full-text screening was conducted by VT.

### Types of studies

We included RCTs with parallel (Jenkinson et al., 1999; Barbé et al., 2001; Montserrat et al., 2001; Chakravorty et al., 2002; Siccoli et al., 2008; Weaver et al., 2012; Batool-Anwar et al., 2016) and crossover design (Engleman et al., 1997; Engleman et al., 1998; Engleman et al., 1999; Faccenda et al., 2001; Barnes et al., 2004; Marshall et al., 2005).

## Type of participants

Included were OSA patients newly diagnosed by a medical professional using nocturnal, laboratory-based PSG or oximetry. The standard criterion of five or more apnoeas/hypopnoeas per hour of sleep was used to diagnose OSA by PSG. OSA patients were diagnosed as mild, moderate and severe, with an AHI greater than 5/hr, 15/hr, and 30/hr, respectively (Iber et al., 2007). In oximetry, an apnoea was defined as a minimum of 10 seconds of airflow cessation, and a hypopnoea was determined by a 30% reduction in airflow preceding a period of normal breathing for a minimum of 10 seconds and oxyhemoglobin desaturation (decrease in $SpO_2 \geq 4\%$) (Berry et al., 2012). Severity of OSA was measured by the number of falls in arterial oxygen saturation ($SaO_2$) of more than 4% in each hour of study (Jenkinson et al., 1999). All participants were treatment naïve at the start of the research. Controls/comparisons were defined as placebo pills, sham CPAP, and conservative treatment.

## The intervention

The intervention was defined as CPAP treatment with a duration of at least two weeks. CPAP devices were titrated to an effective pressure to overcome respiratory disturbances.

## Concept of quality of life and health-related quality of life

The World Health Organization Quality of Life (WHOQoL) group defined QoL as 'an individual's perception of their position in life, in the context of the culture and values in which they live and in relation to their goals, expectations, standards and concerns' (WHOQoL Group, 1994). QoL has several domains, such as functional competence, health-related complaints, and psycho-social functioning. Health-related QoL (HRQoL) is understood as an integral QoL domain and is increasingly used as an outcome of treatment effectiveness. In broad terms, HRQoL serves as a restricted QoL definition, as it was designed to exclude external domains, such as housing, financial situation, living conditions or spirituality. HRQoL is associated with an expanded concept of health status, embracing social interaction as well as emotional and psychological well-being (Krabbe, 2017). The concepts of QoL and HRQoL are closely tied to each other (Dutt et al., 2016). When QoL is discussed in relation to health or diseases, it almost always means HRQoL, unless specified otherwise (Dutt et al., 2016). According to Schipper (1992), QoL in clinical medicine represents the functional effect of disease and its consequent treatment upon patient, as perceived by the patient. It is concluded that the concept of HRQoL as used now is confusing as most of the definitions fail to distinguish between HRQoL and health or between HRQoL and QoL (Carlozzi and Tulsky, 2013; Karimi and Brazier, 2016). Perhaps more reasonable is the variant of the definition, where HRQoL is the aspects of QoL the most significantly affected by ill health. However, in practice, this definition may not eliminate the number of QoL domains much because it is problematic to define 'most' (Karimi and Brazier, 2016). Furthermore, most of the previous systematic reviews and meta-analyses (Moyer et al., 2001; Jing et al., 2008; Schwartz et al., 2018; Patil et al., 2019) as well as all RCTs included in our meta-analysis used the term QoL, while one RCT used both terms interchangebly (Chakravorty et al., 2002). Thus, we will use in this paper the term QoL, with omission of external domains, such as spirituality or living conditions.

## Main comparisons

Based on the type of QoL scales we aimed to conduct the following comparisons: a) the effect of CPAP treatment on overall QoL (using general QoL scales); b) the effect of CPAP treatment on psychological QoL (using psychological QoL subscales); c) the effect of CPAP treatment on physical QoL (using physical QoL subscales).

## Sensitivity analyses

We conducted sensitivity analyses to reveal the potential sources of heterogeneity, such as the number of participants in analysed studies, the duration of CPAP treatment, the level of compliance with CPAP treatment, and risk of bias (RoB). We repeated the analyses with restrcitions regarding: *a) number of participants N>100* (the effect of CPAP treatment on overall/psychological/physical QoL in RCTs involving participants of N>100 (following Dechartres, 2013; Grainge, 2015)); *b) duration of CPAP treatment >6 weeks* (the effect of CPAP treatment on overall/psychological/physical QoL in RCTs with duration of CPAP treatment of more than 6 weeks); *c) compliance level ≥4 h/night* (the effect of CPAP treatment on overall/psychological/physical QoL in RCTs involving participants with CPAP compliance level of ≥4h/night); and *d) low RoB* (the effect of CPAP treatment on overall/psychological/physical QoL restricted to RCTs with low RoB).

## Subgroup analyses

We analysed how the CPAP treatment effect varies across different subgroups of patients or trials. The covariates included type of control group, OSA severity, study design, and type of QoL measures. The following subgroup comparisons were conducted based on: *a) type of control group* (the separate analyses of the effect of CPAP treatment on overall/psychological/physical QoL in RCTs involving controls using placebo pills, sham CPAP, and conservative treatment); *b) OSA severity* (the separate analyses of the effect of CPAP treatment on overall/psychological/physical QoL in RCTs involving patients with mild OSA and moderate to severe OSA); *c) study design* (the separate analyses of the effect of CPAP treatment on overall/psychological/physical QoL in RCTs with a crossover design and parallel design); *d) type of Qol measures* (the separate analyses of the effect of CPAP treatment on overall/psychological/physical QoL in RCTs using generic QoL measures and disease-specific measures).

## Data extraction and management

Two authors (VT, IN) extracted the following information from each study: *a) general:* title, country, language of publication, year of publication; *b) methods:* study design, setting, inclusion and exclusion criteria, follow-up, standardized QoL instruments, QoL domains; *c) participants:* OSA diagnosis, adult population (age of

the whole group > 18 years, ≤ 65 years), no focus on major comorbidid diseases other than OSA (such as stroke, myocardial infarction, neuropsychiatric disorder), age, sex distribution; *d) intervention per treatment group:* use of CPAP treatment, duration of CPAP treatment; compliance with CPAP treatment; *e) controls/comparisons:* placebo pills, sham CPAP, conservative treatment; *f) outcomes:* QoL improvement, overall QoL scores, and psychological/physical QoL; *g) results:* CPAP treatment effect on QoL improvement in OSA patients. In case of disagreement in data extraction, consensus was achieved by discussion between the two review authors (VT, IN). If needed, a third author (UB) was invited to resolve disputes. Mean differences between the groups for the continuous outcomes, and standard deviations/standard errors of the group differences were extracted for the meta-analysis.

### Dealing with missing data

When information for the meta-analysis was missing, we asked the author to provide the information. If the author did not reply, or the information was no longer available, the study was not included in the meta-analysis.

### Assessment of risk of bias

The risk of bias (RoB) was assessed by two authors (VT, UB) using the Cochrane Collaboration tool for assessing RoB, as described in the *Cochrane Handbook for the Systematic Review of Interventions*, version 5.1.0 (Higgins and Green, 2011). The following nine criteria were assessed: Random sequence generation, Allocation concealment, Blinding of participants, Blinding of personnel, Blinding of outcome assessment, Co-interventions avoided, Treatment fidelity, Incomplete outcome data and Selective outcome reporting. We scored the criteria as 'low RoB, 'high RoB', or 'unclear RoB' (Higgins and Green, 2011). When the two independent authors disagreed about the RoB, they tried to reach a consensus. If consensus could not be achieved, a third author (IN) was invited in. Key domains for summary RoB assessment were identified, such as random sequence generation, allocation concealment, and incomplete outcome data (Nieuwenhuijsen et al, 2014). We judged studies to have a high RoB when one or more key domains were rated as high RoB. We judged studies to have an unclear RoB when one or more key domains were rated as "unclear". We judged studies to have a low RoB when all the key domains were rated as low RoB (Higgins and Green, 2011; Nieuwenhuijsen et al, 2014). Subsequently, we calculated the proportion of items that were scored as having low, unclear, or high RoB.

### Assessment of heterogeneity

Heterogeneity was investigated using Cochrane's Q statistic and $I^2$ statistics. Due to differences in sample sizes of the included studies, we used random-effects models, as study weights were defined to be more balanced under the random-effects model than under the fixed-effects model (Borenstein et al., 2009). Furthermore, when studies are gathered from the published literature, the random-effects model is found to be generally a more plausible match (Borenstein et al., 2009). As

Cochrane's Q is considered to be vulnerable to small sample sizes, the $I^2$ provided an estimate of the proportion of real variance caused by extraneous study variables. $I^2$ thresholds have been proposed (Higgins et al., 2003), with 25, 50, and 75% representing low, moderate, and high variance, respectively.

### Assessment of reporting biases

Visual inspection with funnel plots and the Egger test (Egger et al., 1997) were used to evaluate publication bias in the reviewed studies.

### Quality of the evidence

We applied GRADE criteria (Ryan and Hill, 2016) to assess the confidence in the estimated effects within the studies. Two reviewers (VT, IN) worked independently to assess the quality of the evidence and resolve disagreements. At the start of the GRADE assessment we assumed the presence of high quality for all included studies. We downgraded a starting rating of "high quality" evidence by one level (or by two levels for very serious concerns) for RoB, inconsistency, indirectness, imprecision, and publication bias (Ryan and Hill, 2016).

We considered random sequence generation, allocation concealment, and incomplete outcome data as prerequisites for high quality (following Nieuwenhuijsen et al., 2014). We only considered studies with low risks on these items to have a low RoB. To assess the RoB for a comparison, we considered the RoB for each study included in that comparison (following Ryan and Hill, 2016). For each comparison we downgraded the quality due to the RoB (-1) if most of the outcome information was from studies at low or unclear RoB, as this could seriously alter the results. We applied a -2 downgrade in case of a high RoB for one criterion, or multiple criteria, that were considered as likely to very seriously alter the results. For inconsistency, we considered an $I^2$ value of 50% to 75% downgrade (-1). Indirectness of the evidence was not an issue in our review, as all comparisons in the included studies directly addressed the comparison. For imprecision of results, we judged serious imprecision leading to downgrading (-1) if a comparison either included less than 400 participants or a wide CI around the effect estimate. For a non-significant effect, we considered a CI to be wide if it included an effect size of both 0 and a moderate effect size (>0.5 or <-0.5). For a significant effect, we considered a CI to be wide if it included both a small and large effect size (small=0.2 or -0.2; large=0.8 or -0.8). We applied a -2 downgrade in case of imprecision based on the both assessed points.

In the GRADE system, the quality of evidence for each outcome is scored as high, moderate, low, or very low. In high quality studies, further research is very unlikely to change our confidence in the estimate of effect. In studies with moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality of evidence means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. In studies with very low quality of the evidence any estimate of effect is very uncertain (Ryan and Hill, 2016).

## Measures of treatment effect and data synthesis

A total of 13 RCTs were included in the MA. The analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS 23) and Microsoft Office Excel, following Neyeloff et al. (2012). We used random-effects models by calculating the Cohen's d effect sizes (ES) with their standard errors (SE) as the standardized outcome of the CPAP treatment effect (Hedges and Olkin 2014). ES was calculated for each QoL outcome for which a complete assessment was possible. ESs were calculated from means and standard deviations (SD). When the SD was not available it was calculated from the SE of the mean using the following formula: $SD = SE\sqrt{N}$. Cohen's d ES was calculated according to the following formula:

$$ES = \frac{mean\ controls\text{-}mean\ CPAP}{pooled\ SD}\ .$$

ES was positive, if the mean difference was in the predicted direction and favoured real CPAP treatment (where 0.20-0.40 means a small ES; 0.50-0.70 a medium ES; and 0.80 or higher a large ES). The comparison of CPAP treatment effect vs. the control group was described as: 'negative direction of ES' for differences favouring the control group; and 'positive direction of ES' for differences favouring the real CPAP treatment group. Finally, the effect summary ($\overline{ES}_V$) was computed using a random effects model by calculating a new weight ($w_V$) for each QoL outcome adjusted with the constant (v). $\overline{ES}_V$ was calculated using the following formula: $\overline{ES}_V = \frac{\sum (W_V{}^*ES)}{\sum W_V}\ .$

Additionally, the confidence intervals (CIs) for the ES of each study and ($\overline{ES}_V$) were computed with the 95% confidence coefficient used as the default, following Hedges and Olkin (2014). CIs were calculated with the formula $CI = ES \pm 1.96.SE$. Forest plots were used for graphical representations of the MA.

# Results

## Results of the search process

After title, abstract, and full-text screening, 13 RCTs describing the effectiveness of CPAP treatment met the inclusion criteria (see flowchart Figure 3.1). One of the eligible studies (Campos-Rodrigues et al., 2016) was excluded from our MA, as we did not receive the missing, additional information.



*Figure 3.1 Flow diagram of study selection process (Moher et al., 2009)*
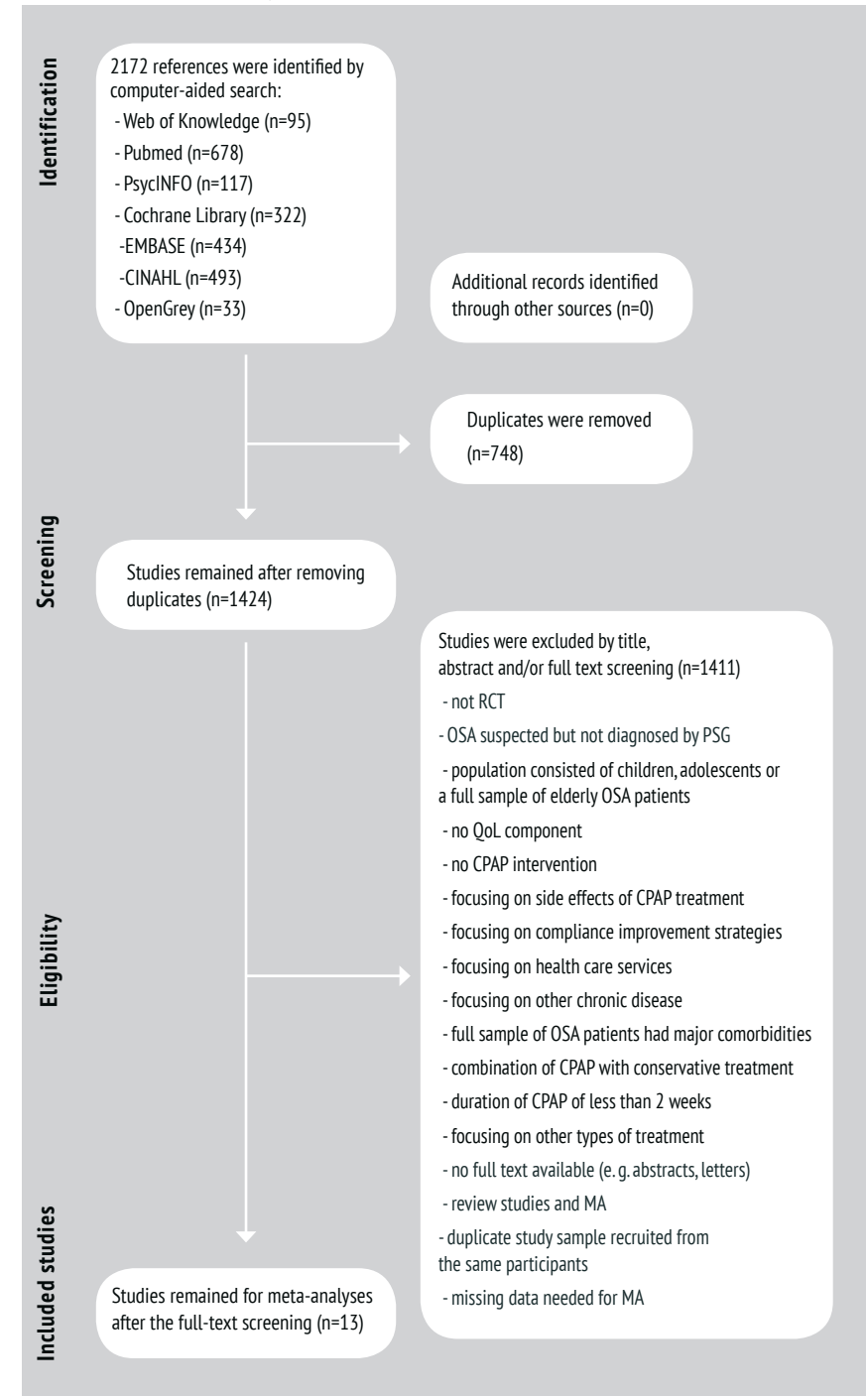
### Description of included studies

All studies included in our meta-analysis investigated whether real CPAP treatment affected QoL more significantly compared to the control condition. Seven RCTs had a parallel design and six RCTs had a crossover design. As the study by Montserrat et al. (2001) combined a partial crossover and parallel design, we analysed the parallel comparisons only. The duration of CPAP treatment ranged between 3 and 24 weeks. Most of the studies used only one treatment centre, two studies were multi-centre studies (Barbé et al., 2001; Batool-Anwar et al., 2016). Data in all the studies were collected during the patients' clinical visits.

A total of 678 participants formed the control group and 795 participants received real CPAP treatment. The number of participants in the reviewed studies varied between 8 (Engleman et al., 1997) and 409 (Batool-Anwar et al., 2016). The reported ages of the patients ranged from 25 to 72 years. The number of female patients varied from 0 to 103. Two studies (Jenkinson et al., 1999; Siccoli et al., 2008) included only male OSA patients. In all included RCTs, all subjects underwent a baseline assessment with PSG first and were then randomised to CPAP, treatment with placebo pills, sham CPAP, or conservative treatment (Table 3.3). Oximetry was used to diagnose OSA in one study by Jenkinson et al. (1999). Patients suffered from mild to severe OSA.

Five crossover studies (Engleman et al., 1997; Engleman et al., 1998; Engleman et al., 1999; Faccenda et al., 2001; Barnes et al., 2004) compared CPAP treatment with placebo pills. With the permission of local ethic comitee, patients were informed that the oral placebo tablet (Glaxo pills, UK) may improve their daytime function in total of three studies (Engleman et al., 1997; Engleman et al., 1998; Engleman et al., 1999). In two studies (Faccenda et al., 2001; Barnes et al., 2004) no specific information on placebo pills was provided.

Six parallel (Jenkinson et al., 1999; Montserrat et al., 2001; Siccoli et al., 2008; Barbé et al., 2001; Weaver et al., 2012; Batool-Anwar, 2016) and one crossover study (Marshall et al., 2005) used a machine set at subtherapeutic pressure, connected to a mask with holes to produce a leak as placebo (sham CPAP). Chakravorty et al. (2002) conducted a study with parallel design and used conservative treatment, including weight loss and sleep hygiene, to compare with CPAP treatment.

When a repeated measures design was used (Batool-Anwar et al., 2016), the longer duration of CPAP treatment on QoL was analysed. If possible, we also included groups of participants with a higher compliance level ($\geq 4$ hours/night) (Engleman et al., 1997; Batool-Anwar et al., 2016) and a longer treatment duration (Batool-Anwar et al., 2016) in the final meta-analysis. If more than one similar QoL estimator was used (Chakravorty et al., 2002; Siccoli et al., 2008), we used the estimator that could provide us with the most comprehensive information related to QoL. More detailed information about the study design, number of included participants, disease severity, type of control group, duration of the intervention, and instruments used to measure QoL is provided in Table 3.3. The criteria for inclusion and exclusion of the participants in the particular study type, sociodemographic data, clinical data, and mean values of CPAP compliance are presented in Supplement 3.2, Table S3.4.

*Table 3.3 Overview of the included studies*

| Study | Design | N | OSA severity | Intervention, type of control group, treatment duration | d; 95%CI | QoL instruments |
|---|---|---|---|---|---|---|
| Engleman et al., 1997* Scotland | -RCT, crossover | -8 patients with compliance >5 -8 CPAP 8 controls | mild | -CPAP patients/ placebo pills -1 month | 1.07; 95%CI (-0.72; 2.14) | NHP |
| Engleman et al., 1998* Scotland | -RCT, crossover -single blind | -23 CPAP -23 controls | moderate to severe | -CPAP patients/ placebo pills -1 month | 0.09; 95%CI (-0.73; 0.91) | NHP |
| Engleman et al., 1999* Scotland | -RCT, -crossover | -34 CPAP -34 controls | mild | -CPAP patients/ placebo pills -1 month | 0.24; 95%CI (-0.43; 0.92) | NHP |
| Jenkinson et al., 1999 UK | -RCT, parallel -double blind | -52 CPAP -49 controls | moderate to severe | -CPAP patients/ sham CPAP -1 month | 1.00; 95%CI (0.46; 1.25) 0.38; 95%CI (0.01; 0.76) | SF-36 mental component SF-36 physical component |
| Barbé et al., 2001 Spain | -RCT, parallel -double blind | -29 CPAP -25 controls | severe | -CPAP patients/ sham CPAP -1.5 month | -0.10; 95%CI (-0.63; 0.44) 0.19; 95%CI (-0.34; 0.73) | SF-36 mental component SF-36 physical component |
| Faccenda et al.,2001 UK | -RCT, crossover | -68 CPAP -68 controls | moderate and severe | -CPAP patients/ placebo pills -1 month | -0.27; 95%CI (-0.73; 0.54) 0.16; 95%CI (-0.30; 0.60) | FOSQ FOSQ |

*Table 3.3 Overview of the included studies - continued*

| Study | Design | N | OSA severity | Intervention, type of control group, treatment duration | d; 95%CI | QoL instruments |
|---|---|---|---|---|---|---|
| Montserrat et al., 2001 Spain | -RCT, parallel (partial crossover) -double blind | -23 CPAP -22 controls | moderate and severe | -CPAP patients/ sham CPAP -1.5 month | 0.52; 95%CI (-0.08; 1.11) | FOSQ |
| | | | | | -0.30; 95%CI (-0.89; 0.29) | SF-36 mental component |
| | | | | | 0.21; 95%CI (-0.38; 0.79) | SF-36 physical component |
| Chakravorty et al., 2002 UK | -RCT, parallel | -32 CPAP -21 CT controls | moderate to severe | -CPAP patients/ CT controls -3 months | 0.00; 95%CI (-0.07; 0.07) | EuroQoL (Usq) |
| Barnes et al., 2004 Australia | -RCT, crossover | -80 CPAP -80 controls | mild to moderate | -CPAP patients/ placebo pills -3 months | 0.00; 95%CI (-0.48; 0.48) | FOSQ |
| Marshall et al., 2005 New Zealand | -RCT, crossover | -29 CPAP -29 controls | mild | -CPAP patients/ sham CPAP -3 weeks | 0.30; 95%CI (-0.50; 1.10) | FOSQ |
| Siccoli et al., 2008 UK | -RCT, parallel -double blind | -50 CPAP -49 controls | moderate to severe | -CPAP patients/ sham CPAP -1 month | 0.42; 95%CI (-0.14; 0.97) | SF-36 mental component |
| | | | | | 0.04; 95%CI (-0.35; 0.44) | SF-36 physical component |
| | | | | | 0.44; 95%CI (-0.12; 0.99) | SAQLI |
| Weaver et al., 2012 USA | -RCT, parallel -double blind | -113 CPAP -110 controls | mild to moderate | -CPAP patients/ sham CPAP/ -2 months | 0.41; 95%CI (0.14; 0.67) | FOSQ |

*Table 3.3 Overview of the included studies - continued*

| Study | Design | N | OSA severity | Intervention, type of control group, treatment duration | d; 95%CI | QoL instruments |
|---|---|---|---|---|---|---|
| Batool-Anwar et al., 2016 USA | -RCT, parallel -double blind | -249 CPAP -160 controls CPAP with compliance >4 | mild to severe | -CPAP patients/ sham CPAP/ -6 months | 0.14; 95%CI (-0.06; 0.34) | SAQLI |
| | | *Subgroup analyses* | | | | |
| | | -mild OSA -16 controls -37 patients with compliance >4 | | -6 months | -0.13; 95%CI (-0.72; 0.46) | |
| | | -moderate to severe OSA -98 controls -146 OSA patients with compliance >4 | | -6 months | 0.27; 95%CI (0.01; 0.53) | |

CPAP: continuous positive air pressure; QoL: quality of life; RCT: randomised control trial; d: effect sizes for subscales comparison of CPAP effect vs. control group; (d - a statistically significant difference favouring the control group; d + a statistically significant difference favouring the treatment group); 0.20-0.40 - small effect size; 0.50-0.70 -medium effect size; 0.80≥large effect size. CI: confidence interval, CT: conservative treatment; *all participants in the studies by Engleman et al. (1997; 1998; 1999) were recruited from the new attenders at the sleep clinic (Engleman et al., 1999).

**Quality of life measures**

QoL was measured using generic questionnaires – the Short Form 36 Health Survey – (SF-36), the Nottingham Health Profile (NHP), the European Quality of Life Questionnaire (EuroQoL) and disease specific QoL questionnaires – the Calgary Sleep Apnea Quality of Life Index (SAQLI) and the Functional Outcomes of Sleep Questionnaire (FOSQ). Out of the 13 analysed RCTs, 12 studies measured overall QoL and four studies assessed the level of psychological and physical QoL.

**Risk of bias in the included studies**

As shown in Table 3.4, we considered the overall RoB to be high in three studies (Chakravorty et al., 2002; Barnes et al., 2004; Siccoli et al., 2008). These studies had either unclear (Chakravorty et al., 2002; Barnes et al., 2004) or inadequate (Siccoli et al., 2008) allocation concealment. Two (Chakravorty et al., 2002; Barnes et al., 2004) of these three studies also had incomplete outcome data. We considered seven studies to have an overall unclear RoB (Engleman et al., 1997; Engleman et al., 1998; Jenkinson et al., 1999; Barbé et al., 2001; Montserrat et al., 2001; Weaver et al., 2012; Batool-Anwar et al., 2016). We judged three studies to have low RoB (Engleman et al., 1999; Faccenda et al., 2001; Marshall et al., 2005). Figure 3.2 shows the proportion of items that were scored as low, unclear, or high RoB.

*Table 3.4 Risk of bias assessment*

| Study ID | Level of RoB* | a | b | c | d | e | f | g | h | i |
|---|---|---|---|---|---|---|---|---|---|---|
| Engleman et al., 1997 | unclear | ? | ? | - | - | ? | + | + | + | + |
| Engleman et al., 1998 | unclear | + | ? | + | - | - | + | + | + | + |
| Engleman et al., 1999 | low | + | + | - | - | ? | + | + | + | + |
| Jenkinson et al., 1999 | unclear | + | ? | + | + | ? | + | ? | + | + |
| Barbé et al., 2001 | unclear | + | ? | + | + | + | + | + | + | + |
| Faccenda et al., 2001 | low | + | + | - | ? | + | + | ? | + | + |
| Montserrat et al., 2001 | unclear | + | ? | + | ? | + | - | + | + | + |
| Chakravorty et al., 2002 | high | + | ? | - | - | ? | + | ? | - | + |
| Barnes et al., 2004 | high | + | ? | - | - | ? | + | + | - | + |
| Marshall et al., 2005 | low | + | + | - | + | ? | + | + | + | + |
| Siccoli et al., 2008 | high | + | - | + | + | - | + | + | + | + |
| Weaver et al., 2012 | unclear | ? | ? | + | + | + | ? | + | ? | + |
| Batool-Anwar et al., 2016 | unclear | + | ? | + | + | ? | + | + | + | + |

+ Low risk of bias; - High risk of bias; ? Unclear risk of bias; a. Random sequence generation, b. Allocation concealment, c. Blinding of participants; d. Blinding of personnel; e. Blinding of outcome assessment; f. Co-interventions avoided; g. Treatment fidelity; h. Incomplete outcome data; i. Selective outcome reporting; *Level of RoB per study based on a, b, and h.

*Figure 3.2 Flow chart of the risk of bias graph: judgements about each risk of bias item presented as percentages across all the included studies*
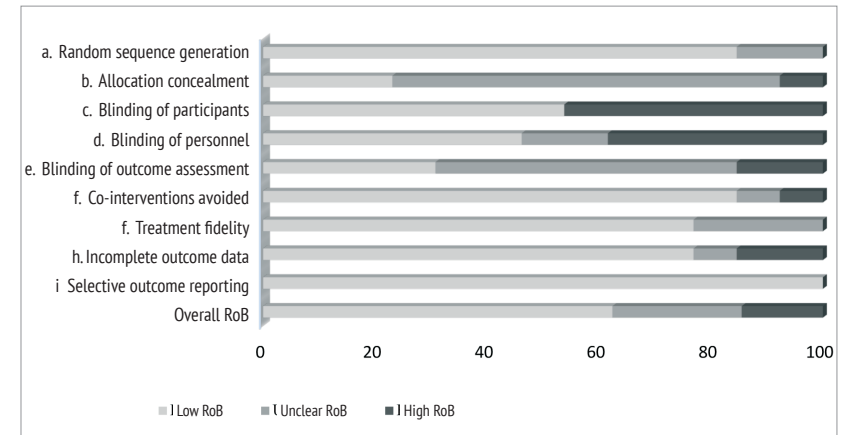


*Assessment of reporting biases*

A total of three estimators favoured the control group, and two estimators showed no difference in CPAP treatment effects when compared to controls (Figure 3.3 a, b, c). In general, the funnel plots showed a low possibility of publication bias. The results of the Egger tests for publication bias were not significant for the overall QoL (p=0.59), the psychological QoL domain (p=0.44), and the physical QoL domain (p=0.29).

*Figure 3.3 a Funnel plot of publication bias for overall QoL*
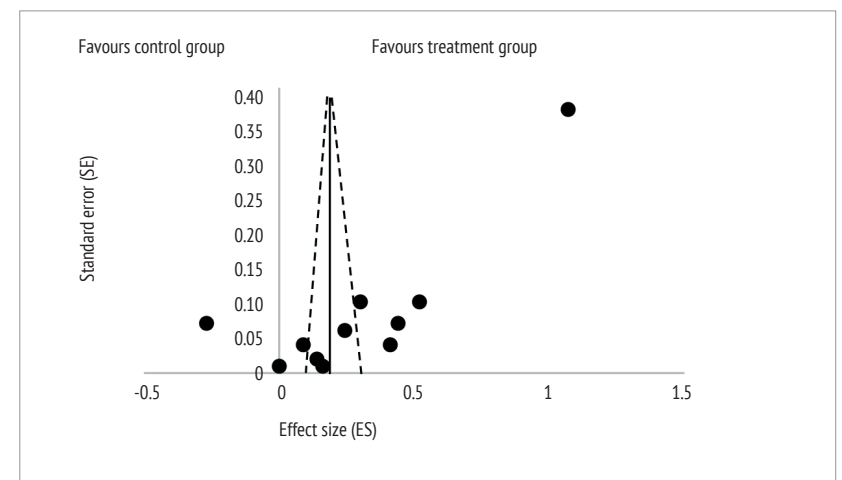
*Figure 3.3 b Funnel plot of publication bias for psychological QoL*
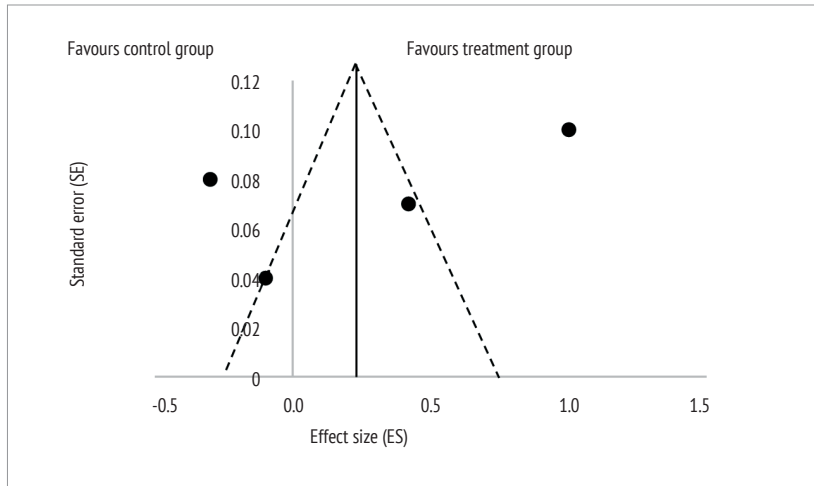


*Figure 3.3 c Funnel plot of publication bias for physical QoL*
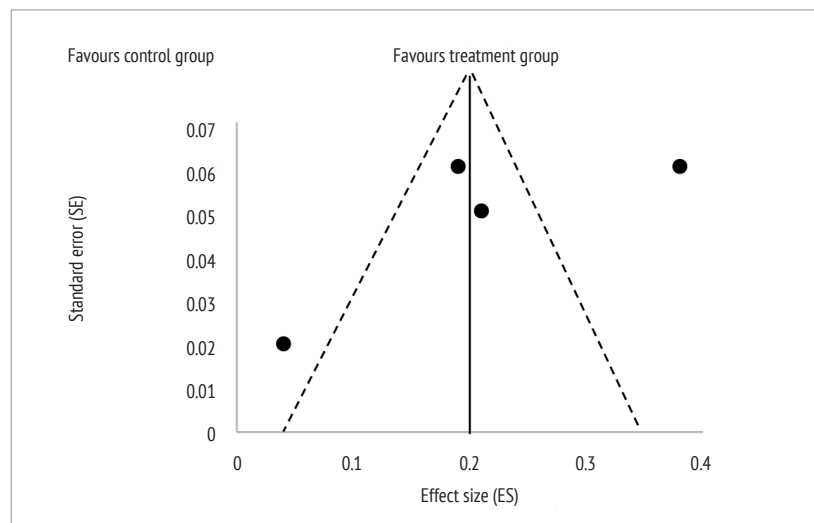
## Meta-analyses

Meta-analyses were conducted with 13 RCTs. ESs were computed for overall QoL and the physical and psychological domains. $\overline{ES}_V$ was used as the standardized outcome of the CPAP treatment effect. The forest plots show the ESs with CIs for scales and subscales and the final $\overline{ES}_V$ obtained by using a random effects model.

## Overall QoL score

The effect of CPAP treatment compared to placebo pills, sham CPAP treatment, and conservative treatment was examined in 12 RCTs. The meta-analysis demonstrated a negligible improvement in overall QoL score with CPAP treatment (0.18; 95%CI=0.10, 0.26) in OSA patients compared to controls. A moderate $I^2$ (68%) was found (Figure 3.4 a).

*Figure 3.4 a Meta-analysis of CPAP treatment effect on improvement in overall QoL score; effect sizes and 95% confidence intervals*
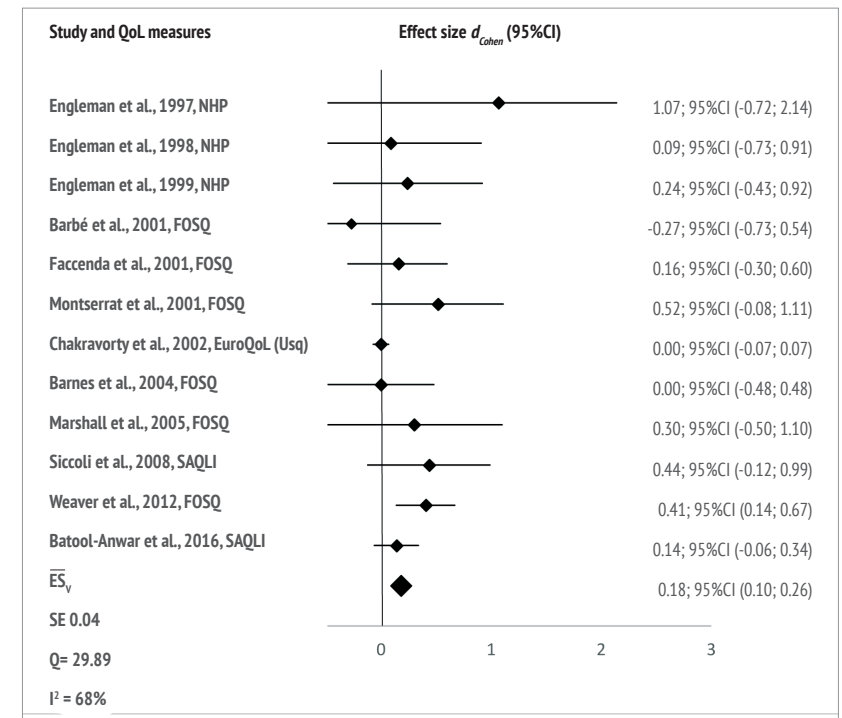


## Psychological QoL score

CPAP did not show significant superiority to controls in terms of psychological QoL (0.25; 95%CI=-0.23; 0.72). A low $I^2$ (31%) was found (Figure 3.4 b).

*Figure 3.4 b Meta-analysis of CPAP treatment effect on improvement in psychological QoL score; effect sizes and 95% confidence intervals*
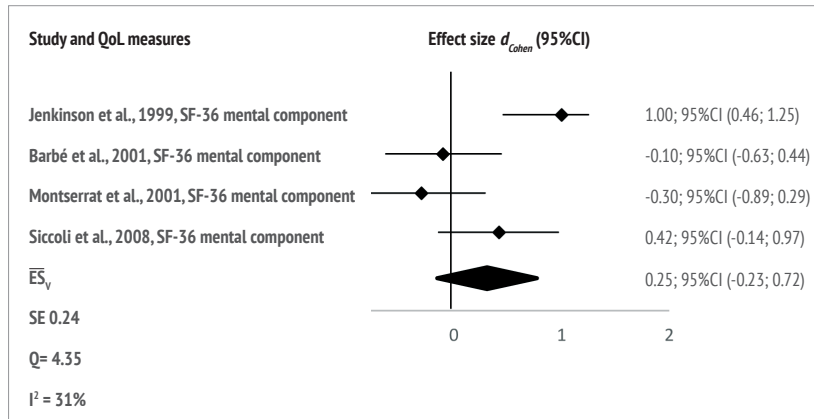


**Physical QoL score**

The meta-analysis demonstrated a small, but significant improvement in physical QoL (0.20; 95%CI=0.04, 0.35) with CPAP treatment in OSA patients compared to controls. A low $I^2$ (26%) was observed (Figure 3.4 c).

*Figure 3.4 c Meta-analysis of CPAP treatment effect on improvement in physical QoL score; effect sizes and 95% confidence intervals*
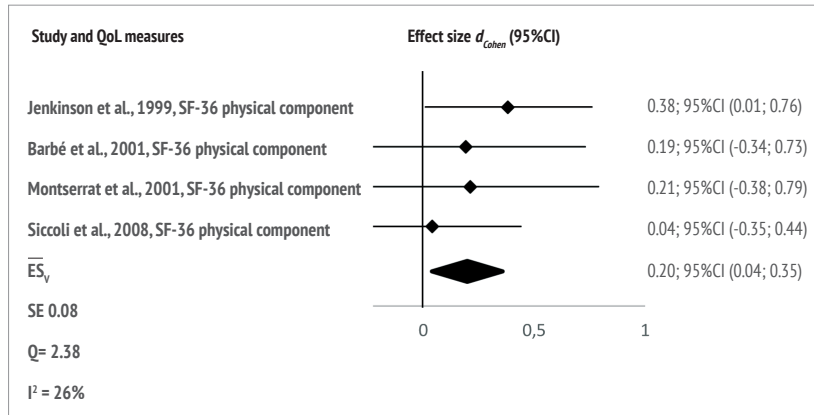


**Sensitivity analyses**

We performed sensitivity analyses to assess the effect of CPAP treatment on overall QoL when controlled for the number of included participants, duration of intervention, level of compliance with CPAP treatment, and RoB. As the studies measuring psychological and physical QoL (Jenkinson et al., 1999; Barbé et al., 2001; Montserrat et al., 2001; Siccoli et al., 2008) were homogenous in terms of the number of included participants (N≤100), duration of intervention (≤ 6 weeks),

compliance level (≥4 hours/night), and RoB, not enough data were available to conduct sensitivity analyses for psychological and physical QoL.

*The effect of CPAP treatment on overall QoL controlled for number of participants (N>100)*

Sensitivity analysis of four studies (Faccenda et al., 2001; Barnes et al., 2004; Weaver et al., 2012; Batool-Anwar et al., 2016), controlled for the number of participants (N>100), showed small, non-significant improvement in overall QoL score with CPAP treatment (0.19; 95%CI =-0.01; 0.38; $I^2$=4%).

*The effect of CPAP treatment on overall QoL controlled for duration of CPAP (>6 weeks)*

CPAP did not show superiority to controls in terms of effect on overall QoL score (0.13; 95%CI =0.03; 0.22; $I^2$=31%) in the four studies (Chakravorty et al., 2002; Barnes et al., 2004; Weaver et al., 2012; Batool-Anwar et al., 2016) with a treatment duration of more than 6 weeks.

*The effect of CPAP treatment on overall QoL controlled for compliance with CPAP treatment (≥4.0 hrs/night)*

We found no significant difference in overall QoL comparing CPAP treated patients with controls (0.32; 95%CI =-0.20; 0.79; $I^2$=10%) in four studies with a CPAP compliance level of at least 4 hours per night (Engleman et al., 1997; Barbé et al., 2001; Marshall et al., 2005; Siccoli et al., 2008).

*The effect of CPAP treatment on overall QoL controlled for risk of bias*

CPAP showed superiority to controls in terms of the effect on overall QoL score (0.20; 95%CI= 0.12; 0.27; $I^2$=13%) in three studies with low RoB (Engleman et al., 1999; Faccenda et al., 2001; Marshall et al., 2005).

**Subgroup analyses**

We performed subgroup analyses to investigate whether the effect of CPAP treatment on overall QoL varies across different subgroups of patients or trials. We analysed subgroups based on the type of control group, OSA severity, study design, and type of QoL measures. As studies measuring psychological and physical QoL (Jenkinson et al., 1999; Barbé et al., 2001; Montserrat et al., 2001; Siccoli et al., 2008) were homogenous in terms of the type of the control group (sham CPAP), OSA severity (moderate to severe), study design (parallel), and type of QoL measures (generic), not enough data were available for the predefined subgroup comparisons.

*The effect of CPAP treatment on overall QoL controlled for type of control group*

We found a small but significant improvement in overall QoL in subgroup analyses of six studies (Barbé et al., 2001; Montserrat et al., 2001; Marshall et al., 2005; Siccoli et al., 2008; Weaver et al., 2012; Batool-Anwar et al., 2016) using sham

CPAP as a control condition (0.25; 95%CI =0.04; 0.46). A value of 32% indicated moderate heterogeneity. CPAP led to negligible improvement in overall QoL in the subgroup analyses of five studies (Engleman et al., 1997; Engleman et al., 1998; Engleman et al., 1999; Faccenda et al., 2001; Barnes et al., 2004) using placebo pills (0.14; 95%CI=0.03; 0.25). A value of 52% indicated moderate heterogeneity. CPAP did not show superiority to controls receiving conservative treatment in terms of effect on overall QoL score (0.00; 95%CI=-0.07; 0.07) in a single study by Chakravorty et al. (2002).

*The effect of CPAP treatment on overall QoL controlled for OSA severity*
Subgroup analyses of mild OSA patients showed small CPAP treatment effect on overall QoL (0.31; 95%CI=0.13; 0.50; $I^2$=27%) in four studies (Engleman et al. 1997; Engleman et al. 1999; Marshall et al., 2005; Batool-Anwar et al., 2016). A negligible improvement in overall QoL was found in subgroup analyses of six studies (Engleman et al. 1998; Barbé et al., 2001; Faccenda et al., 2001; Montserrat et al., 2001; Sicoli et al., 2008; Batool-Anwar et al., 2016) with participants suffering from moderate to severe OSA (0.19; 95%CI=0.03; 0.34; $I^2$=53%).

*The effect of CPAP treatment on overall QoL controlled for study design*
CPAP led to a small but significant improvement in overall QoL score (0.22; 95%CI=0.07, 0.38; $I^2$=70%) in six studies with a parallel design (Montserrat et al. 2001; Barbé et al., 2001; Chakravorty et al., 2002; Siccoli et al., 2008; Weaver et al., 2012; Batool-Anwar et al., 2016). CPAP did not show superiority to controls in terms of the effect on overall QoL (0.16; 95%CI=0.10, 0.26; $I^2$=35%) in subgroup analyses of six studies with a crossover design (Engleman et al. 1997; Engleman et al. 1998; Engleman et al. 1999; Faccenda et al., 2001; Barnes et al., 2004; Marshall et al., 2005).

*The effect of CPAP treatment on overall QoL score controlled for the type of QoL measures*
A total of four studies (Engleman et al. 1997; Engleman et al. 1998; Engleman et al. 1999; Chakravorty et al., 2002) using generic QoL questionnaires showed non-significant improvement in overall QoL with CPAP treatment (0.13; 95%CI=-0.001; 0.28; $I^2$=53%). A negligible improvement in overall QoL score was found in eight studies (Barbé et al., 2001; Faccenda et al., 2001; Montserrat et al., 2001; Barnes et al., 2004; Marshall et al., 2005; Siccoli et al., 2008; Weaver et al., 2012; Batool-Anwar et al., 2016) using OSA-specific QoL questionnaires (0.14; 95%CI=0.04, 0.24; $I^2$=64%).

**Summary of the quality of the findings**
The quality of the evidence within the studies was assessed based on levels of RoB, inconsistency, indirectness, and imprecision (Ryan and Hill, 2016). The evidence for improvement in overall QoL was of low quality and was downgraded by one level, as most of the studies had an unclear selection bias. For inconsistency, we considered an $I^2$ value of 68% to downgrade by one level.

The meta-analysis of psychological QoL provided very low quality of evidence. The evidence for psychological QoL was downgraded by one level due to a small number of included studies, and an unclear allocation concealment in most of the included studies. We also downrated the quality of evidence by two levels for imprecision due to a small sample size (N<400) and a wide CI around effect estimate that included an effect size of 0 and moderate effect size.

The evidence for physical QoL provided low quality of evidence. The evidence for improvement in physical QoL was downgraded by one level due to a small number of included studies and an unclear allocation concealment in most of the included studies. We also downrated the quality of evidence by one level for imprecision due to a small sample size (N<400).

## Discussion

The aim of this study was to systematically evaluate the effect of continuous positive airway pressure (CPAP) treatment on quality of life (QoL) in patients with obstructive sleep apnoea (OSA) compared to sham CPAP, placebo pills, and conservative treatment. We found no significant differences in overall and psychological QoL between CPAP treated patients and controls. However, physical QoL improved in CPAP treated patients compared with control treatments. Furthermore, subgroup analyses and sensitivity analyses showed that the type of control group, the study design, OSA severity, and risk of bias (RoB) may be relevant in capturing the effect of CPAP on QoL.

We found that patients undergoing CPAP treatment reported significantly higher physical QoL compared to controls. This result provided additional support for the effect of CPAP on physical QoL revealed in an earlier meta-analysis by Jing et al. (2008). These findings may be of clinical importance, as physical QoL was found to be related to nocturnal parameters indicating sleep disruption (Sforza et al., 2003; Jing et al., 2008). However, no treatment effect of CPAP compared to controls was found for psychological QoL. This finding may be explained by the low severity of psychological symptoms at baseline. As we excluded studies with focus on major comorbidities, it is possible that the occurence or severity of some confounders related to comorbid medical illnesses that could negatively affect psychological QoL in OSA patients may have been low. Furthermore, meta-analysis by Huang et al. (2017) demonstrated the significant alterations of brain structural and functional response in OSA patients possibly explaining psychic disorders. Patients with OSA showed both decreased grey matter volume and functional response in orbital frontal cortex compared to healthy controls, while the cerebellum VI bilateral anterior (para)cingulate gyri and the amygdala/hipocampus exhibited atrophy of grey matter volume but increased activity. These changes suggest that early diagnosis and treatment are crucial (Huang et al., 2019). However, recent histopathological investigations of autopsy of brain tissue from OSA patients further indicate that myelin in OSA patients is impacted and not protected by CPAP treatment (Owen et al., 2018). Therefore, the suboptimal effect of CPAP treatment on psychological

QoL may also be explained by the irreversible OSA-related brain injuries, that may further contribute to the development of the psychological symptomatology in OSA patients (Owen et al., 2018; Huang et al., 2019).

Subgroup analyses showed non-significant improvements in overall QoL with CPAP treatment when controlled for type of QoL measures. The results of the subgroup comparisons are not particularly surprising given the fact that disease-specific and generic QoL measures in OSA patients were found to be highly correlated (Flemons and Reimer, 2002; Silva et al., 2016). However, recent meta-analysis by Patil et al. (2019) identified significant effect of CPAP treatment on QoL using disease specific measures. The explanation for this inconsistence in results may be that Patil et al. (2019) included only studies with longer duration of CPAP treatment (6 weeks), while we used cut-off of 2 weeks.

We found a significant improvement in overall QoL when controlled for OSA severity. This result may be surprising as self-reported health outcomes are usually discordant with polysomnography (PSG) measures of OSA severity (Weaver et al., 2005). Issues such as abbreviated PSG monitoring, night-to-night variability, or the "first-night effect" of the PSG may partly explain the variability of OSA severity across different studies (Punjabi, 2008). Nevertheless, the significant effect of CPAP treatment on QoL in patients with mild OSA may also be caused by the low RoB in two (Engelman et al., 1999; Marshall et al., 2005) of the four studies included in subgroup analysis.

In line with the meta-analysis by Jing et al. (2008) we found only a negligible CPAP treatment effect on overall QoL scores in studies with a crossover design compared to a small but significant effect revealed in studies with a parallel design. This result is consistent with previous research, as long-term parallel-group trials were found to be more efficient at capturing the important information regarding the benefits of CPAP treatment (Richens, 2001; Jing et al., 2008). Furthermore, the crossover study design was found to be less effective in assessment of CPAP treatment effects, as the washout period is usually too short to eliminate the effects of first treatment (Richens, 2001). The washout period in crossover studies included in our meta-analysis ranged from 0 to 2 weeks (Engleman et al., 1997; Engleman et al., 1998; Engleman et al., 1999; Faccenda et al., 1999; Barnes et al., 2004; Marshall et al., 2005). Consequently, it is understandable that these short washout periods could not eliminate CPAP treatment effects.

Subgroup analyses also showed that CPAP led to a small but significant improvement in overall QoL in studies with controls receiving sham CPAP compared to the negligible improvement revealed in controls using placebo pills. This result is surprising, as sham CPAP is supposed to worsen both sleep and gas exchange (Sanner et al., 2000; Engleman et al., 1999). An explanation may be that most of the studies that used placebo pills as a control condition also had a very low number of participants (Engleman et al.1997; Engleman et al. 1998; Engleman et al. 1999). Furthermore, all studies with placebo pills as a control condition had a crossover design, identified as less sensitive in capturing the effect of CPAP treatment (Richens et al., 2001).

Sensitivity analyses that controlled for the number of included participants, duration of intervention, and compliance level showed only small, non-significant effects of CPAP treatment on overall QoL scores. The results of our meta-analysis may be explained by the relatively small sample sizes, the short durations of the interventions, and the relatively low CPAP compliance level (with the highest value of 5.0 hours per night) in the included studies. For example, a compliance of ≥4 hours per night has been considered acceptable (e.g. Masa and Corral-Peñafiel, 2014). However, the adequate use of CPAP treatment may vary for different outcomes. For instance, to obtain an improvement in daytime sleepiness, at least 4 hours per night of compliance with CPAP are required (Weaver et al., 2007); 6 hours per night are needed for memory improvement (Zimmerman et al., 2006) and 7.5 hours per night is considered to be adequate for improvement in sleep-related quality of life (Weaver et al., 2007). But, there are individuals who are not able to achieve normal functional status or remain excessively sleepy despite optimal CPAP treatment of more than 7 hours per night (Weaver et al., 2007; Antic et al., 2011; Jackson et al., 2018). As adherence with CPAP treatment appears to be associated with positive changes in QoL (Lynch et al., 2019), future research and clinical practice should examine strategies for its improvement. More attention should be given to educational and behavioural intervention strategies that were found to be efficient in improving adherence with CPAP (Sawyer et al., 2011), while device improvements were found to have only modest impact on adherence with CPAP treatment (Smith et al., 2009).

Finally, we found a small, non-significant effect of CPAP treatment when controlled for the number of included participants. This result is not surprising as cut-offs based on study size introduce an extra element of subjectivity and thus may not ameliorate bias if the large studies are insufficiently critiqued (Turner et al., 2009). Although we stated the cut-off value of 100 participants following previous recommendations (Dechartres, 2013; Grainge, 2015), the concept of single threshold to distinguish small trials from large trials in the area of medical interventions is not straightforward. A solution may therefore be to make a separate exclusion of studies with high and unclear RoB. In line with this assumption, we found a small but significant CPAP treatment effect on QoL in studies with low RoB (Engleman et al., 1999; Faccenda et al., 2001; Marshall et al., 2005).

### Strengths and limitations

The strenght of this review and meta-analysis is that randomised controlled trials (RCTs) were conducted in different countries, which adds to the generalizability of our results. The results of our study are applicable to adult patients of both genders with mild to severe OSA. We tried to avoid meta-bias by searching in multiple databases. As most of the participants in the included studies were diagnosed by PSG in the same way, misclassification based on differences in sensitivity and specificity of diagnostic measures can be excluded. All studies included in our review and meta-analysis used the SF-36 to measure psychological and physical QoL. Despite some limitations, the mental health component of the SF-36, and in particular the

"vitality" domain, is still considered to be the most suitable generic health-related QoL measure for OSA patients (Abma et al., 2016). However, a potential drawback may be that the questions of the SF-36 related to daily activities or social functioning are assessed by asking about limitations due to "emotional problems" or "physical health". Moreover, neither of these categories is considered to clearly cover the main reasons for impaired functioning that OSA patients experience (i.e., fatigue, sleepiness, or poor sleep quality) (Abma et al., 2016). One of the eligible studies was excluded from our MA, as we did not receive the missing, additional information. However, the results of the excluded study were consistent with our findings, i.e. QoL improvement was found only in the physical QoL domain and not in the psychological QoL domain (Campos-Rodriguez et al., 2016). We also have to be careful in the interpretation of the results, as many studies had a high or unclear RoB. Next, the studies in our review consistently rated poorly on allocation concealment and blinding. Because inadequately concealed trials and lack of proper blinding may show even more favourable treatment effects than adequately blinded and concealed studies (Wood et al., 2008; Higgins and Green, 2011), careful attention must be paid when interpreting CPAP treatment effect on QoL in OSA patients. We also tried to avoid biases in the assessment of CPAP treatment effect on QoL by exclusion of studies with full samples of OSA patients with major comorbidities that may affect QoL; i.e. heart failure, stroke, or comorbid sleep disorders. However, the limitation of our study may be that comorbidities may not be fully eliminated as the exclusion criteria in analysed studies varied from not specified (Barnes et al., 2004), to less strict (Engleman et al., 1997; Engleman et al., 1998; Engleman et al., 1999; Jenkinson et al., 1999; Faccenda et al., 2001; Montserrat et al., 2001; Chakravorty et al., 2002; Siccoli et al., 2008); or led to exclusion of all chronic conditions (Barbé et al., 2001; Weaver et al., 2012; Batool-Anwar et al., 2016). Finally, since the reported treatment duration ranged from three weeks to six months, this review cannot conclude on the long-term effects of CPAP treatment.

**Implications and recommendations for practice and future research**
More high-quality RCTs with larger samples are needed to learn more about the effectiveness of CPAP treatment on QoL improvement. Most of the studies included in our review had a moderate duration of CPAP treatment; thus, repetitions with longer treatment duration is recommended. Future RCTs should also consider evaluating secondary outcome measures, such as sleep-related problems.

**Conclusion**
In conclusion, when comparing CPAP with control treatment, our meta-analysis showed no significant impact of CPAP on overall and psychological QOL. However, CPAP was found to improve physical QoL compared with control treatments. Moreover, we found that CPAP may significantly affect overall QoL in studies with sham CPAP controls, parallel design, low risk of bias, and mild OSA patients. More high-quality trials are needed for further investigation of the effects of CPAP treatment on QoL improvement.

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# Are disease severity, sleep-related problems and anxiety associated with work functioning in patients with obstructive sleep apnoea?

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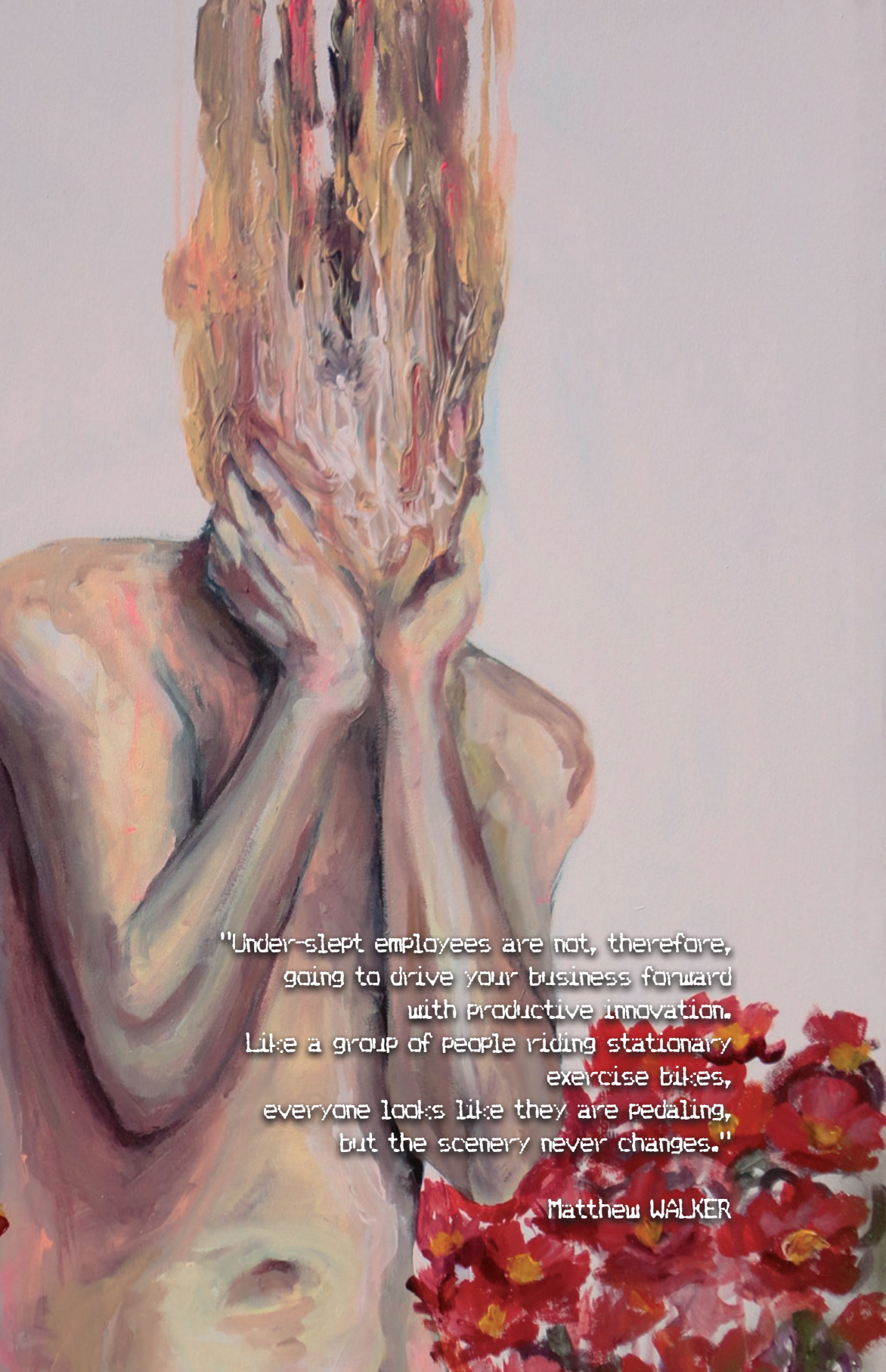
"Under-slept employees are not, therefore,
going to drive your business forward
with productive innovation.
Like a group of people riding stationary
exercise bikes,
everyone looks like they are pedaling,
but the scenery never changes."

Matthew WALKER

# Abstract

### Background and aim

Obstructive Sleep Apnoea (OSA) has a substantial economic impact on healthcare systems as well as on individuals. We aimed to examine whether OSA severity, sleep-related problems, and anxiety are associated with work functioning in OSA patients when controlled for age, gender, and type of occupation. We also aimed to investigate whether anxiety moderates the associations between sleep-related problems and work functioning

### Methods

We included 105 OSA patients (70% male; mean age 46.62±9.79 years). All patients completed the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale, the Beck Anxiety Inventory, and the Work Role Functioning Questionnaire-2.0.

### Results

OSA severity, poor night-time sleep quality, and anxiety were univariately associated with impaired work functioning. Multivariate analyses revealed that poor perceived sleep quality was more strongly associated with work functioning than sleep efficiency and daily disturbances. Anxiety was strongly associated with impaired work functioning. After adding anxiety, the explained variance in work functioning increased from 20% to 25%. Anxiety moderated the association between low and medium level of night-time sleep quality problems and work functioning.

### Conclusion

Poor perceived sleep quality and anxiety were strongly associated with impaired work functioning in OSA patients. These findings may help to optimize management, standard treatment and work functioning in people with OSA when confirmed in longitudinal studies.

# Introduction

Obstructive Sleep Apnoea (OSA) is an incapacitating chronic disease caused by pharyngeal collapse during sleep (Manarino et al., 2012). OSA is considered to be one of the most prevalent sleep disorders (Manarino et al., 2012), with an estimated prevalence of 2–10% among the adult population (Leger et al., 2012). The disease is characterized by repeated breathing pauses which cause frequent awakenings, fragmented sleep and, consequently, excessive sleepiness and fatigue (Tippin et al., 2016). Besides physical disorders, OSA patients may also have substantial mental health problems, such as depression, anxiety (Borak et al., 1996; Sharafkhaneh et al., 2005; Kang et al., 2012; Lin and Winkelman, 2012; Krakow et al., 2015), post-traumatic stress syndrome (Sharafkhaneh et al., 2005) or panic attacks (Su et al., 2015). OSA has a substantial economic impact on healthcare systems as well as on individuals and their households. Studies show a significant impairment of functional status, including work functioning, in these patients; i.e. undiagnosed OSA is associated with notable increases in healthcare costs (Wittmann and Rodenstein, 2004; Reuveni et al., 2008) but also with reduced work capacity and work disability (Leger et al., 2012, Mulgrew et al., 2007; Sivertsen et al., 2008).

Earlier studies report an impairment of work functioning in OSA patients (Mulgrew et al., 2007; Sivertsen et al., 2008; Omachi et al., 2009). Tregear et al. (2009) described the occurrence of microsleeps and accidents, while Sivertsen et al. (2008) showed that self-reported OSA symptoms were an independent risk factor for subsequent long-term sick leave and permanent work disability. The association between OSA severity and the individual experience of work limitations was dependent on job type (Mulgrew et al., 2007); i.e. OSA severity did not affect work performance (time management, physical, mental-interpersonal, and output demands) in white-collar workers, while it did in blue-collar workers. Most of the previous research on work correlates in OSA patients has quantified the outcomes using objective variables, such as absenteeism (Sivertsen et al., 2008) or occupational accidents (Noda et al., 1998; Pizza et al., 2009), which may be lower-incidence events when compared to work functioning impairment. Others have assessed the economic impact of OSA on public health systems (Wittman and Rodenstein, 2004; Reuveni et al., 2008). Furthermore, some older studies on work functioning in OSA patients did not use polysomnography (PSG) to diagnose OSA (Sivertsen et al. 2008; Ulfberg et al; 1996), nor did they use validated measures of work role performance (Ulfberg et al; 1996; Grunstein et al., 1995). Thus, more studies are needed in which OSA is diagnosed with reliable methods and occupational variables are assessed with standardized and validated questionnaires (Guglielmi et al., 2015).

Moreover, despite the acceptance of continuous positive airway pressure as the standard OSA treatment, there is a lack of consensus regarding the positive evidence of continuous positive airway pressure treatment effect on functional status (Tippin et al., 2016; Weaver et al., 2007; Weaver et al., 2013). Furthermore, a large proportion of the population is at risk of experiencing a sleep disorder (Hiestand et

al., 2005); thus, it is important to quantify work-related outcomes in these persons. Sleep-related OSA symptoms were also found to contribute to decreased employee productivity (Rosekind et al., 2010; Nena et al., 2010) and are related to high costs for employers (Rosekind et al., 2010). According to Swanson et al. (2011), sleep disorders adversely affect work performance, while mood and affective symptoms impact relationships with co-workers and presenteeism.

Many OSA patients suffer from anxiety symptoms (Borak et al., 1996; Krakow et al., 2015; Yue et al., 2003; Li et al. 2004; Shapiro et al., 2014), but these are rarely studied systematically (Krakow et al., 2015; Shapiro et al., 2014). The omission of anxiety associated with OSA symptomatology may contribute to poor treatment acceptance and adherence (Aloia et al., 2004), and consequently, to an overall worsening of OSA symptoms and increased risk of morbidity (Shapiro et al., 2014). Although previous research on OSA patients suggests that there may be a considerable association between sleep-related problems and anxiety (Borak et al., 1996), these may also occur separately from each other (Krakow et al., 2015). Anxiety can have a major impact on functional status and may interfere with work productivity (Erickson et al., 2009). However, the findings are inconclusive; e.g. Mughal et al. (1996) found that employees with high trait anxiety exerted greater work effort than those with low trait anxiety, which resulted in better work performance.

We sought to address several gaps in the existing literature, because to the best of our knowledge, no studies have investigated the associations between night-time sleep quality, anxiety and work functioning in OSA patients. Increased awareness of the associations between OSA and affective problems might improve diagnostic accuracy as well as treatment outcomes (Krakow et al., 2015; Schroder and O'Hara, 2005). Insight into which specific OSA symptomatology, such as sleep-related and mental health problems, are associated with impaired work functioning, may provide opportunities for preventive strategies for productivity-loss among workers with OSA. Therefore, the present research and clinical practice should focus not only on the standard treatment of OSA, but also on ensuring that symptoms such as sleep-related problems or mental health impairment are managed. To do that, we first need to understand how these symptoms relate to functioning in OSA untreated patients. Thus, the aims of this study were 1) to examine whether OSA severity, sleep-related problems and anxiety are associated with work functioning in OSA patients, and 2) to investigate whether anxiety moderates the associations between sleep-related problems and work functioning.

## Materials and methods

### Sample and procedure

This cross-sectional study was conducted at the Department of Pneumology and Phtiseology, L. Pasteur University Hospital and the Medical Faculty of PJ Safarik University in Kosice, Slovak Republic. All patients who visited the Department for one-night polysomnography (PSG) from July 2013 to April 2016 and underwent PSG were eligible for the study. Indication for PSG was based on a general practitioner referral form. OSA was diagnosed based on an overnight sleep examination. PSG was used to determine whether the diagnosis of OSA was present and to identify the severity of the disorder. PSG consists of a simultaneous recording of multiple physiological parameters related to sleep and wakefulness, which directly monitor and quantify the number of respiratory events, related hypoxemia and arousals. PSG comprised the overnight recording of left and right electrooculograms, standard central and occipital electroencephalogram, submental electromyogram (EMG), bilateral tibialis EMG, nasal and oral airflow using a thermistor and thoracic and abdominal excursions using respiratory inductive plethysmography.

The study sample consisted of working patients with an Apnoea Hypopnoea Index (AHI; number of apnoeas + hypopnoeas per hour of sleep) score of 5 or more (American Academy of Sleep Medicine, 2005) who had not undergone any continuous positive airway pressure therapy or other OSA treatment, were Slovak-speaking and had no major comorbidities. Patients with non-respiratory sleep-related complaints (e.g. circadian rhythm sleep disorder, insomnia) were routinely referred to another group of clinical specialists and were therefore not represented in our sample. Only OSA patients between 18 and 65 years of age were included due to possible functional changes, increased vulnerability and a decline in abilities and performance related to age.

Out of N=152 eligible OSA patients, a total of N=33 were excluded because of major comorbidities (a coexisting major sleep disorder such as insomnia, narcolepsy, or circadian rhythm sleep disorder; major cardiovascular diseases, primary pulmonary hypertension, chronic obstructive pulmonary disease, diabetes, Pickwick syndrome, a history of cancer in the past twelve months, neurological deficit, a major psychiatric diagnosis in the medical record, and/or current usage of psychiatric medications which may affect cognitive functions (e.g. antipsychotics, benzodiazepines, or antidepressants), or drug abuse in the past six months) and regular shift work in the past six months. Screening for comorbidities was based on medical data and an initial clinical interview prior to data collection. The clinical diagnoses of the comorbidities were established according to the standard International Classification of Diseases, 10 Revision codes. Medical examinations of patients were conducted by a pulmonologist specialized in sleep-disordered breathing. Another N=14 patients refused to participate in the study (response rate 89%). A total of N=105 OSA patients (70% male; mean age 46.62±9.79 years) constituted the final study sample.

The invitation letter, the informed consent and the self-reporting questionnaires were sent to participants by postal mail three weeks before the medical examination. One week before the medical examination, patients were reminded about the questionnaires by a phone call. Patients filled in the questionnaires at home. Each patient completed and signed an informed consent form prior to their participation in the study, which was fully voluntary and included no incentives for participation. The study was approved by the Ethics Committee of PJ Safarik University (approval no. 115/2011).

## Measures

*Sociodemographic and clinical data*

Information on age, gender, and marital status was obtained from patient records. Patients were asked to identify the one industry that best characterized their current employment (over the last 24 months) from a list of International Standard Classification of Occupations (1990). Patients were also asked to specify their occupation to reduce the obtaining of incorrect or inconsistent information. OSA patients in the following industries were classified as blue-collar workers: primary resource industry, construction industry, manufacturing industry, warehousing, trade, and transportation. Patients employed in public administration, armed forces, government and the service sector (including tourism, business services, education, healthcare, legislators, managerial occupations, professional, and utilities) were classified as white-collar workers. Body Mass Index (height and weight) was assessed by a physician. BMI was used to sort patients into categories: underweight (<18.5), normal (18.5-24.99), overweight (25.0-29.99), and obese (30+). The diagnosis of OSA was determined using PSG and was based on the Apnoea Hypopnoea Index (AHI; number of apnoeas + hypopnoeas per hour of sleep) starting with a score of 5 or more according to the standard criteria (American Academy of Sleep Medicine, 2005). According to this, OSA severity is mild (AHI≥5≤15), moderate (AHI>15≤30), or severe (AHI>30). An obstructive apnoea or hypopnoea can be defined as an event that lasts for ≥ 10 seconds and is characterized by an absence or a decrease from baseline in the amplitude of a valid measure of breathing during sleep that either reaches >50% with an oxygen desaturation of 3% or an arousal (alternatively a 30% reduction with 4% desaturation) (American Academy of Sleep Medicine, 2005).

*Sleep-related problems*

Sleep-related problems concerned night-time sleep quality and daytime sleepiness. *Night-time sleep quality* was measured using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI is a self-rated questionnaire to assess sleep quality and disturbances over a one-month time interval. The PSQI consists of 19 self-reported questions which cover seven domains: sleep latency, subjective sleep quality, sleep duration, sleep disturbances, habitual sleep efficiency, daytime dysfunction, and use of sleep medication. The score ranges from 0 to 21, with higher scores reflecting poor night-time sleep quality. A cut-off score of 5 separates good from poor sleepers (Buysse et al., 1989). The results of some previous studies suggested that the seven PSQI domains are best represented by three latent factors (Cole et al., 2006; Casement et al., 2012). Empirical examination of the factor structure of the PSQI identified three distinct factors: perceived sleep quality, sleep efficiency, and daily disturbances. The PSQI subscales for subjective sleep quality, sleep medications and sleep latency were loaded onto the latent variable *perceived sleep quality*; the PSQI subscales for sleep duration and habitual sleep efficiency were loaded onto the latent variable *sleep efficiency*; and the PSQI subscales for sleep disturbances and daytime dysfunction were loaded onto the latent variable

*daily disturbances* (Cole et al., 2006). *Sleep efficiency* is defined as closely related to sleep quantity (Casement et al., 2012), while the *daily disturbances* factor reflects sleep-related daytime impairment (i.e., trouble performing daytime activities) and interruptions in sleep due to physical or psychological symptoms (Casement et al., 2012). In our sample, Cronbach's alpha was 0.85 for the total PSQI scale.

*Daytime sleepiness* was measured using the self-report Epworth Sleepiness Scale (ESS), an eight-item questionnaire assessing the tendency to fall asleep in various daytime scenarios (Miletin and Hanly, 2003). The score ranges from 0 to 24, with higher scores indicating greater daytime sleepiness. An ESS total score greater than 10 indicates excessive daytime sleepiness (Miletin and Hanly, 2003). Cronbach's alpha for ESS in our sample was 0.87.

*Anxiety*

Anxiety was measured using the Beck Anxiety Inventory (BAI), which consists of 21 items defining the most common anxiety symptoms (Beck and Steer, 1990). The BAI is a brief measure of anxiety with a focus on somatic symptoms and was developed as a measure adept at discriminating between anxiety and depression (Beck et al., 1988). Scores range from 0 to 63, with higher scores indicating a higher anxiety level. The following categories were defined: no anxiety symptoms (score 0-9), mild anxiety (score 10-18), severe anxiety (score 19-29), and very severe anxiety (score 30-63) (Beck and Steer, 1990). Cronbach's alpha in our sample was 0.90.

*Work functioning*

Work functioning was assessed with the Work Role Functioning Questionnaire (WRFQ 2.0) (Abma et al., 2013). The WRFQ measures the perceived difficulties in performing work demands among workers, given their emotional or physical health problems. The WRFQ consists of 27 items divided into subscales: work scheduling demands and output demands, physical demands, mental and social demands, and flexibility demands. In addition, a total score can be calculated. Items are answered on a five-point scale: 0= difficult all the time (100%), 1= difficult most of the time (75%), 2= difficult half of the time (50%), 3= difficult some of the time (25%), 4= difficult none of the time (0%). There is also a response option 'Does not apply to my job'. The total score is calculated by adding all answers and dividing by the number of items and then multiplying by 25 to obtain percentages between 0 and 100. Higher scores indicate better work functioning. The scores on 'Does not apply to my job' are transformed into missing values (Abma et al., 2013). To identify the prevalence of impaired work functioning, we used the cut-off value (<90) for patients with a chronic disease according Amick et al. (2004). In our sample, Cronbach's alpha was 0.93 for the total scale, 0.97 for the work scheduling and output demands, 0.90 for the physical demands, 0.90 for the flexibility demands and 0.94 for the mental and social demands subscale.

## Statistical analyses

All analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS 23) and Modgraph. We started with a description of the background characteristics of the sample and determined the prevalence of OSA severity, night-time sleep quality (PSQI), daytime sleepiness (ESS), anxiety (BAI), and impaired work functioning (WRFQ). Descriptive analyses included frequencies and percentages for categorical variables and mean values and standard deviations (SD) for continuous variables. Next, we investigated the correlations between all variables. Then, we examined the associations between OSA severity, night-time sleep quality, daytime sleepiness, anxiety, and work functioning in crude and adjusted linear regression analyses, including interactions between sleep-related problems and anxiety. We applied the enter method in linear regression to identify the factors associated with summary scores of work functioning for the total scale and the subscales. For each factor, unstandardised beta coefficients represent the mean variation of work functioning. The first model of the variables included sociodemographic data (age, gender). The second model included a clinical variable (OSA severity - measured by AHI); the third model included the night-time sleep quality total scale. In addition, each of the three subscales of sleep quality was analysed separately. In the fourth model anxiety was included to assess the increase in the explained amount of total variance in work functioning. Multicollinearity was assessed using the variance inflation factor (VIF<2.0). Finally, we used moderation analyses to examine whether the associations between night-time sleep quality total scale as well as the three subscales and work functioning were moderated by anxiety. A p-value of <0.05 was considered to be statistically significant. Power analysis revealed that the statistical power for multivariate analysis exceed 86% with medium effect size at $\alpha$=0.05. The statistical power for univariate analyses was 93% with medium effect size at $\alpha$=0.05 (Faul et al., 2009).

# Results

## Patient characteristics

Most of the patients were male (70%) and had secondary education (60%). A total of 55% were obese, with severe OSA (47%). Poor night-time sleep quality was present in 84% of the OSA patients, and the prevalence of daytime sleepiness was 59%. The majority (80%) of OSA patients were anxious and reported mild to very severe anxiety. Impaired work functioning was present among 82% of OSA patients. Participants worked 39.5±7.8 hours and 5.3±1.1 days a week (Table 4.1).

*Table 4.1 Baseline characteristics of the OSA patients (AHI ≥5)*

| Characteristics | N=105 |
|---|---|
| Age in years; mean, sd | 46.62±9.79 |
| Gender; N, % male | 73 (70%) |
| Education; N, % | |
|     Elementary | 4 (4%) |
|     Secondary | 63 (60%) |
|     University | 38 (36%) |
| Occupation type; N, % white-collar | 51 (49%) |
| Marital status; N, % single | 21 (20%) |
| Body Mass Index; N, % | 31.27±7.04 |
|     Underweight (<18.5) | 0 (0%) |
|     Normal (18.5-24.99) | 23 (22%) |
|     Overweight (25.0-29.99) | 24 (23%) |
|     Obese (30+) | 58 (55%) |
| Apnoea-hypopnoea index; mean, sd | 37.03±22.75 |
| OSA severity; N, % | |
|     Mild (AHI≥5<15) | 16 (15%) |
|     Moderate (AHI>15<30) | 40 (38%) |
|     Severe (AHI>30) | 49 (47%) |
| Night-time sleep quality (PSQI); mean, sd (0-21) | 10.31±4.31 |
|     Perceived sleep quality; mean, sd | 4.78±2.36 |
|     Sleep efficiency; mean, sd | 1.81±1.83 |
|     Daily disturbances; mean, sd | 3.74±1.32 |
| Prevalence of night-time sleep quality disturbance; N, % (cut-off score >5) | 88 (85%) |
| Excessive daytime sleepiness (ESS); mean, sd (0-24) | 11.09±5.29 |
| Prevalence of increased daytime sleepiness; N, % (cut-off score >10) | 62 (59%) |
| Anxiety (BAI); mean, sd (0-63) | 32.99±13.03 |
| Prevalence of anxiety; N, % (cut-off score >9) | 84 (80%) |
|     Prevalence of mild anxiety (10-18) | 31 (30%) |
|     Prevalence of severe anxiety (19-29) | 35 (33%) |
|     Prevalence of very severe anxiety (30-63) | 18 (17%) |
| Work functioning (WRFQ) total scale; mean, sd (0-100%) | 52.58±28.76 |
|     Work Scheduling and Output demands | 49.19± 31.69 |
|     Physical demands | 57.43± 30.57 |
|     Mental and Social demands | 52.74± 31.15 |
|     Flexibility demands | 56.25± 30.04 |
| Impaired Work functioning; N, % (cut-off score <90) | 82 (82%) |
| Workdays per week; mean, sd | 5.32±1.10 |
| Work hours per week; mean, sd | 39.73±7.82 |

AHI – Apnoea-Hypopnoea Index; OSA – Obstructive Sleep Apnoea; PSQI – Pittsburgh Sleep Quality Index; ESS – Epworth Sleepiness Scale; BAI – Beck Anxiety Inventory; WRFQ – Work Role Functioning Questionnaire; Missing data: Occupation type: 1%; PSQI: 1%, WRFQ: 4%.

## Correlations between OSA severity, sleep-related problems, anxiety and work functioning

Table 4.2 displays the correlations between the study variables. High OSA severity, poor overall night-time sleep quality, poor perceived sleep quality, poor sleep efficiency, high level of daily disturbances, and severe anxiety were significantly correlated with impaired work functioning. Daytime sleepiness was not correlated with work functioning.

*Table 4.2 Correlation coefficients between OSA severity, night-time sleep quality the total scale and its three subscales, daytime sleepiness, anxiety and work functioning*

|  | OSA severity | Night-time sleep quality | Perceived sleep quality | Sleep efficiency | Daily disturbances | Daytime sleepiness | Anxiety |
|---|---|---|---|---|---|---|---|
| Night-time sleep quality | **0.23*** | - | - | - | - | - | - |
| Perceived sleep quality | **0.26*** | **0.68*** | - | - | - | - | - |
| Sleep efficiency | 0.14 | **0.65*** | **0.43*** | - | - | - | - |
| Daily disturbances | **0.33*** | **0.62*** | **0.62*** | **0.20*** | - | - | - |
| Daytime sleepiness | **0.34*** | **0.20*** | 0.14 | 0.04 | **0.49*** | - | - |
| Anxiety | 0.18 | **0.58*** | **0.34*** | **0.32**** | **0.44*** | **0.31**** | - |
| Work role functioning | **-0.20*** | **-0.41*** | **-0.47*** | **-0.23*** | **-0.36*** | -0.09 | **-0.45*** |

OSA – Obstructive Sleep Apnoea; *p<0.05; **p<0.01; ***p<0.001

## Associations between OSA severity, sleep-related problems, anxiety and work functioning (total scale)

A crude effect on work functioning was found for all variables, except for age (B: -0.22; 95%CI= -0.79; 0.36; p=0.46), type of occupation (B: -4.03; 95%CI= -15.40; 7.34; p=0.49) and daytime sleepiness (B: -0.61; 95%CI= -1.70; 0.48; p=0.27) (Table 4.3). A weak association between OSA severity (B: -0.27; 95%CI= -0.53; -0.01; p<0.05) and poor work functioning was found in crude analyses but was no longer significant (B: -0.18; 95%CI= -0.45; 0.08; p=0.17) in the subsequent multivariate models (Model 2-Model 5). Poor night-time sleep quality total scale (B: -2.63; 95%CI= -3.85; -1.42; p<0.001) was significantly associated with impaired work functioning (Model 3). The association between poor night-time sleep quality total scale and work functioning attenuated (B: -1.64; 95%CI= -3.07; -0.23; p<0.05) when anxiety (B: -0.61; 95%CI= -1.10; -0.15; p<0.01) was added to the model (Model 4). After adding anxiety (Model 4), the explained variance in work functioning increased from 20% to 25% (Table 4.3).

*Table 4.3 Multiple linear regression analysis: associations of OSA severity, night-time sleep quality, daytime sleepiness and anxiety with work functioning*

**Work functioning (WRFQ)**

|  | Crude B (95%CI) | Model 1 B (95%CI) | Model 2 B (95%CI) | Model 3 B (95%CI) | Model 4 B (95%CI) | Model 5 B (95%CI) |
|---|---|---|---|---|---|---|
| Age | -0.22 (-0.79; 0.36) | -0.06 (-0.62; 0.51) | -0.01 (-0.56; 0.58) | -0.02 (-0.55; 0.50) | -0.14 (-0.66; 0.39) | -0.17 (-0.68; 0.34) |
| Gender | **14.70 (2.56; 26.84)*** | **16.11 (3.67; 28.59)*** | **14.41 (1.76; 27.05)*** | 9.83 (-2.03; 21.60) | 7.20 (-4.54; 18.85) | 3.82 (-7.87; 15.44) |
| Occupation | -4.03 (-15.40; 7.34) | - | - | - | - | - |
| OSA severity | **-0.27 (-0.53; -0.01)*** | - | -0.18 (-0.45; 0.08) | -0.08 (-0.33; 0.17) | -0.08 (-0.32; 0.16) | -0.08 (-0.32; 0.15) |
| Night-time sleep quality | **-2.95 (-4.12; -1.79 )*** | - | - | **-2.63 (-3.85; -1.42)*** | **-1.64 (-3.07; -0.23)*** | **-6.10 (-9.80; -2.40)*** |
| Daytime sleepiness | -0.61 (-1.70; 0.48) | - | - | - | - | - |
| Anxiety | **-1.02 (-1.40; -0.63)*** | - | - | - | **-0.61 (-1.10; -0.15)*** | **-1.93 (-3.05; -0.80)*** |
| Nighttime sleep quality x Anxiety | **-0.05 (-0.07; -0.03)*** | - | - | - | - | **0.12 (0.03; 0.22)*** |
| F Change | - | 3.55 | 1.88 | 18.45*** | 6.25* | 6.61* |
| Adjusted R² | - | 0.05 | 0.06 | 0.20 | 0.25 | 0.29 |

Crude effects: effect of each variable separately on work functioning; Model 1: effect of age and gender on work functioning; Model 2: effect of age, gender, OSA severity and night-time-sleep quality on work functioning; Model 3: effect of age, gender, OSA severity and night-time-sleep quality and anxiety on work functioning; Model 4: effect of age, gender, OSA severity, night-time-sleep quality and anxiety on work functioning; Model 5: interaction between night-time sleep quality and anxiety; Blue-white collar – white collar was set as the reference; Gender – male gender was set as the reference; OSA – Obstructive Sleep Apnoea; F Change – significance of prediction improvement in the model fit; Adjusted R2 – explained variance adjusted for the number of predictors in the model; *p<0.05; **p<0.01; ***p<0.001.

A crude effect on work functioning was found for all of the three night-time sleep quality subscales. Multivariate analyses of the three subscales revealed that perceived sleep quality (B: -5.28; 95%CI= -7.48; -3.08; p<0.001) was more strongly associated with work functioning (Model 3, Supplementary Table S4.1, Supplement 4.1) than sleep efficiency and daily disturbances (Model 3, Supplementary Table S4.2, Supplementary Table S4.3, Supplement 4.1). The associations between sleep efficiency (B: -3.31; 95%CI= -6.35; -0.27; p<0.05), daily disturbances (B: -6.45; 95%CI= -10.92; -1.99; p<0.01) and work functioning (Model 3, Supplementary Table S4.2, Supplementary Table S4.3, Supplement 4.1) were no longer significant when anxiety was added to the model (Model 4, Supplementary Table S4.2, Supplementary Table S4.3, Supplement 4.1). The explained amount of total variance in work functioning varied from 22% for models with sleep efficiency and daily disturbances included to 27% for the model with sleep efficiency included.

**Associations between OSA severity, sleep-related problems, anxiety and work functioning by subscale**

A crude effect on work functioning subscales was found for all variables, except for age, type of occupation and daytime sleepiness. OSA severity was associated with physical demands only. Overall night-time sleep quality and anxiety were significantly associated with all work functioning subscales. Multivariate analyses showed that night-time sleep quality and anxiety were significantly associated with the work scheduling-output demands and physical demands in the final models (with an explained total variance of 26% for work scheduling and output demands, and 16% for physical demands) (Supplementary Table S4.4).

**Moderation analyses**

To test the moderation effects, the interaction terms between anxiety and overall night-time sleep quality were added into the equation (Model 5). The interaction of overall night-time sleep quality and anxiety was statistically significant (B: 0.12; 95%CI= 0.03; 0.22; p<0.05) (Table 4.3). Anxiety moderated the association between low and medium night-time sleep quality problems and work functioning. The impact of anxiety on the association between night-time sleep quality and work functioning was negligible in the case of high night-time sleep quality problems (Figure 4.1).

*Figure 4.1 Anxiety as a moderator of the association between night-time sleep quality and work functioning*
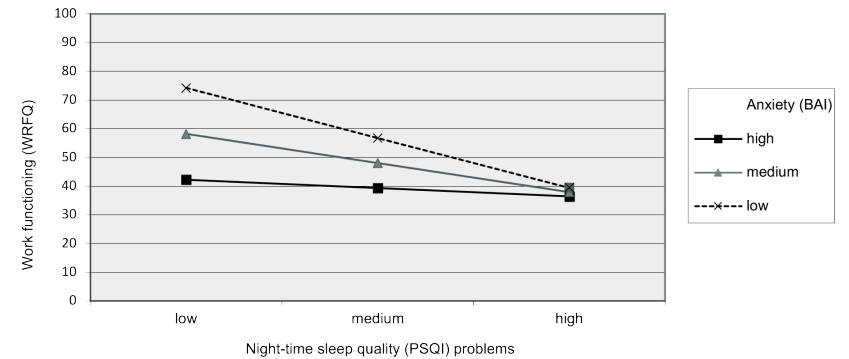


PSQI – Pittsburgh Sleep Quality Index; BAI – Beck Anxiety Inventory; WRFQ – Work Role Functioning Questionnaire; Higher WRFQ scores indicated better work functioning.

Separate analyses of the three night-time sleep quality subscales showed that the interactions of perceived sleep quality (B: 0.18; 95%CI= 0.10; 0.35; p<0.05) and daily disturbances (B: 0.56; 95%CI= 0.22; 0.90; p<0.01) with anxiety were statistically significant (Model 5, Supplementary Table S4.1, Supplementary Table S4.3, Supplement 4.1). The interaction of sleep efficiency and anxiety was not significant (B: 0.09; 95%CI= -0.14; 0.32; p=0.45) (Model 5, Supplementary Table S4.2). The moderating effect of anxiety in the association between perceived sleep quality, daily disturbances and work functioning was especially profound in the case of low and medium perceived sleep quality problems and low and medium levels of daily disturbances (Figure 4.2, Figure 4.3).
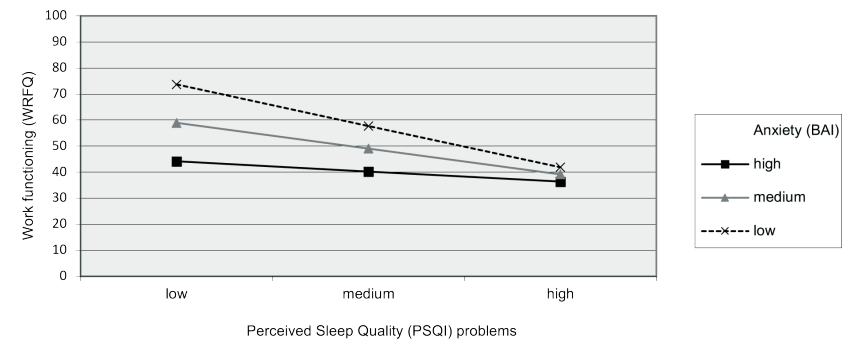
*Figure 4.2 Anxiety as a moderator of the association between perceived sleep quality and work functioning*



PSQI – Pittsburgh Sleep Quality Index; BAI – Beck Anxiety Inventory; WRFQ – Work Role Functioning Questionnaire; Higher WRFQ scores indicated better work functioning.

PSQI – Pittsburgh Sleep Quality Index; BAI – Beck Anxiety Inventory; WRFQ – Work Role Functioning Questionnaire; Higher WRFQ scores indicated better work functioning.
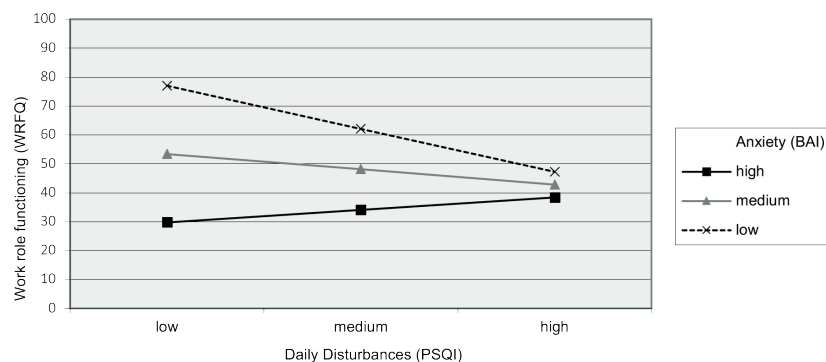
## Discussion

The aims of this study were 1) to examine whether OSA severity, sleep-related problems, and anxiety are associated with work functioning in OSA patients when controlled for age, gender, and type of occupation, and 2) to investigate whether anxiety moderates the associations between sleep-related problems and work functioning. Our results provided suggestive evidence that poor night-time sleep quality and increased anxiety were associated with impaired work functioning. Further, the moderating effect of anxiety on the association between night-time sleep quality and work functioning was especially profound in patients with better sleep quality, while the effect of anxiety on the association between work functioning and night-time sleep quality was negligible in the case of high night-time sleep quality problems.

Separate analyses of the three night-time sleep quality subscales showed that perceived sleep quality was more strongly associated with work functioning than sleep efficiency and daily disturbances. The associations between sleep efficiency, daily disturbances and work functioning were weak and no longer significant when anxiety was added to the models. Additionally, the moderating effect of anxiety on the association between perceived sleep quality, daily disturbances and work functioning was especially present in OSA patients with better-perceived sleep quality and a lower level of daily disturbances. No moderating role of anxiety in the association between sleep efficiency and work functioning was found.

We found a weak association between OSA severity and impaired work functioning; only significant in crude analyses. In the study by Mulgrew et al. (2007), patients with the lowest apnoea-hypopnoea index (AHI) scores exhibited an even more significant level of work limitation, and this association was dependent on the type of occupation and particular subscale of the Work Limitation Questionnaire.

In contrast, no association between the type of occupation and work functioning for the total scale, not even for subscales was found in our study. An explanation for the lack of clear association between OSA severity and work functioning could be the use of polysomnography (PSG) to determine the diagnosis of OSA. Although a one-night PSG is sufficient for a diagnosis of OSA (Scholle et al., 2003; Gouveris et al., 2010), current techniques to measure OSA are a matter of some controversy; i.e. PSG-based AHI has been discussed as being inadequate to detect OSA severity (Ryu et al., 2016; Lee at al., 2016). Our findings confirm the suggestion of Macey et al. (2010) that mechanisms other than the AHI may contribute to adverse health effects in OSA patients.

Our study revealed an association between poor night-time sleep quality and impaired work functioning, whereas daytime sleepiness was not related to work functioning. Contrary to this finding, previous studies in patients referred for OSA described an association between excessive sleepiness (measured by ESS) and work limitation (Mulgrew et al., 2007; Ulfberg et al., 1996; Grunstein et al., 1995). There are a variety of potential explanations for the lack of clear association between daytime sleepiness and work functioning. The study of Ulfberg et al. (1996) did not use PSG to diagnose OSA, and measures of work limitation and daytime sleepiness were combined into a single questionnaire, making interpretation difficult. Similarly, Grunstein et al. (1995) did not use validated measures of work role performance. Furthermore, the concepts used by Ulfberg et al. (1996) and Omachi et al. (2009), such as recent work disability and longer-term work duty modification, do not fully capture the scope or nature of subjective work functioning impairment measured in our study. Another possible explanation for these discrepancies could be that daytime sleepiness, measured by ESS, is assessed predominantly in a setting of decreased activity level (e.g. watching TV, sitting, reading etc.) compared with the higher mental or physical activity level usually expected in the working environment. The lack of association between daytime sleepiness and work functioning can be explained based on the hypothesized pathophysiology of insomnia; i.e. the symptoms of poor sleep quality and anxiety might be linked to each other by some form of underlying "hyperarousal" (Perlis et al., 2005). Anxiety in OSA patients may develop into a chronic state of hypervigilance (Krakow et al., 2015), which refers to the predisposition to be on high alert much more than is considered normal. This arousal ultimately leads to a state of chronic anxiety and eventually sleeplessness. All these cases epitomize the related phenomenon of an anxiety process that may obliterate natural sleepiness (Perlis et al., 2005; Krakow et al., 2015). In line with the delineated hyperarousal theory, we found that anxiety was more strongly associated with poor overall night-time sleep quality and its three separate factors than with daytime sleepiness.

The fact that the association between night-time sleep quality and work functioning was greatly attenuated after anxiety was added to the model is not surprising. Sleep disturbances are closely related to anxiety symptoms, as sleep disturbances are both a precursor and a symptom of anxiety (Shanahan et al., 2014). Moreover, we found a moderating effect of anxiety on the association between low and medium

night-time sleep quality problems and work functioning. Based on our results, it can be hypothesized that work functioning in OSA patients may be impacted by anxiety more significantly than by poor night-time sleep quality. However, the moderating role of anxiety in the association between work functioning and sleep quality was weakened in patients with the highest levels of sleep quality problems. Thus, high night-time sleep quality problems may become more significant in the association with poor work functioning than anxiety, while the moderating effect of anxiety on work functioning was especially profound in patients with better sleep quality. In line with the evidence that poor perceived sleep quality is more predictive of negative affectivity and impaired physical health than sleep efficiency, i.e. sleep quantity (Pilcher et al., 1997), we found that perceived sleep quality was more strongly associated with work functioning than sleep efficiency and daily disturbances. The association between sleep efficiency and work functioning was only weak and no longer significant when anxiety was added to the model.

Regarding the role of sociodemographic variables, we identified a higher impairment of work functioning in male when compared with female OSA patients. In contrast to our study, general functional status was found to be more impaired in female OSA patients when compared with males in some previous studies (Chervin 2000; Quintana-Gallego et al., 2004; Silva et al., 2016). A potential explanation for these discrepancies can be that men more often than women work in jobs that are incompatible with increased sleep-related symptoms. Hence, male OSA patients may more often than females face demands in their jobs that cannot be dealt with when sleep-related problems are above a certain level (Bültmann et al., 2013). Furthermore, in our sample, 70% of OSA patients were men; thus, our results may be less generalizable to the female population of OSA patients.

Although, it may be assumed that some OSA symptoms, such as sleep-related problems, may be more difficult to overcome due to the sedentary nature of work in the group of white-collar OSA patients, we found no significant difference regarding work functioning impairment in blue- and white-collar workers. However, the fact that white-collar workers in particular may have modified and more flexible work options or benefits enabling those with more severe OSA symptoms to continue to work without significant impairment should be considered (Mulgrew et al., 2007).

### Strengths and limitations
The strengths of this study are that we shed light on several novel aspects of work functioning among OSA patients. Patients in our study were diagnosed using PSG, which is an asset of the study. To our knowledge, this is the first time that the PSQI factor structure has been used in a sample of OSA patients. It is also the first study using the Work Role Functioning Questionnaire in an OSA population. Some limitations should also be noted. Due to the cross-sectional design of the study, causal inferences cannot be made. Next, work functioning has not been objectively evaluated. Nevertheless, the used instrument has been found to be appropriate to measure health-related work functioning in the occupational health care practice or

in the rehabilitation process of disabled workers (Ramada et al., 2014). We can also assume that anxiety symptoms assessed in our study may be associated with panic disorder, rather than with anxiety in general. Although the Beck Anxiety Inventory (BAI) may be used as an indicator of anxiety in primary care patients with different anxiety disorders (Wetherell and Gatz, 2005) it has been disputed for its focus on psychophysiological symptoms linked to panic disorder (Beck and Steer, 1991; Cox et al., 1996), such as a racing heart or dizziness (Julian, 2011). The associations identified in our study may also occur due to latent mental health problems or somatic disease; i.e. sleep disturbances have also been identified to be both a precursor and a consequence of depression (Ford and Cooper-Patric, 2001). Nevertheless, the measure of anxiety used in our study was found to be suitable to distinguish an overlap between anxiety and depressive symptoms (Beck et al., 1988). Furthermore, considering that patients with any major somatic or mental health comorbidity in the medical record were excluded from our study, this bias is rather unlikely. Previous study showed that OSA patients had difficulties to complete the work tasks and they subjectively felt a lack of trust from co-workers, which consequently caused subsequent embarrassment related to this (Reishtein et al., 2006). Thus, it should be considered that increased anxiety may also be work (e.g. working environment, cutting down jobs) and not only OSA-related.

### Implications for practice and future research
This study shows that poor night-time sleep quality and anxiety were strongly associated with impaired work functioning in OSA patients. Thus, employee assessment of their work functioning may be an important proxy for the economic burden of OSA (Mulgrew et al., 2007). Although patients with any major somatic or mental health comorbidity in the medical record were excluded, we found that 80% of OSA patients experienced increased symptoms of anxiety, which varied from mild (30%) to severe (17%). Thus, the study suggests that early detection and treatment of OSA and anxiety should be one of the priorities on the stakeholders' agenda. Furthermore, identifying patients with overlapping diagnoses of mental health problems and OSA in clinical care may help to improve their treatment outcomes through careful dosing of pharmacotherapy and use of continuous positive airway pressure treatment (Gupta and Simpson, 2015). Compared with sleep efficiency, perceived sleep quality was more strongly associated with work functioning. These results indicate that health care professionals, in their efforts to understand the role of sleep in the daily life of patients with OSA, should rather focus on sleep quality than on sleep quantity. In clinical and research settings, these qualitative aspects of sleep may be captured by clinical interviews and specific patient-reported outcomes. There is a need for workplace strategies that encourage behaviours and practices that may be helpful in reducing OSA-related symptoms and improve work functioning in OSA patients. Employers can play a role in educating employees about effective management of sleep loss through a variety of proven strategies, including better managed work demands, regular exercise, duty hour considerations, and instructing them on the basics of sleep hygiene (Jansson and Linton, 2006).

Some recent evidence shows that workplace flexibility (allowing more flexible work start and end times) may contribute to positive health-related behaviours and may play an important role in effective workplace health promotion programs (Moen et al., 2011). Previous studies have also shown that enabling "unwinding" time between work and home may improve sleep patterns; as reduced work-to-home interference has the potential to decrease the risk of poor night-time sleep quality (Nylen et al., 2007).

As boundaries between work and private life become more blurry, there is a real need to examine the associations between work habits, sleep and other related aspects, especially in common diseases such as OSA. Further research should identify risk groups of patients with impaired work functioning and increased anxiety levels and tailor the counseling and interventions suitably for these patients. Although PSG is considered to be a gold standard for making a diagnosis of OSA, it is not easily applicable in large population-based studies due to its intrusiveness and high costs (Sivertsen et al., 2008). Therefore, screening instruments based on self-reported symptoms of OSA have been important in order to gain information on the prevalence, comorbid conditions of OSA or continuous positive airway pressure treatment effectiveness, which would be difficult to obtain without using scale surveys (Sivertsen et al., 2008). As BAI does not assess other symptoms of anxiety, such cognitive aspects, futher research may be accompanied by additional anxiety measures to distinguish between panic symptoms and other anxiety disorders (e.g. generalized anxiety disorder). Moreover, the possibility that anxiety may mask the certain amount of daytime sleepiness in OSA patients (Krakow et al., 2015) should be examined in the future studies. Further prospective, longitudinal research is needed to elucidate the pathways from OSA, sleep-related problems, and anxiety to impaired work functioning. As perceived sleep quality and sleep efficiency are influenced by a range of factors related to age or health (Foley et al., 2004), there is a need for further studies examining the factor structure of the PSQI in OSA patients. Finally, we studied OSA patients without major comorbidities, as these are assumed to influence sleep and affective OSA symptoms (Macey et al., 2010). As a group with minimal comorbidities and recent diagnosis is not fully representative of the general OSA population, it may be assumed that work functioning and other health-related outcomes would be even more significantly impaired in a sample of OSA patients with comorbid diseases (Macey et al., 2010).

## Conclusion

Poor sleep quality and anxiety were significantly associated with impaired work functioning in OSA patients. We also found that perceived sleep quality was more strongly associated with work functioning than sleep efficiency; i.e. sleep quantity. Further, the moderating effect of anxiety on work functioning was especially strong in patients with better sleep quality. The role of anxiety in the association between sleep quality and work functioning was weakened in the case of poor night-time sleep quality. Impaired work functioning in OSA patients may represent a possible cause of disability, which may be improved by workplace strategies focused on decreasing poor sleep quality and anxiety when confirmed in longitudinal studies. As many people with OSA are undiagnosed, our results demonstrate to employers and health care professionals the need to encourage patients for OSA screening, especially in the situation of impaired work functioning, increased anxiety and poor sleep quality.

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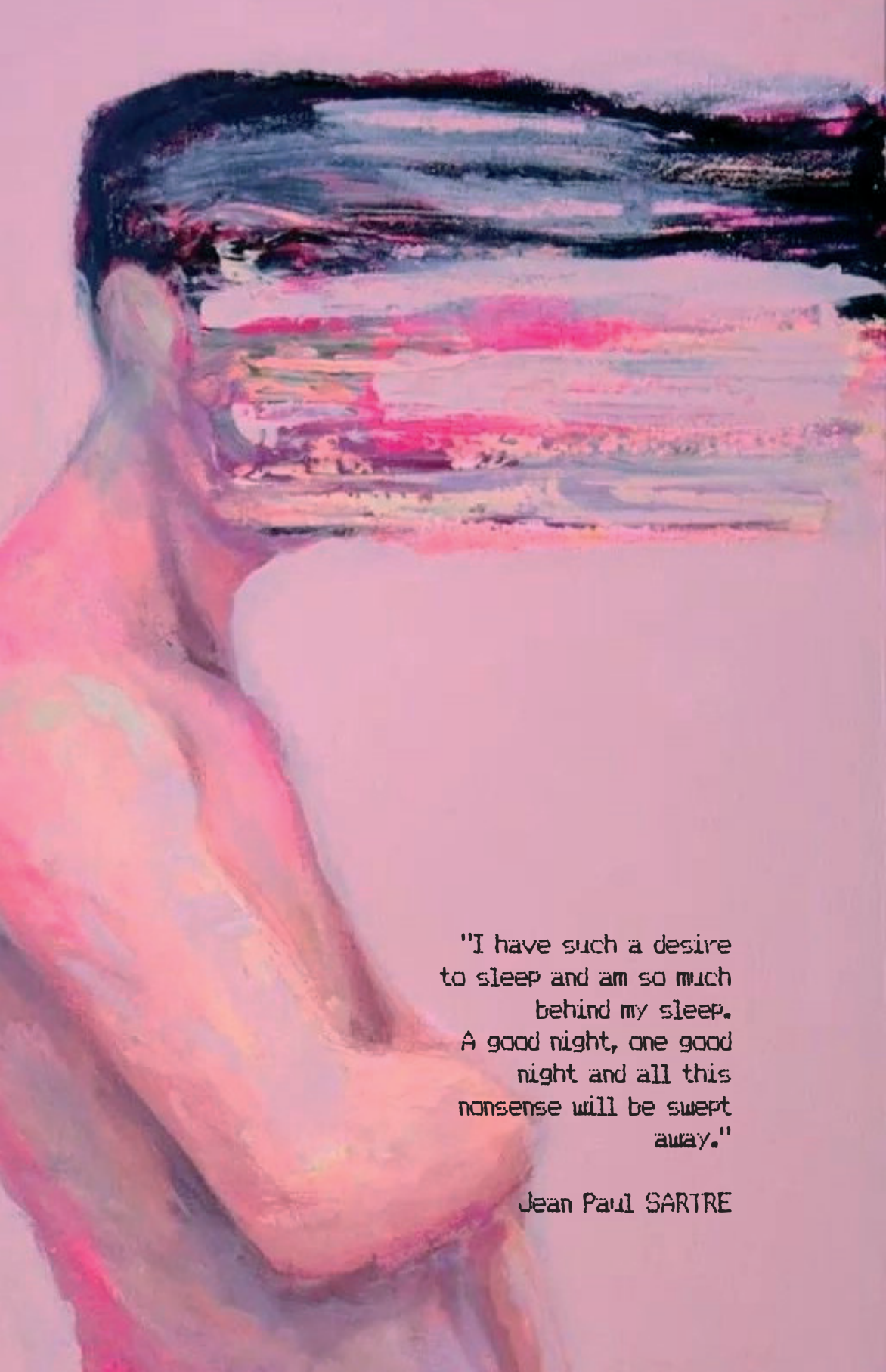
# Psychological distress in patients with obstructive sleep apnoea: the role of hostility and coping self-efficacy

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"I have such a desire to sleep and am so much behind my sleep. A good night, one good night and all this nonsense will be swept away."

Jean Paul SARTRE

## Abstract

### Background and aim

So far, very little is known about the association between hostility, coping self-efficacy and psychological distress in Obstructive Sleep Apnoea (OSA) patients. We aimed to assess whether hostility and coping self-efficacy are associated with psychological distress in OSA patients. Furthermore, we examined whether coping self-efficacy mediates the association between hostility and psychological distress.

### Methods

We included 150 OSA patients (Apnoea-Hypopnoea Index–AHI≥5; 68% male; mean age 48.9±9.5 years), diagnosed by a full-night polysomnography. Patients completed the General Health Questionnaire-28, the Coping Self-efficacy Scale, the Cook-Medley Hostility Scale, the Pittsburgh Sleep Quality Index and the Epworth Sleepiness Scale. Multiple linear regression and mediation analyses were used to analyse the data.

### Results

Regression models showed that hostility and poor coping self-efficacy were strongly associated with psychological distress in OSA patients. All assessed coping self-efficacy dimensions mediated the association between hostility and psychological distress. Coping self-efficacy for stopping unpleasant emotions and thoughts showed the strongest association with a lower level of psychological distress.

### Conclusion

This study has led us to conclude that the presence of psychological distress in OSA patients may not be solely due to the effect of OSA itself. Rather, hostility and the choice of coping strategies may play a key role in examining which OSA patients will experience higher level of psychological distress.

## Introduction

Obstructive Sleep Apnoea (OSA) is considered one of the most prevalent sleep disorders (Manarino et al., 2012), affecting 2–10% of the adult population (Leger et al., 2012). OSA leaves patients exhausted due to sleep disruption (Tkacova and Dorkova, 2010; Manarino et al., 2012; Rezaeitalab et al., 2014). Besides physical symptoms, OSA patients may experience psychological distress (Kang et. al, 2012; Rezaeitalab et al., 2014; Su et al., 2015), irritability and hostility (Yue et al., 2003; Booth et al., 2006; Lau and Lee, 2014; Unal et al., 2017). Sleep-related OSA symptoms, such as poor night-time sleep quality and daytime sleepiness, have been shown to have a negative impact on patients' psychological well-being and overall quality of life (Tsara et al., 2009; Antic et al., 2011).

Hostility has previously been found to be associated with the presence of OSA, the degree of daytime sleepiness (Yue et al., 2003) and poor night-time sleep quality (Xiao et al., 2016, Freitag et al., 2017) but not with severity of the apnoea-hypopnoea index (AHI) or oxygen desaturation (Yue et al., 2003). Hostility is conceptualized as a negative cynical attitude toward others, with a propensity for anger, aggression (Cook and Medley, 1954; Ireland and Culpin, 2006), distrust or cynicism (Barefoot et al., 1989). Hostility may represent a risk factor for all-cause mortality (Nabi et al., 2008) and impaired mental health outcomes, with evidence being especially strong in patients with cardiovascular diseases (Silarova et al., 2016). Furthermore, hostility may be linked to increased negative emotionality (Brissette and Cohen, 2002), depression (Heponiemi et al., 2006), suicidal ideation and attempts (Brezo et al., 2006; Lemogne et al., 2011), sleep disruption (Brissette and Cohen, 2002) and poor sleep quality (Freitag et al., 2017). This symptomatic sleep disruption often causes serious decreases in blood oxygen levels, with potentially life-threatening cardiovascular consequences (Bardwell et al., 2001; Leger et al., 2012), while these mechanisms may be even more strongly aggravated by hostility (Hall et al., 2004; Mezick et al., 2010). Several mechanisms explaining the link between hostility and health consequences have been proposed. For instance, hostile persons exhibit increased sympathetic reactivity in some situations, experience more interpersonal conflicts and and may display more unhealthy behaviours (Smith, 1992; Vandervoort, 2006).

Effective coping strategies may be beneficial in handling chronic diseases, including OSA (Bardwell et al., 2001; Gassara et al., 2017). Coping can be defined as an effort to manage a situation and involves various cognitive and behavioural strategies to overcome external or internal demands, which are appraised as either taxing or exceeding the person's resources (Folkman et al., 1986). The terms coping and coping self-efficacy are closely linked (Park and Folkman, 1997; Bandura et al. 1999; Chesnay et al., 2006). The concept of coping self-efficacy is based on the integration of two well established theories within health research: the self-efficacy theory of Bandura (1999) and the coping theory of Lazarus and Folkman (1984). In the framework of these theories, coping-self efficacy addresses which coping strategy a person will apply based on the perceived self-efficacy, and thus, it represents an important prerequisite to coping behaviour (Park and Folkman, 1997).

The choice and level of coping self-efficacy in a particular circumstance reflects prior-relevant experiences (Bandura et al., 1977). As such, greater levels of coping self-efficacy were found to be associated with more effective regulation of emotional distress (Luberto et al., 2014). The ability to regulate emotions is crucial in diminishing psychological distress; however, healthy emotion-regulation may not merely be about using the "right" strategies (Haines et al. 2016). According to the strategy-situation-fit hypothesis, emotion-regulation strategies are able to diminish psychological distress only when used in appropriate contexts (Bonanno and Burton, 2013; Haines et al. 2016).

Previous research has focused on the effect of coping self-efficacy and coping behaviour on patients' self-reported health outcomes in various diseases, such as heart failure (Graven and Grant, 2013), multiple sclerosis (Mikula et al., 2016) or chronic obstructive pulmonary disease (Tiemensma et al., 2016; Vaske et al., 2017). Previous studies have shown that a higher level of coping self-efficacy was associated with a better adjustment to various chronic diseases (Chesney et al., 2006; Benka et al., 2014; Mikula et al., 2016). Only a few studies have thus far addressed this concept, but these have shown an association between coping self-efficacy and psychological distress (Chesney et al. 2006; Benka et al., 2014) and better quality of life (Mikula et al., 2016) in the context of various chronic diseases. Overall, these results suggest that coping self-efficacy has direct effects on distress/well-being outcomes, beyond the impact of clinical and personality variables. Some studies indicate that problem-focused coping was the most beneficial in handling disease (Graven and Grant, 2013; Tiemensma et al., 2016), especially in the mental health domain (Scharloo et al., 2000). Nevertheless, in some studies, avoidance-oriented coping, such as coping self-efficacy for the ability to stop unpleasant emotions and thoughts, were defined as most effective in dealing with the disease (Mackay et al., 2012; Harmell et al., 2011). Recent studies have concluded that the more active and less passive coping strategies reported by OSA patients, the lower the level of depressive symptoms experienced by patients (Bardwell et al., 2001; Gassara et al., 2017). Moreover, a mediating role of coping self-efficacy in the association between personality traits and psychological health was identified in patients with multiple sclerosis (Mikula et al., 2016). Coping strategies were found to play a mediating role in the relationship between hostility and self-rated health outcomes in a sample of healthy individuals (Vandervoort, 2006). Unfortunately, the nature of coping styles utilized by hostility-prone individuals has received scant empirical attention.

So far, very little is known about the association between hostility, coping self-efficacy and psychological distress in OSA patients. To our knowledge, only two studies have directly focused on the association between coping and self-rated health outcomes, i.e. depression, in OSA patients (Bardwell et al., 2001; Gassara et al., 2017). Due to a lack of general consensus regarding the continous positive airway pressure treatment effect on self-reported (Weaver, 2013; Tippin et al., 2016) and objective (Dimsdale et al., 2000) health outcomes, the present research and clinical practice should also focus on the identification of adequate internal resources which may diminish psychological distress in OSA patients. Thus, the aims of this study were 1) to assess whether hostility and coping self-efficacy are associated with psychological distress in OSA patients when controlled for sociodemographic, clinical and sleep-related variables, and 2) to examine whether coping self-efficacy mediates the association between hostility and psychological distress.

## Methods

### Sample and procedure

This cross-sectional study was conducted at the Department of Pneumology and Phtiseology, L. Pasteur University Hospital and the Medical Faculty of PJ Safarik University in Kosice, Slovak Republic. All patients who visited the department for one-night polysomnography (PSG) from July 2013 to June 2016 were eligible for the study. The indication for PSG was based on a general practitioner referral form. OSA was diagnosed based on an overnight sleep examination.

Only OSA patients between 18 and 65 years of age were included due to possible increased vulnerability, functional changes and a decline in abilities and/or performance related to age. The study sample consisted of patients with an Apnoea Hypopnoea Index (AHI; number of apnoeas + hypopnoeas per hour of sleep) score of 5 or more (American Academy of Sleep Medicine, 2005), who had not undergone any previous continuous positive airway pressure (CPAP) treatment or other OSA treatment, had no regular shift work in the past six months, were Slovak-speaking and had no major comorbidities.

Out of N=263 patients, N=41 refused to participate in the study (response rate 84.0%). Another N=72 patients were excluded because of major comorbidities. The reasons for exclusion were major comorbidities related to sleep (a coexisting sleep disorder such as insomnia, narcolepsy, or circadian rhythm sleep disorder), major cardiovascular diseases (e.g. angina pectoris, myocardial infarction, primary pulmonary hypertension), pulmonary conditions (e.g. Pickwick syndrome, chronic obstructive pulmonary disease) and a history of cancer in the past twelve months. Neurological and psychological comorbidities included a neurological condition (e.g. epilepsy, stroke), a major psychiatric diagnosis (e.g. major depression, psychotic disorders) in the medical record and/or current usage of psychiatric medications which may affect cognitive functions (e.g. benzodiazepines, antidepressants or antipsychotics), drug abuse in the past six months, and regular shift work in the past six months. The clinical diagnoses of the comorbid diseases were established according to the standard International Classification of Diseases 10 revision Codes. Screening for comorbidities was based on medical data and an initial clinical interview prior to data collection. Medical examinations of patients were conducted by a pulmonologist specialized in sleep-disordered breathing. Patients with non-respiratory sleep-related complaints (e.g. narcolepsy, insomnia) were routinely referred to another group of clinical specialists.

The invitation letter, informed consent and questionnaires were sent to participants by postal mail three weeks before the medical examination. One week before the medical examination, patients were reminded about the questionnaires by

telephone. Patients filled in self-report questionnaires at home. All patients' signed the informed consent form prior to study participation. Participation in the study was fully voluntary, with no incentives offered to participate in the research. The study was approved by the Ethics Committee of PJ Safarik University in Kosice (approval no. 115/2011).

**Measures**

*Psychological distress*

Psychological distress was assessed using the General Health Questionnaire (GHQ-28) (Goldberg and Hillier, 1979). The GHQ-28 is a 28-item measure of psychological distress in the general population and within community or non-psychiatric clinical settings, such as among primary care or general medical out-patients. The GHQ-28 was developed as a screening tool to detect those likely to be at risk of developing psychiatric disorders. The questionnaire is divided into four subscales: somatic symptoms (items 1–7); anxiety/insomnia (items 8–14); social dysfunction (items 15–21) and severe depression (items 22–28) (Goldberg and Hillier, 1979). Psychological distress was defined as a continuous variable (0-3), ranging from 0 to 84. A total score of 23/24 represents the threshold for the presence of psychological distress (Goldberg and Hillier, 1979). Psychological distress is understood as the opposite continuum to psychological well-being (Goldberg and Hillier, 1979; Spiteri et al., 2013). Higher scores indicated a higher level of psychological distress. In our sample the Cronbach's alpha for the total GHQ-28 scale was 0.83.

*Hostility*

Hostility was measured by the abbreviated 27-item version of the Cook-Medley Hostility Scale (CMHo) (Cook and Medley, 1954). The CMHo scale is a widely used self-report measure of trait hostility. The scale primarily assesses the cognitive aspects of hostility, cynicism and distrust. Cynicism items are defined as statements of belief; aggressive response items reflect behaviour and hostile affect items reflect emotional experiences. Each item is rated on a dichotomised scale (1="true", 0="false"). The score ranges from 0 to 27, with a higher score indicating more hostility (Cook and Medley, 1954). Cronbach's alpha for the total scale in our sample was 0.85.

*Coping self-efficacy*

Coping self-efficacy (CSE) was measured using the 26-item CSE Scale developed specifically for people suffering from chronic disease (Chesney et al., 2006). The CSE scale represents a measure of an individual's confidence in performing coping behaviours when faced with life challenges. The term CSE relates to the tendency to make certain attributions about control not in one context but in many (Lazarus and Folkman, 1984). The CSE scale advances our ability to explore the theoretical links between the secondary appraisal of stress, which asks 'what can I do?', and the major coping functions postulated by stress and coping theory – the regulation of distress and the management of underlying problems (Chesney et al., 2006). The term coping self-efficacy is understood as a prerequisite for using

actual coping strategies, as people need to be sure that they can perform coping actions before they act upon them (Chesney et al., 2006). Patients were asked to respond to the following question: 'When things are not going well for you, or when you are having problems, how confident or certain are you that you can do the following': 'sort out what can be changed, and what cannot be changed', 'break an upsetting problem down into smaller parts', 'look for something good in a negative situation', and 'get emotional support from friends and family', or 'take your mind off unpleasant thoughts'. The CSE consists of three subscales representing self-efficacy for the use of 'problem-focused coping' strategies (ranging from 0 to 120), 'ability to get support from friends and family' (ranging from 0 to 50) and the 'ability to stop unpleasant emotions and thoughts' (ranging from 0 to 90). Coping self-efficacy for the use of 'problem-focused coping' consists of items that measure an individual's self-efficacy with respect to overcoming problems by analysing the nature of the problem and employing cognitive strategies to make the respondent's perception of the problem less severe (e.g. 'break an upsetting problem down into smaller parts'). Coping self-efficacy for the 'ability to stop unpleasant emotions and thoughts' measures a respondent's self-efficacy with respect to trying not to dwell on negative feelings and altering the emotional response to an unsettling event or problem rather than addressing the characteristics of the problem itself (e.g. 'take your mind off negative thoughts'). The 'ability to get support from friends and family' represents a set of items that captures the social dimension by tapping the respondent's perception of their ability to seek help from friends and family to cope with problems (e.g. 'get emotional support from friends and family') (Chesney et al., 2006). The three factors in the CSE scale are consistent with the three major aspects of coping – problem-focused coping, emotion-focused coping and social support. Although the scales are moderately correlated, the results of the concurrent validity analyses indicate that the scales assess self-efficacy with respect to different types of coping and lend support to using the factors separately (Chesney et al., 2006). Respondents answered on an 11-point scale. A higher score indicates a higher ability to cope with a particular situation (Chesney et al., 2006). In our sample, the Cronbach's alphas were 0.94 for self-efficacy for the use of problem-focused coping, 0.86 for coping self-efficacy for the ability to get support, and 0.93 for the ability to stop unpleasant emotions and thoughts, respectively.

*Sleep-related problems*

Sleep-related problems concerned night-time sleep quality and daytime sleepiness. *Night-time sleep quality* was measured using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI is a self-rated questionnaire to assess sleep disturbances and sleep quality over a one-month time interval. The PSQI consists of 19 self-report questions which cover seven domains: sleep duration, subjective sleep quality, sleep latency, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. The score ranges from 0 to 21, with higher scores reflecting poor night-time sleep quality. A cut-off score of 5 separates good from poor sleepers (Buysse et al., 1989). Cronbach's alpha in our sample was 0.85.

*Daytime sleepiness* was measured using the self-report Epworth Sleepiness Scale (ESS), an eight-item questionnaire describing the tendency to fall asleep in various daytime scenarios (Miletin and Hanly, 2003). The score ranges from 0 to 24, with higher scores indicating higher daytime sleepiness. An ESS total score greater than 10 indicates excessive daytime sleepiness (Miletin and Hanly, 2003). Cronbach's alpha in our sample was 0.86.

*Sociodemographic and clinical data*
Information on age, gender and marital status was obtained from patient records. Body Mass Index (BMI; height and weight) was assessed by a physician. BMI was categorized as: underweight (<18.5), normal (18.5-24.99), overweight (25.0-29.99) and obese (30+). Polysomnography (PSG) was used to determine whether the diagnosis of OSA was present and to identify the severity of the disorder. PSG consists of a simultaneous recording of multiple physiological parameters related to sleep and wakefulness which directly monitor and quantify the number of respiratory events, related hypoxemia and arousals. PSG included standard central and occipital electroencephalogram, bilateral electrooculogram, submental electromyogram (EMG), oral and nasal airflow using a thermistor, thoracic and abdominal excursions using respiratory inductive plethysmography and bilateral tibialis EMG. OSA severity was determined based on an AHI score (American Academy of Sleep Medicine, 2005), with three categories: mild OSA (AHI ≥5 and ≤15), moderate OSA (AHI >15 and ≤30) and severe OSA (AHI >30).

**Statistical analyses**
Firstly, we described the background characteristics of the sample and calculated means and standard deviations for hostility (CMHo), coping self-efficacy (CSE) and psychological distress (GHQ-28) and sleep-related problems. We calculated frequencies and percentage for sociodemographic and clinical variables. Secondly, we assessed the correlations between the variables under study. Thirdly, using regression analyses we assessed the crude associations of hostility and coping self-efficacy with psychological distress. Multicolinearity was assessed using the variance inflation factor (VIF<2.0). We applied the enter selection in multiple linear regression models to determine the factors associated with psychological distress. For each factor, beta coefficients represent the mean variation of the psychological distress score. As the choice of coping strategies may be influenced by clinical and sleep-related variables, the associations between hostility, coping self-efficacy and psychological distress were adjusted for OSA severity, night-time sleep quality and daytime sleepiness. The first model of the variables included sociodemographic data (age, gender). A second model included a clinical variable (OSA severity - measured by AHI), and a third model included night-time sleep quality and daytime sleepiness. In the fourth and fifth model, hostility and all dimensions of coping self-efficacy were included separately (following Bardwell et al., 2001; Mikula et al., 2016; Gassara et a., 2017) to assess the explained amount of the total variance of psychological distress.

Finally, we performed mediation analyses to investigate whether the associations between hostility and psychological distress were mediated by the coping self-efficacy. According to Baron and Kenny (1986), the following conditions must be met to establish mediation: the independent variable (hostility) must affect the dependent variable (psychological distress); secondly, the independent variable (hostility) must affect the mediator (separate coping self-efficacy dimensions); and lastly, the mediator (separate coping self-efficacy dimensions) must affect the dependent variable (psychological distress). The proportion of the effect which is mediated was calculated as the indirect effect divided by the total effect and multiplied by 100, while the as-advised standardized total effect was at least ±0.2 (Kenny, 2016). Sobel z-tests were used to examine the mediating effects of the coping self-efficacy on the associations between hostility and psychological distress. Power analysis revealed that the statistical power for multivariate analysis exceed 95% at α=0.05. The statistical power for univariate analysis was 0.99 at α=0.05 (Faul et al., 2009). A p-value of <0.05 was considered to be statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS 23) and MedGraph.

## Results

### Sample characteristics

A total of N=150 OSA patients (68% male; mean age 48.9±9.5 years) were included in the study. The majority of patients had secondary education (57.3%). A total of 44.7% were obese and 49.3% had severe OSA (Table 5.1).

*Table 5.1 Baseline characteristics of the OSA patients (AHI≥5)*

| Characteristics | N=150 |
|---|---|
| Age in years; mean, sd | 48.9±9.5 |
| Gender; male, N (%) | 102 (68.0%) |
| Marital status; single, N (%) | 36 (24.0%) |
| Education; N (%) | |
|     Elementary | 8 (5.3%) |
|     Secondary | 86 (57.3%) |
|     University | 56 (37.3%) |
| Body Mass Index; mean, sd | 30.2±7.7 |
| Body Mass Index; N (%) | |
|     Underweight (<18.50) | 9 (6.0%) |
|     Normal (18.50-24.99) | 42 (28.0%) |
|     Overweight (25.00-29.99) | 32 (21.3%) |
|     Obese (≥30.00) | 67 (44.7%) |
| Apnoea-hypopnoea index (AHI) in events/h; mean, sd | 36.1±22.3 |
| OSA severity; N (%) | |
|     Mild (AHI≥5≤15) | 23 (15.3%) |
|     Moderate (AHI>15≤30) | 52 (34.7%) |
|     Severe (AHI>30) | 74 (49.3%) |
| Night-time sleep quality; mean, sd (PSQI; 0-21) | 9.7±4.1 |
| Excessive daytime sleepiness; mean, sd (ESS; 0-24) | 11.0±5.3 |
| Hostility (CMHo; 0-27) | 15.1±5.6 |
| Problem-focused coping self-efficacy (CSE; 0-120) | 79.5±24.1 |
| Get support from friends and family (CSE; 0-50) | 32.9±10.0 |
| Stopping unpleasant emotions and thoughts (CSE; 0-90) | 56.1±19.6 |
| Psychological distress (GHQ-28; 0-84) | 32.6± 18.4 |
| Psychological distress (GHQ-28 ≥24) | 79 (56.0%) |

AHI – Apnoea-Hypopnoea Index; OSA – Obstructive Sleep Apnoea; PSQI – Pittsburgh Sleep Quality Index; ESS – Epworth Sleepiness Scale; CMHo – Cook-Medley Hostility Scale; CSE – Coping Self-Efficacy Scale; GHQ-28 – General Health Questionnaire; Missing values: OSA severity (0.7%), age (1.0%), ESS (1.0%), PSQI (1.0%), CMHo (1.0%), GHQ-28 (6.0%), Problem-focused coping self-efficacy (6.0%), Get support from friends and family (2.0%), Stopping unpleasant emotions and thoughts (3.0%).

### Correlations between hostility, coping self-efficacy and psychological distress

Table 5.2 shows the correlations between between hostility, coping self-efficacy and psychological distress. Small but significant correlations were found between hostility, self-efficacy for the use of problem-focused coping and coping self-efficacy for getting support from family and friends. A moderate correlation was found between hostility and ability to stop unpleasant emotions and thoughts. The correlations between hostility, all dimensions of coping self-efficacy and psychological distress were high.

*Table 5.2 Correlation coefficients between hostility, coping self-efficacy and psychological distress*

| | Hostility | Problem-focused coping self-efficacy | Get support from friends and family | Stopping unpleasant emotions and thoughts |
|---|---|---|---|---|
| **Problem-focused coping self-efficacy** | -0.24* | - | - | - |
| **Get support from friends and family** | -0.23* | 0.89*** | - | - |
| **Stopping unpleasant emotions and thoughts** | -0.26** | 0.90*** | 0.82*** | - |
| **Psychological distress** | 0.58*** | -0.50*** | -0.35*** | -0.53*** |

*p<0.05; **p<0.01; ***p<0.001. Higher score indicates higher psychological distress.

### Associations between hostility, coping self-efficacy and psychological distress

A crude effect on psychological distress was found for OSA severity, sleep-related problems, hostility and coping self-efficacy (Table 5.3). The associations between hostility, coping self-efficacy and psychological distress were adjusted for sociodemographic variables (age, gender), the clinical variables (OSA severity, BMI) and sleep-related variables (night-time sleep quality, daytime sleepiness). Model 4, with hostility added, explained 59% of the total variance of psychological distress. All coping self-efficacy dimensions were strongly associated with a lower level of psychological distress. The regression models for coping self-efficacy for the ability to get support from family and friends, self-efficacy for the use of problem-focused coping and coping self-efficacy for the ability to stop unpleasant emotions and thoughts explained 63%, 67%, and 70% of the total variance of psychological distress (Model 5 A, B, C), respectively.

*Table 5.3 Hostility and coping self-efficacy on psychological distress (N=150)*

**Psychological distress (GHQ-28)**

| | Crude | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 A | Model 5 B | Model 5 C |
|---|---|---|---|---|---|---|---|---|
| | B (95%CI) | B (95%CI) | B (95%CI) | B (95%CI) | B (95%CI) | B (95%CI) | B (95%CI) | B (95%CI) |
| Age | -0.22 (-0.54; 0.12) | -0.26 (-0.59; 0.06) | -0.33 (-0.65; -0.02)* | -0.33 (-0.56; -0.11)** | -0.22 (-0.44; 0.03) | -0.19 (-0.39; 0.00) | -0.21 (-0.42; 0.00) | -0.18 (-0.37; 0.00) |
| Gender | 6.06 (-0.43; 12.55) | 6.63 (-0.09; 13.17) | 5.40 (-0.91; 11.70) | 1.85 (-2.92; 6.61) | 0.97 (-3.61; 5.55) | 0.18 (-3.91; 4.26) | 0.63 (-3.63; 4.88) | 0.46 (-3.46; 4.39) |
| Body mass index | 0.62 (0.23; 1.02)** | - | 0.91 (-0.30; 0.69) | 0.13 (-0.22; 0.49) | 0.06 (-0.29; 0.40) | -0.06 (-0.36; 0.25) | -0.01 (-0.36; 0.31) | 0.01 (-0.28; 0.30) |
| OSA severity | 0.24 (0.11; 0.36)** | - | 0.20 (0.03; 0.37)* | 0.06 (-0.07; 0.81) | 0.08 (-0.04; 0.20) | 0.12 (-0.01; 0.23) | 0.13 (-0.01; 0.24) | 0.13 (-0.03; 0.23) |
| Night-time sleep quality | 2.89 (2.32; 3.45)*** | - | - | 2.60 (2.08; 3.13)*** | 2.15 (1.59; 2.71)*** | 1.85 (1.34; 2.36)*** | 2.00 (1.48; 2.53)*** | 1.79 (1.29; 2.27)*** |
| Daytime sleepiness | 1.44 (0.91; 1.97)*** | - | - | 0.89 (0.46; 1.32)*** | 0.71 (0.29; 1.14)** | 0.68 (0.31; 1.06)*** | 0.69 (0.30; 1.09)** | 0.68 (0.33; 1.04)*** |
| Hostility | 1.91 (1.47; 2.36)*** | - | - | - | 0.79 (0.36; 1.23)*** | 0.72 (0.33; 1.12)** | 0.72 (0.31; 1.12)** | 0.67 (0.30; 1.05)*** |
| Problem-focused | -0.37 (-0.48; -0.26)*** | - | - | - | - | -0.23 (-0.31; -1.15)*** | - | - |
| Get support | -0.62 (-0.91; -0.34)*** | - | - | - | - | - | -0.39 (-0.59; -0.20)*** | - |
| Stopping emotions/thoughts | -0.49 (-0.62; -0.35)*** | - | - | - | - | - | - | -0.32 (-0.41; -0.22)*** |
| **F Change** | - | 2.99 | 6.35** | 59.88*** | 12.78*** | 33.83*** | 16.62*** | 44.59*** |
| **Adjusted R²** | - | 0.03 | 0.12 | 0.54 | 0.59 | 0.67 | 0.63 | 0.70 |

Crude: effect of each variable separately on functional status; Model 1: effect of age and gender on GHQ-28 score; Model 2: effect of age, gender, BMI and OSA severity on GHQ-28 score; Model 3: effect of age, gender, BMI, OSA severity, sleep-related problems on GHQ-28 score; Model 4: effect of age, gender, BMI, OSA severity, sleep-related problems and hostility on GHQ-28 score; Model 5 A: effect of age, gender, BMI, OSA severity, sleep-related problems, hostility and coping self-efficacy for the ability to get support from friends and family on GHQ-28 score; Model 5 B: effect of age, gender, BMI, OSA severity, sleep-related problems, hostility and coping self-efficacy for stopping unpleasant emotions and thoughts on GHQ-28 score; Model 5 C: effect of age, gender, BMI, OSA severity, sleep-related problems, hostility and coping self-efficacy for stopping unpleasant emotions and thoughts on GHQ-28 score; B: unstandardized regression coefficient; BMI: body mass index; CI – confidence interval; Gender – male gender was set as the reference; OSA – Obstructive Sleep Apnoea; GHQ-28 – General Health Questionnaire; F Change – significance of prediction improvement in model fit; Adjusted R² – explained variance adjusted for the number of predictors in the particular model; GHQ-28 – higher score indicates higher psychological distress; *p<0.05; **p<0.01; ***p<0.001.

**Coping self-efficacy as a mediator between hostility and psychological distress**

The mediation analyses showed that all three coping self-efficacy dimensions partially mediated the associations between hostility and psychological distress in OSA patients. The indirect effects of all three coping self-efficacy dimensions were significant. They accounted for 10.0% of coping self-efficacy for getting support from family and friends, 15.0% of self-efficacy for the use of problem-focused coping and 17.0% of coping self-efficacy for the ability to stop unpleasant emotions and thoughts (Table 5.4). Figure 5.1 shows the mediating effects of separate coping self-efficacy dimensions on the association between hostility and psychological distress.

*Table 5.4 Mediating effect of coping self-efficacy on the association between hostility and psychological distress*

| Coping self-efficacy | Psychological distress | | |
|---|---|---|---|
| | Sobel z-value | Direct effect | Indirect effect |
| Problem-focused coping self-efficacy | 2.60*** | 0.49*** | 15.0% |
| Get support | 2.16* | 0.53*** | 10.0% |
| Stopping emotions and thoughts | 2.85*** | 0.48*** | 17.0% |

*p<0.05; *** p<0.001.

*Figure 5.1 Mediating role of coping self-efficacy on the association between hostility and psychological distress*
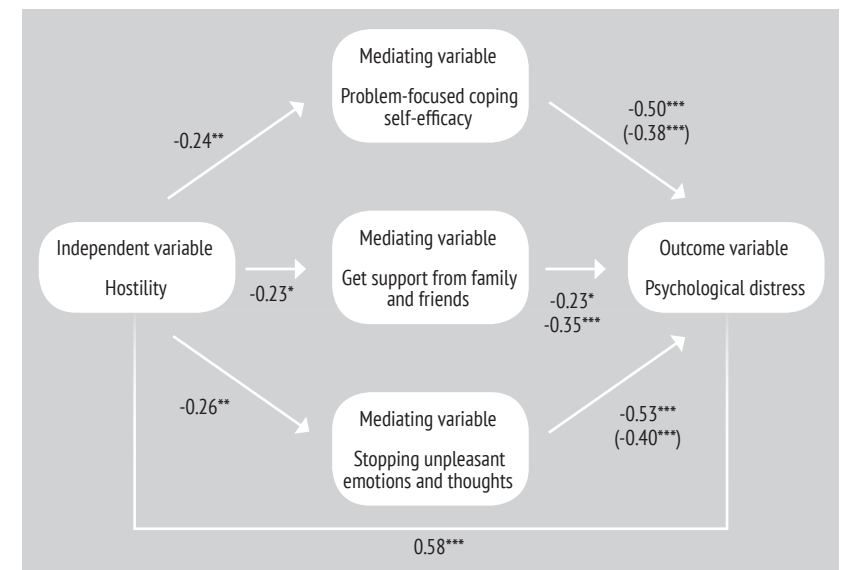


Mediations were conducted separately for each particular coping-self-efficacy dimension *p<0.05; **p<0.01; *** p<0.001.

# Discussion

The aims of this study were 1) to assess whether hostility and coping self-efficacy are associated with psychological distress in Obstructive Sleep Apnoea (OSA) patients when controlled for sociodemographic, clinical and sleep-related variables, and 2) to examine whether coping self-efficacy mediates the association between hostility and psychological distress. We found that high levels of hostility and poor coping self-efficacy were strongly associated with psychological distress in OSA patients. Compared with self-efficacy for the use of problem-focused coping and coping self-efficacy for the ability to get support from friends and family, poor coping self-efficacy for stopping unpleasant emotions and thoughts was more strongly associated with psychological distress. All coping self-efficacy dimensions mediated the association between hostility and psychological distress. Coping self-efficacy for stopping unpleasant emotions and thoughts was identified as the strongest mediator in the association between hostility and psychological distress.

We found a strong association between high levels of hostility and psychological distress in OSA patients, even after controlling for sociodemographic variables, disease severity, body-mass index and sleep-related problems. Earlier, it was shown that individuals with OSA demonstrated along with the presence of irritability, also frustration and increased engagement in conflict (Bardwell et al., 1999; Yue et al., 2003, Unal et al. 2017). Hostility and anger were also found to be higher in OSA patients when compared to healthy controls in a Korean population (Lau and Lee, 2014). Vandervoort et al. (2006) showed that individuals with a high level of hostility reported poorer mental health and used avoidant coping strategies more often than individuals with a low level of hostility (Vandervoort, 2006).

As sleep-related symptoms in OSA may increase hostility, which may consequently potentiate the negative health consequences of the disease, coping self-efficacy may represent one of the key determinants in adaptation to sleep disorders. Our analyses showed that poor coping self-efficacy was strongly associated with psychological distress in OSA patients. This results confirm previous findings on the association between coping self-efficacy and a lower level of psychological distress (Chesney et al. 2006; Benka et al., 2014) and a better quality of life (Mikula et al., 2016) in the context of chronic diseases. Self-efficacy for the ability to stop unpleasant emotions and thoughts in our sample explained the most variance of all the coping self-efficacy dimensions in the psychological distress. One possible explanation why stopping unpleasant emotions and thoughts might be the most adaptive coping self-efficacy dimension in OSA is that the patients have very little control (e.g. Cheng, 2001) over the symptoms of their disease. When patients do not have the ability to control the disease and have to learn how to live with it, this kind of coping self-efficacy can help them to reduce the stress that breathing and sleep-related symptoms bring and thus may diminish their psychological distress. In line with the strategy-situation-fit hypothesis, well-being may thus represent a function of the "goodness of fit" between emotion-regulation efforts and the contextual characteristics (Conway and Terry, 1992) of OSA. This interpretation is consistent with previous research on chronic conditions, which suggests that coping self-efficacy

for stopping unpleasant emotions and thoughts is more adaptive when little control over disease is possible (De Ridder and Schreurs 2001; Mikula et al., 2014). In line with our findings, previous research also showed that individuals scoring higher on hostility were also more likely to employ escape-avoidance coping styles while handling psychological distress (Vandervoort, 2006) and were less likely to use problem-focused coping (Sasaki and Yamasaki, 2002).

Next, we found the ability to get support from friends and family to be the least adaptive coping self-efficacy domain in the association with psychological distress, including diminishing the negative effect of hostility on psychological well-being. This finding may be explained by the results of previous research, in which sleep-related problems represented an important predictor of daytime functioning, including engagement in social activities (Dew et al., 1994). Therefore, due to sleep-related OSA symptoms, such as daytime sleepiness, the sources of social support may be less utilized and thus may be of less importance. As hostility was found to be associated with poor levels of social support (Smith, 1992), social dysfunction (Sasaki and Yamasaki, 2002) and involves an oppositional orientation toward others and negative beliefs and feelings toward others (Houston and Vavak, 1991), it may be assumed that patients with OSA may be even less motivated to participate in social activities, when potentiated by the presence of hostility. Furthermore, hostility was found to lead to difficulty in extracting the needed social support (Vandervoort, 1999).

In contrast, Bardwell et al. (2001) concluded that the more active and less passive coping strategies reported by OSA patients, the lower level of depressive symptoms they experienced. Depressive symptoms were associated with more emotional coping and with less problem-focused coping in the study by Gassara et al. (2017). Although our results differ from those of previous studies (Bardwell et al., 2001; Gassara et al., 2017), these discrepancies may be associated with the difference in OSA diagnosis criteria; e.g. patients in the study by Bardwell et al. (2001) were diagnosed using a Respiratory Disturbance Index of ≥ 15, while in our study OSA diagnosis was stated based on an Apnoea-Hypopnoea Index of ≥ 5. Another possible explanation for the inconsistency in the above studies could be caused by the use of univariate statistical procedures in the study by Gassara et al. (2017). Moreover, the discrepancies in the role of passive coping strategies could be influenced by the different assessment of psychological distress, with a focus on depression. These discrepancies may also concern the difference in theoretical perspective of the tools used to measure coping (e.g. Vaske et al., 2017).

We also found that all coping self-efficacy dimensions mediated the association between hostility and psychological distress. Thus, active as well as passive coping may be adaptive when dealing with OSA. Moreover, coping self-efficacy may serve as a trigger or perpetuator for psychological distress in OSA patients. In line with our findings, efficient coping strategies were associated with a low levels of hostility in previous research (Comijs et al., 1999). One of the first investigations on coping and hostility in people with a chronic condition found that efficient coping was associated with reacting to stress with a minimum of hostility either expressed

or suppressed (Schill et al., 1985). The transactional model of the relationship between hostility and disease suggests that personality, cognitive and behavioural factors operate in reciprocal interaction with the environment and lead to a variety of frequent physiological reactions and related pathophysiological consequences (Williams and Williams, 2001).

Mediation analyses in our study revealed that coping self-efficacy for stopping unpleasant emotions and thoughts was the most effective in diminishing the strengh of the association between hostility and psychological distress in OSA patients. In line with these findings, previous research also showed that escape-avoidance-oriented coping strategies had a significant mediating role in the relationship between hostility and self-rated health outcomes in a sample of healthy individuals (Vandervoort, 2006). This finding is not surprising, as the affective component of hostility consists of the tendency to experience several negative emotions (Barefoot et al., 1989).

Finally, we wanted to ensure that the choice of coping self-efficacy and its association with psychological distress was not simply a result of sociodemographic or clinical variables. Therefore, gender and age were employed as controlled variables, along with body mass index (BMI), AHI and sleep-related problems. We found no significant association between sociodemographic variables and psychological distress. Similarly, the association between clinical variables, measured as OSA severity and BMI, was no longer significant in complex models. Previous studies have shown that age (Ryff and Singer, 2013), overweight and obesity were found to be associated with poor levels of subjective health status, particularly in terms of physical well-being (Doll et al., 2000). Other studies, have not found any association between BMI and psychological disturbances or psychosocial functioning (Klesges et al., 1992). The missing associations between age, obesity and psychological distress may be a result of confounding by the presence of accompanying chronic illness (Doll et al., 2000).

### Strengths and limitations

Patients in our sample were diagnosed by polysomnography, which is an asset of the study. Moreover, this is the first study which examines the mechanism between hostility, coping self-efficacy and psychological distress using comprehensive measurements in a rarely studied population of OSA patients. It is plausible that a number of limitations could have influenced our findings. First, we used cross-sectional data; thus, we can not make any causal inferences. Second, self-report hostility may be prone to providing socially acceptable answers (Davidson and Hall, 1997); thus, replication with more objective measures would provide an important comparison. Finally, although emotional suppression may reduce the outward expression of emotion and possibly the subjective experience of emotion in the short term, it was found to be less effective in reducing emotion and physiological arousal over a long-term period (Gross and Thompson, 2007). Previous studies have also suggested that long-term suppression of negative thoughts may prevent habituation to emotional stimuli and as such may result in hypersensitivity to psychological

distress and symptoms (Wenzlaff and Wegner, 2000). Thus, longitudinal studies are needed to assess the influence of coping self-efficacy for the ability to stop unpleasant emotions and thoughts on psychological distress.

### Implications for future research and practice

Psychological distress in OSA patients is clearly associated with hostility and poor coping self-efficacy and requires attention in both clinical care and research. We recommend that our study should be replicated with a larger sample and a longitudinal design. Further, future research is needed to understand the causal mechanisms between hostility, coping self-efficacy and psychological distress in OSA patients. It would also be interesting to examine the actual sleep disturbances among patients scoring high and low on the Cook-Medley hostility scale in the laboratory. Hostility levels are well known to fluctuate considerably over time, and thus a longitudinal study including repeated measures is needed. Poor coping self-efficacy may represent a background factor partially underlying the adverse effect of hostility on psychological well-being.

Psychological distress was found to have the capacity for interventions (Farrand et al., 2016; and various protective efforts, including self-efficacy and effective coping strategies (Hopman et al., 2009; Trojan et al., 2012; Mikula et al., 2016). From a clinical perspective, knowing which coping strategies a patient uses and how much hostility they experience and express may be useful in OSA management. Therefore, the assessment of hostility and particular coping self-efficacy dimension may help to identify those patients who might benefit most from the direct treatment of psychological symptoms, in addition to treatment of sleep-disordered breathing itself. Our findings suggest that it is necessary to monitor hostility in OSA patients during clinical care. Understanding these associations may be beneficial for therapy, as well. A person who believes in his/her ability to produce a desired effect can conduct a more active and self-determined health-behaviour (Schwarzer and Renner, 2000). Therefore, education about the role of coping self-efficacy can be included in shorter pragmatic programs (Goudsmith et al., 2009; Wersebe et al., 2018). As disease occurs in people having premorbidly varying coping self-efficacy in general and illness-related stress in particular, personality and behavioural patterns may play a key role in determining which OSA patients will experience higher levels of psychological distress. Thus, rather than solely focusing on patients medical parameters and standard OSA treatment, patients should be encouraged to use adaptive coping strategies. When our findings are confirmed in longitudinal studies, screening for hostility and treatment focused on decreasing high levels of hostility, in addition to standard therapy of the disordered breathing, might help to handle psychological distress experienced by OSA patients. Feelings of hostility may be decreased by cognitive behavioural therapy (Seligman et al., 2005), controlled interventions and behavioural modifications (Barefoot et al., 1989).

## Conclusion

This study has led us to conclude that the presence of psychological distress in OSA patients may not be solely due to the effect of OSA itself. Rather, hostility and the choice of coping strategies may play a key role in examining which OSA patients will experience higher level of psychological distress. Thus, interventions focused on reducing hostility and enhancement of adaptive coping may help to optimize standard treatment in OSA patients and be paramount in diminishing psychological distress in OSA patients. Further longitudinal research is necessary to confirm the causality, however.

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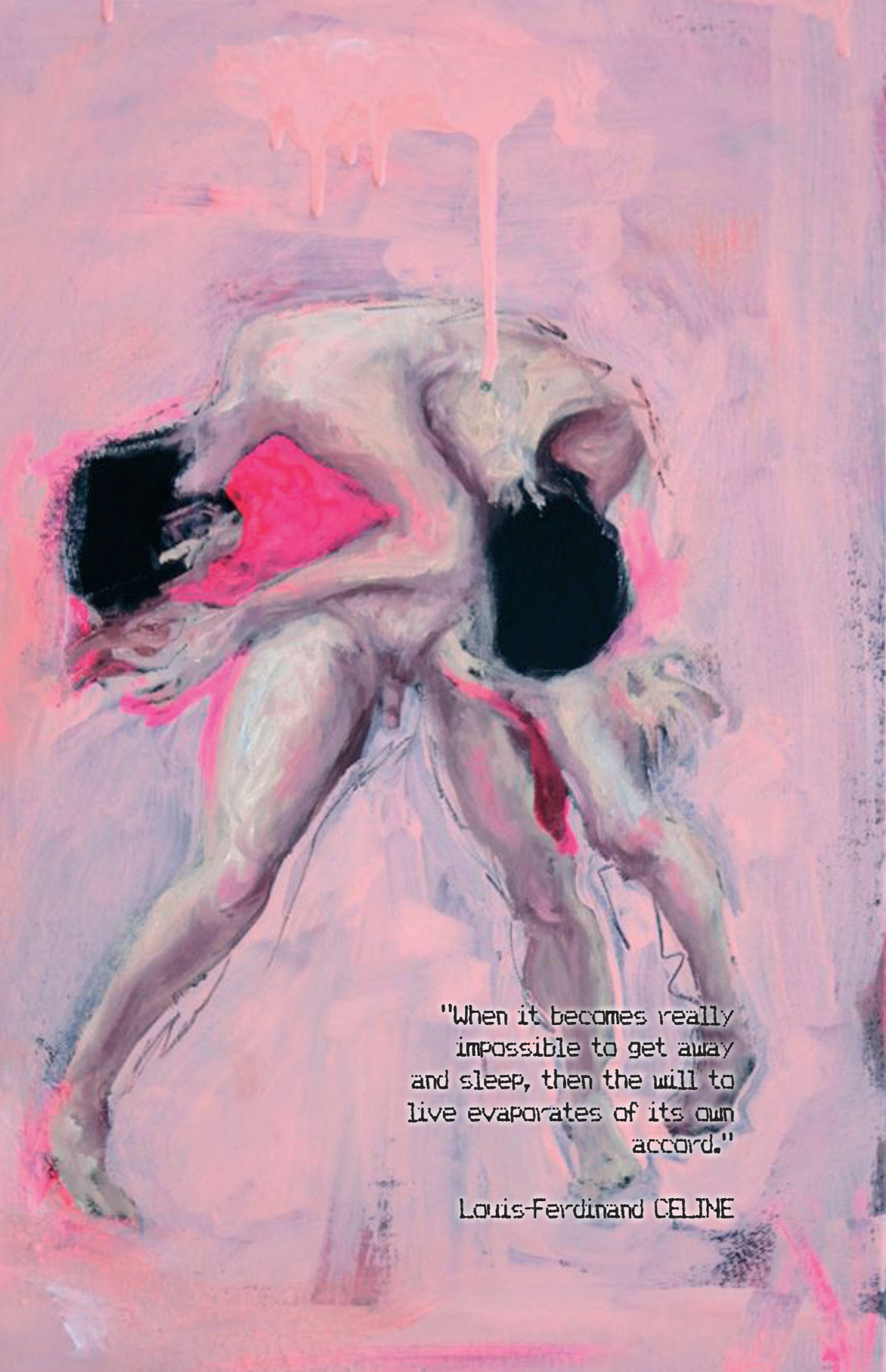
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# Suicidal ideation in patients with obstructive sleep apnoea and its relationship with disease severity, sleep-related problems and social support

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"When it becomes really impossible to get away and sleep, then the will to live evaporates of its own accord."

Louis-Ferdinand CELINE

# Abstract

## Background and aim

Recently, an increased level of Suicidal Ideation (SI) has been observed in Obstructive Sleep Apnoea (OSA) patients. Social support has been shown to have relevance in many chronic diseases and is supposed to decrease SI. However, evidence is lacking on the association between sleep-related problems and social support with SI in OSA patients. Thus, we aimed to assess the prevalence of SI and to examine the relationships OSA severity, sleep-related problems, social support and SI in OSA patients.

## Methods

We included 149 patients (68% male; mean age 48.99±9.57 years) with diagnosed OSA (Apnoea-Hypopnoea Index–AHI≥5) based on full-night polysomnography. All patients completed the General Health Questionnaire-28 subscale regarding SI, the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale, the Multidimensional Fatigue Inventory and the Multidimensional Scale of Perceived Social Support. Structural equation modelling (SEM) was used to analyze the data.

## Results

The prevalence of SI among OSA patients was 20.1%. Structural equation modelling showed that SI in OSA was strongly related to poor sleep quality and high fatigue levels. No relationship between social support and SI in OSA patients was found.

## Conclusion

SI in OSA is strongly related to poor sleep quality and high fatigue levels. Understanding the pathways among these symptoms and SI in OSA patients is important, as it may contribute to better disease management.

# Introduction

Obstructive Sleep Apnoea (OSA) is an incapacitating chronic disease caused by pharyngeal collapse during sleep (Manarino et al., 2012), which is characterized by repeated breathing pauses. OSA, along with insomnia, is one of the most common sleep disorders in adults (Subramanian et al., 2011), with an estimated prevalence of 2–10% (Leger et al., 2012).

Recently an increased level of suicidal ideation (SI) has been observed in patients treated in medical sleep centres (Krakow et al., 2011), including among OSA patients (Choi et al., 2015). Suicide is an important cause of death worldwide. Globally more than 800,000 people take their own life every year, and there are many more suicide attempts (World Health Organization, 2016). Recent approaches have defined suicide as a health behaviour, in the sense that a person makes a decision to take his/her own life, so an appreciation of the psychology of the suicidal mind is crucial to suicide prevention (O'Connor, 2017). The annual prevalence of SI in the general population according the World Mental Health Survey is around 2% (Borges et al., 2010). The cross-national lifetime prevalence of SI in the general population is 9.2% (Nock et al., 2008), while 13% of participants treated in medical sleep centres reported SI, 4.5% of whom had clinically significant SI (Krakow et al., 2011). In 2015, Choi et al. (2015) reported an SI prevalence of 20.5% in a South Korean population of OSA patients, but information about the prevalence of SI in OSA patients in other countries is lacking.

Sleep disturbances were not included in the recent suicide risk factor lists compiled by the World Health Organization (2012). Nonetheless, the potential association between sleep-related problems and suicide has been recognized. In a meta-analysis by Pigeon et al. (2012), sleep disturbances were identified as a risk factor for SI and suicidal behaviour beyond the effects of depression in various clinical and healthy population groups. Poor sleep quality was found to be associated with an increased risk of committing suicide in one decade, even when adjusted for depressive symptomatology (Bernert et al., 2014). Krakow et al. (2011) found an association between sleep-related problems and SI in patients treated in medical sleep centres, which remained significant after controlling for depression. A Korean study on OSA patients found that they suffered from insomnia and SI, and that the concepts of SI, insomnia and depression showed overlap (Choi et al., 2015).

Adequate social support may have a positive influence on SI and suicidal behaviour (Kleiman and Liu, 2013). In recent years, increasing attention has been paid to the protective effect of social support in many chronic diseases (Reblin and Uchino, 2008). Lower social support was associated with worse health status (Bucholz et al., 2014) and more depressive symptoms (Bucholz et al., 2014; Lee et al., 2016a) in men and women with acute myocardial infarction (Bucholz et al., 2014) and chronic arthritis pain (Lee et al., 2016a). However, OSA patients may experience lower levels of social support compared to other populations. Some previous studies have demonstrated for example that the partners of OSA patients were unable to engage in social activities due to poor energy levels (Luyster et al., 2016), and their overall

quality of life was adversely affected by OSA (McArdle et al., 2001; Luyster et al., 2016).

Another source of concern is that individuals with sleep problems suffering from psychological distress rarely seek formal mental health evaluation and treatment (Weissman et al., 1997; Wojnar et al., 2009). Therefore, the idea of depending solely on the available psychological and psychiatric care to detect individuals at risk of SI may be insufficient for early suicide prevention efforts, especially for people with chronic diseases such as OSA. However, in general little is known about the relationships between OSA severity, sleep-related problems, social support and SI in OSA patients. Understanding the pathways of and interrelationships between these constructs is of major importance, as better knowledge may contribute to better disease management and may be useful in enhancing our ability to predict and prevent death by suicide.

The aims of the present study were to: (a) assess the prevalence of SI, and (b) examine the relationships between OSA severity, sleep-related problems, social support and SI, in OSA patients. Based on previous findings in OSA populations, we hypothesized that OSA severity is related to poor night-time sleep quality, contributing to higher levels of fatigue and daytime sleepiness which may in turn contribute to a higher level of SI. Further, we hypothesized that OSA severity and sleep-related problems may be directly related to higher level of SI. Social support was expected to be associated with SI; i.e. poorer social support could contribute to a higher level of SI.

## Methods

### Sample and procedure

This cross-sectional study was conducted at the Department of Pneumology and Phtiseology, L. Pasteur University Hospital and the Medical Faculty of PJ Safarik University in Kosice, Slovak Republic. All patients who visited the Department for one-night polysomnography (PSG) from July 2013 to June 2016 and underwent PSG were eligible for the study. Indication for PSG was based on a general practitioner referral form. OSA was diagnosed based on an overnight sleep study. PSG was used to determine whether the diagnosis of OSA was present and to identify the severity of the disorder.

Only patients between 18 and 65 years old were included due to possible functional changes, increased vulnerability and a decline in abilities and performance related to age. The study sample consisted of patients with an Apnoea Hypopnoea Index (AHI; number of apnoeas + hypopnoeas per hour of sleep) score of 5 or more (American Academy of Sleep Medicine, 2005), who had no previous continuous positive airway pressure treatment or other OSA treatment, were Slovak-speaking and had no major comorbidities. Out of N=260 patients, N=39 refused to participate in the study (response rate 85.0%). Another N=72 patients were excluded because of major comorbidities (a coexisting major sleep disorder such as insomnia, narcolepsy, or circadian rhythm sleep disorder; major cardiovascular diseases,

primary pulmonary hypertension, chronic obstructive pulmonary disease, diabetes, Pickwick syndrome, a history of cancer in the past twelve months, neurological deficit, a major psychiatric diagnosis in the medical record such as schizophrenia, bipolar disorder or cognitive decline, and/or current usage of psychiatric medications such as sedative-hypnotics, or narcoleptics or drug abuse in the past six months) and regular shift work. Medical examinations were conducted by a pulmonologist specialized in sleep-disordered breathing. Clinical diagnoses were stated according to the International Classification of Diseases-10 codes. Screening on comorbidities was based on medical data and an initial clinical interview prior to data collection. The final sample consisted of N=149 OSA patients (68% male; mean age 48.99±9.57 years). Patients received a self-reporting questionnaire.

The study was approved by the Ethics Committee of PJ Safarik University in Kosice (approval no. 115/2011). All patients signed a written informed consent prior to study participation. Participation in the study was fully voluntary, with no incentives for participation.

### Measures

#### Sociodemographic and clinical data

Information on age, gender and marital status was obtained from patient records. The Body Mass Index (BMI; height and weight) was assessed by a physician. BMI was used to sort patients into categories: underweight (<18.50), normal (18.50-24.99), overweight (25.00-29.99) and obese (≥30.00). OSA severity was determined using PSG and was based on the Apnoea Hypopnea Index (AHI; number of apnoeas + hypopneas per hour of sleep), starting with a score of 5 or more according to the standard criteria (American Academy of Sleep Medicine, 2005). According to this, OSA severity is mild (AHI≥5≤15), moderate (AHI>15≤30) or severe (AHI>30).

#### Sleep-related problems

Sleep-related problems included night-time sleep quality, daytime sleepiness and fatigue. *Night-time sleep quality* was measured using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI consists of 19 self-reported responses to questions covering seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. The total score with a maximum of 21 was used, with higher scores reflecting poor night-time sleep quality. A cut-off score of 5 points separates good sleepers from poor ones (Buysse et al., 1989). Cronbach's alpha in our sample was 0.86.

*Daytime sleepiness* was measured using the self-reporting Epworth Sleepiness Scale (ESS), an eight-item questionnaire assessing the tendency to fall asleep in various daytime scenarios (Miletin and Hanly, 2003). The score ranges from 0 to 24, with higher scores indicating higher daytime sleepiness. An ESS total score greater than 10 indicates excessive daytime sleepiness (Miletin and Hanly, 2003). Cronbach's alpha in our sample was 0.87.

*Fatigue* was measured using the Multidimensional Fatigue Inventory (MFI-20) (Smets et al., 1995). It consists of 20 individual items measuring five dimensions of fatigue: general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue. Each dimension contains four items with a five-point response format; the total score in each dimension ranges from 4 (no fatigue) to 20 (highest possible fatigue). The values for Cronbach's alphas were: general fatigue: 0.80; physical fatigue: 0.89; reduced activity: 0.75; reduced motivation: 0.81; and mental fatigue: 0.83.

*Social support*
Social support was measured using the Multidimensional Scale of Perceived Social Support (MSPSS), a 12-item measure of subjectively-assessed social support using a seven-point Likert-type scale with responses ranging from 'very strongly disagree' (score 1) to 'very strongly agree' (score 7). The total score ranges from 12 to 84, with higher scores indicating perceived higher social support (Zimet et al., 1988). The scale, with four items for each subscale, measures support provided by a significant other, family and friends. In our sample Cronbach´s alpha was 0.90 for each of the three items, and Cronbach´s alpha for the total scale was 0.94.

*Suicidal ideation*
Suicidal ideation (SI) was assessed using the General Health Questionnaire (GHQ-28) (Goldberg and Hillier, 1979). Four items directly dealing with SI were used: "Have you thought about the possibility of killing yourself?", "Do you wish to be dead and far away from everything?", "Do you have continual thoughts about ending your life?", and "Do you have the impression that life is not worth of living?" The validated four-item SI subscale of the GHQ-28 has been previously used to assess SI (Gili-Planas et al., 2001; Watson et al., 2001). In some previous studies the threshold of SI≥1 was used to assess the presence of SI (Gili-Planas et al., 2001; Biddle et al., 2004). However, the GHQ threshold is partly determined by the prevalence of multiple diagnoses, with higher thresholds being associated with higher rates of both single and multiple diagnoses (Goldberg, et al. 1998). Thus, based on the presence of severe physical illness raising the best threshold to be adopted (Goldberg, et al. 1998), we determined the prevalence of SI with a cut off of SI≥2, in a binary manner, with the negative responses given a score of zero and the positive responses a score of one. The sum-score of the four items of SI therefore ranged from 0 to 4. SI was also used as a continuous variable (1-4) in SEM, with a range from 4 to 16. Higher scores indicated a higher level of SI. In our sample Cronbach´s alpha was 0.83.

**Statistical analyses**
The analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS 23). Structural equation modelling (SEM) was performed with Mplus 7.1 (Muthén and Muthén, 2015). Firstly, we described the background characteristics of the sample, determined the SI prevalence and calculated the mean values of OSA severity, night-time sleep quality (PSQI), fatigue (MFI), daytime sleepiness (ESS) and social support (MSPSS) for the total sample and stratified by SI yes/no (SI≥2). Chi-square analyses were conducted on dichotomous variables. T-tests were conducted to assess the differences between OSA patients with SI (yes/no). Secondly, we used correlation analysis to assess the association between social support and SI when controlled for age, gender and marital status. Thirdly we used SEM to examine the relationships between OSA severity, night-time sleep quality, fatigue, daytime sleepiness, social support and SI in OSA patients. The used model fit criteria were: chi-square test, RMSEA (90% confidence interval, CI), Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI). Swain's corrections of the model fit criteria were used because the sample size was small (Herzog and Boomsma, 2009). A p-value of <0.05 was considered statistically significant.

## Results
### Sample characteristics
The majority of the patients were male (68.0%), had secondary education (57.4%), had a partner (77.6%), 44.9% were obese, and 50.0% had severe OSA. Patients reporting SI scored significantly higher on sleep-related problems compared to non-SI patients. We observed no significant differences in the main clinical and sociodemographic data, OSA severity and social support between OSA patients with and without SI. Based on the increased level of the threshold due to the presence of physical disorder, the prevalence of SI among OSA patients was stated at 20.1% (Table 6.1).

*Table 6.1 Baseline characteristics of the OSA patients (AHI ≥ 5), total sample and stratified by SI yes/no (SI≥2)*

| | OSA (N=149) | OSA SI (N=30) | OSA non-SI (N=119) | p-value |
|---|---|---|---|---|
| Age in years, mean, sd | 48.99±9.57 | 46.47±10.76 | 49.50±9.34 | 0.15 |
| Gender, male, N (%) | 101 (68.0%) | 18 (60.0%) | 83 (69.7%) | 0.22 |
| Education level, mean, sd | 4.99±1.74 | 5.13±1.91 | 4.97±1.70 | 0.66 |
| Education level, N (%) | | | | 0.07 |
|   Elementary | 8 (5.3%) | 3 (10%) | 5 (4.2%) | |
|   Secondary school | 86 (57.4%) | 14 (46.6%) | 72 (60.0%) | |
|   University | 55 (36.3%) | 13 (43.3%) | 42 (34.7%) | |
| Employed, N (%) | 127 (84.7%) | 26 (86.6%) | 101 (84.8%) | 0.53 |
| Marital status, single, N (%) | 35 (23.4%) | 3 (10.0%) | 32 (26.8%) | 0.52 |
| Body Mass Index, mean, sd | 30.24±7.66 | 32.15±7.70 | 29.80±7.61 | 0.13 |
| Body Mass Index, N (%) | | | | 0.28 |
|   Underweight (<18.5) | 9 (6.0%) | 0 (0%) | 9 (7.5%) | |
|   Normal (18.5-24.99) | 41 (27.5%) | 8 (26.6%) | 33 (27.7%) | |
|   Overweight (25.0-29.99) | 32 (21.4%) | 5 (16.6%) | 27 (22.6%) | |
|   Obese (≥30) | 67 (44.9%) | 17 (56.6%) | 50 (42.0%) | |
| Apnoea-hypopnoea index, mean, sd | 35.64±22.30 | 40.37±18.16 | 34.66±23.12 | 0.21 |
| OSA severity, N (%) | | | | 0.41 |
|   Mild (AHI≥5≤15) | 22 (15.0%) | 0 (0%) | 22 (18.5%) | |
|   Moderate (AHI>15≤30) | 52 (35.0%) | 10 (33.3%) | 41 (33.11%) | |
|   Severe (AHI>30) | 74 (50.0%) | 20 (66.7%) | 55 (48.3%) | |
| Night-time sleep quality, mean, sd (PSQI; 0-21) | 9.65±4.14 | 12.90±4.18 | 8.88±3.70 | <0.001*** |
| Daytime sleepiness, mean, sd (ESS; 0-24) | 10.97±5.30 | 12.76±5.75 | 10.51±5.10 | 0.04* |
| Fatigue, mean, sd (MFI; 4-20) | | | | |
|   General fatigue | 14.01±4.71 | 17.76±2.47 | 13.02±4.56 | 0.001** |
|   Physical fatigue | 13.52±4.77 | 17.6±3.39 | 12.45±4.62 | <0.001*** |
|   Reduced activity | 11.91±4.94 | 16.43±3.29 | 10.77±4.63 | <0.001*** |
|   Reduced motivation | 9.13±3.63 | 12.26±3.52 | 8.34±3.28 | <0.001*** |
|   Mental fatigue | 11.97±4.82 | 16.93±2.79 | 10.71±4.39 | <0.001*** |
| Social support, mean, sd (MSPSS; 12-84) | 63.11±13.48 | 58.86±14.68 | 64.18±12.99 | 0.05 |
| SI, mean, sd (GHQ; 4-16) | 6.67±3.30 | 12.03±2.14 | 5.31±1.75 | <0.001*** |
| Prevalence of SI, N (%) (GHQ-28 SI≥1) | | 54 (36.2 %) | - | |
| Prevalence of SI, N (%) (GHQ-28 SI≥2) | | 30 (20.1%) | - | |
| Prevalence of SI, N (%) (GHQ-28 SI≥3) | | 19 (12.8%) | - | |
| Prevalence of SI, N (%) (GHQ-28 SI=4) | | 13 (8.8%) | - | |

OSA – Obstructive Sleep Apnoea; SI – Suicidal Ideation; PSQI – Pittsburgh Sleep Quality Index; ESS – Epworth Sleepiness Scale; MFI – Multidimensional Fatigue Inventory; MSPSS – Multidimensional Scale of Perceived Social support; GHQ-28 – General Health Questionnaire; *p<0.05; **p<0.01; ***p<0.001. Missing values: OSA severity: (0.7%); age, PSQI, MFI, ESS (1.0%); MSPSS: (2.0%).

## Relationships between OSA severity, night-time sleep quality, daytime sleepiness, fatigue, social support and SI

Daytime sleepiness and social support were not significantly related to night-time sleep quality and SI in the hypothesized model (Figure S6.1, Supplement 6.1). As our hypothesis was not confirmed, we tested an alternative, modified model without sleepiness and social support (Figure 6.1, Table 6.2). The model fit criteria of the modified model were chi-square test = 29.909 (p value 0.04) and RMSEA = 0.066 (90%CI = 0.016, 0.107). The CFI was 0.984; TLI was 0.975. Swain's correction factor was 0.972. Swain's corrected chi-square statistic was 29.063 (p-value: 0.05). Swain's corrected RMSEA was 0.064 (90%CI = 0.007, 0.106), Swain's corrected TLI was 0.971 and Swain's corrected CFI was 0.991.

Sleep quality (β = 0.28, p<0.001) and fatigue (β = 0.49; p<0.001) were strongly related to SI. Sleep quality mediated the effect of OSA severity on SI (β = 0.06, p<0.05), OSA severity was associated with poor sleep quality (β = 0.21; p<0.01) while fatigue was associated with poor sleep quality (β = 0.60; p<0.001). Social support was not significantly associated with SI using complex modelling, and adjustment for sociodemographic variables as potential confounders (age, gender and marital status) did not change the association between social support and SI either.

*Figure 6.1 Modified model of the relationships among OSA severity, night-time sleep quality, fatigue and SI: beta (standard error)*
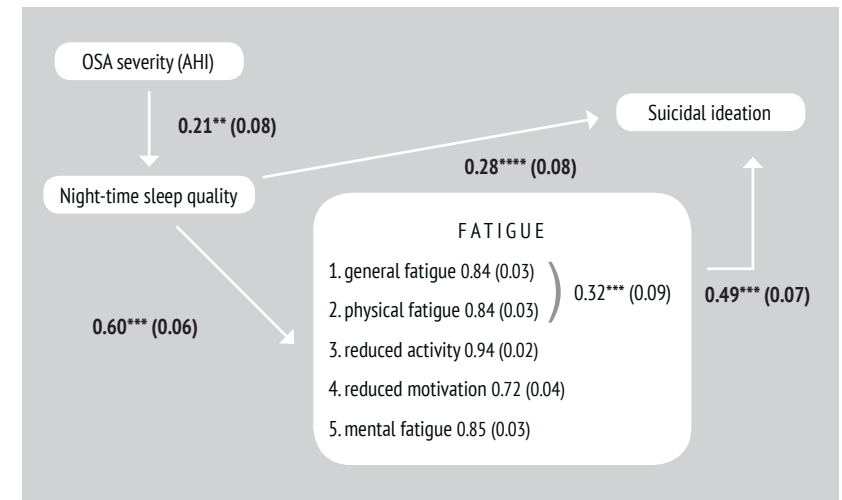


AHI – Apnoea-Hypopnoea Index; OSA – Obstructive Sleep Apnoea; **p<0.01; ***p<0.001.

*Table 6.2 Relationships between OSA severity, night-time sleep quality, fatigue and SI*

| | Standardized coefficients (S.E.) |
|---|---|
| **Direct paths** | |
| OSA severity – Night-time sleep quality | 0.21** (0.08) |
| Night-time sleep quality – Fatigue | 0.60*** (0.06) |
| Night-time sleep quality – Suicidal ideation | 0.28*** (0.08) |
| Fatigue – Suicidal ideation | 0.49*** (0.07) |
| **Indirect paths** | |
| OSA severity – Night-time sleep quality – Suicidal ideation | 0.06* (0.03) |
| OSA severity – Night-time sleep quality – Fatigue – Suicidal ideation | 0.06* (0.03) |

OSA – Obstructive Sleep Apnoea; S.E. – Standard Error; *p<0.05; **p<0.01; ***p<0.001.

## Discussion

This study shows a 20.1% prevalence of Suicidal ideation (SI) in people with Obstructive sleep apnoea (OSA). Patients reporting SI scored higher on sleep-related problems compared to non-SI patients. Poor night-time sleep quality and fatigue were directly related to SI. Night-time sleep quality mediated the effect of OSA severity on SI. We found no relationship between social support and SI in OSA patients.

Based on the presence of OSA, which represents severe physical illness consistently raising the best threshold to be adopted (Goldberg et al., 1998), we can assume that 20.1% of OSA patients in our study reported SI. This finding is in line with Choi et al. (2015), who found an SI prevalence of 20.5% in a Korean population of OSA patients. This SI prevalence of 20.1% among OSA patients is alarming, especially when compared to the cross-national lifetime prevalence of SI (9.2%) in the general population (Borges et al., 2010) and the annual prevalence (2.0% to 2.1%) of SI in the general population (Borges et al., 2010).

OSA severity was not directly related to SI in our study. Choi et al. (2015) also found no correlation between OSA severity and SI in OSA patients. However, night-time sleep quality mediated the effect of OSA severity on SI in our study. Although one-night polysomnography (PSG) is sufficient for diagnosis of OSA (Scholle et al., 2003; Gouveris et al., 2010), significant variability in the apnoea-hypopnoea indexes (AHI) taken from two nights was revealed in people with OSA (Gouveris et al., 2010). Thus, the missing direct relationship between OSA severity and SI may be related, according to Choi et al. (2015), to individuals' adaptation to the combination of the hospital environment and the recording equipment. However, some previous studies suggest that AHI based on numbers of all apnoeas and hypopnoeas, but not severity of apnoeic events, may not be the most appropriate measure of OSA severity when considering the clinical impact of OSA on subjective quality of life assessment (Weaver et al., 2005; Lee at al., 2016b).

Our findings demonstrate that disturbed night-time sleep quality was directly related to SI. This finding aligns with Bernert et al. (2014), who showed that poor night-time sleep quality in an older population was associated with increased risk of committing suicide, even after adjustment for depressive symptomatology. Therefore, SI may not only represent a symptom of major depression but has also been found to be driven by neurobiological processes (Fried and Nesse, 2015; Du et al., 2017). Another recent meta-analysis revealed that psychiatric patients with sleep disturbances, including sleep-related breathing disorders, are about twice as likely to report suicidal behaviours compared to patients without sleep related-problems (Malik et al., 2014). Similarly, Choi et al. (2015) found that higher insomnia levels correlated with higher level of SI in OSA patients.

We found that fatigue was most strongly related to SI. Patients reporting SI scored significantly higher on daytime sleepiness, but the association was weak and no relationship between daytime sleepiness and sleep quality or SI was observed using complex modelling. Within a medical framework, excessive daytime sleepiness and fatigue are generally considered a result of sleep deprivation or poor sleep quality (Nicassio et al., 2002; Fava, 2004). However, according to Chervin (2000), some OSA patients report fatigue more often than daytime sleepiness, and therefore treatment of fatigue complaints in the absence of clear daytime sleepiness warrants more attention in OSA treatment. Nevertheless, the possibility that daytime sleepiness in OSA patients may simply be masked by the presence of psychological distress associated with a chronic state of hypervigilance (Krakow et al., 2015) should also be considered.

Unexpectedly, the relationship between social support and SI was not significant. Some previous analyses have revealed that social support had a greater impact on well-being (Antonucci and Akiyama, 1987; Walen and Lachman, 2000) and health (Walen and Lachman, 2000) in female compared with male populations. However, we found no significant impact of gender on the association between social support and SI when controlled for sociodemographic variables.

Given the evidence that sleep disturbances may represent an important predictor of daytime functioning, including engagement in social activities (Dew et al., 1994), it may also be hypothesized that in the case of extreme fatigue or daytime sleepiness, the sources of social support may not be adequately utilized and thus may be of less importance. On the other hand, it is also plausible that the reverse pathway is true; i.e. sleep disturbances may lead to a more negative perception of the social environment (Troxel et al., 2010). Furthermore, social interactions may represent stressful situations for patients with OSA; e.g. OSA patients subjectively felt a lack of trust from co-workers which caused them subsequent embarrassment (Reishtein et al., 2006). In line with these assumptions, OSA symptoms were also found to be associated with reduced social participation (Liu et al., 2016). Nevertheless, Choi et al. (2015) identified significant correlation between social support and SI in OSA patients with comorbid insomnia. In line with their findings, most subjects in our study had a partner, were employed and had relatively high education. However, the patients in our study were observed to have higher mean scores for social support (63.11±13.48) compared to the mean score of 44.38±7.81 found by Choi et al. (2015) using the Multidimensional Scale of Perceived Social

Support. Another possible explanation may be that discrepancies in the results were caused by the different statistical methods used.

**Strengths and limitations**

To our knowledge, this is one of the first studies examining OSA severity, sleep-related problems, social support and SI in a rarely studied population of OSA patients using structural equation modelling (SEM). Another strength is that the patients in our sample were diagnosed by means of polysomnography, which is considered the criterion standard for diagnosing OSA and determining the severity of the disease. However, in interpreting our data one has to consider certain limitations. Firstly, the diagnosis of OSA was stated based on a single sleepover. Secondly, no formal psychiatric diagnosis of SI was established, but on the other hand the GHQ-28 items are frequently used to assess the presence of SI in various populations (Hamilton and Schweitzer 2000; Gili-Planas et al., 2001; Watson et al., 2001; Romeo et al., 2013; Kawabe et al., 2016). Furthermore, it should be noted that the four-item GHQ-28 SI subscale has shown good concurrent validity with Beck's Suicide Intent Scale (Watson et al., 2001). Different cut-off values of the GHQ-28 SI subscale were used in some previous studies (Gili-Planas et al., 2001; Biddle et al., 2004). In our study we set the cut-off value of SI≥2, considering this threshold to be a good representation of the clinical picture (Goldberg, et al. 1998). Another limitation to be mentioned is gender bias. In our sample 68% of the OSA patients were men; thus, our results may be less generalizable to the female population. However, the number of participants in our study is consistent with the man-to-woman ratio in OSA (3:1). Finally, the cross-sectional nature of this study does not allow firm conclusions about causality in the relationships between the variables. Nevertheless, it has been argued that SEM methods may offer the potential for tentative causal effects to be drawn when used with specified and controlled designs (Bullock et al., 1994).

**Implications for practice and future research**

This study shows that disturbed night-time sleep quality and fatigue are directly related to SI. Our findings, if confirmed in longitudinal studies, may highlight the necessity of monitoring SI in OSA patients during clinical care. Intervention studies may be helpful in determining whether the continuous positive airway pressure (CPAP) treatment is effective in reducing the level of SI via reduction of fatigue, although the results of previous research are less encouraging, indicating that OSA patients suffering from psychological distress have poor compliance with CPAP treatment (Kjelsberg et al. 2005; Hussain et al., 2014), which means that the role of compliance bias should additionally be considered. Next, in research and clinical practice, symptoms common to OSA and depressive symptomatology such as daytime sleepiness and fatigue represent obstacles in determining the presence, causality and severity of one condition in the presence of the other (Harris et al., 2009). As such, severe fatigue can contribute to longer and more severe depression, or

vice versa, fatigue may be aggravated by depressive symptomatology (Carney et al., 2014), and therefore the presence of reverse causality should be examined in OSA patients. However, the latter pattern may be more applicable to the general population than to OSA patients, as previous longitudinal studies defined OSA and its symptoms as risk factors for psychological distress. In particular, sleep fragmentation was identified as a primary cause of daytime sleepiness and fatigue in OSA patients, which is assumed to result in depressive symptomatology (Schröder and O'Hara, 2005).

Due to a lack of general consensus regarding the CPAP treatment effects on self-reported health outcomes such as functional status or quality of life in people with OSA (e.g. Weaver, 2013), current research and clinical practice should focus not just on treating OSA, but also on ensuring that the symptoms such as poor night-time sleep quality, fatigue or daytime sleepiness as well as depression and anxiety are managed. Based on the strong relationship between poor sleep quality, fatigue and SI, clinicians should consider investigating SI in people with sleep-related disorders. Furthermore, SI may suddenly lead to suicidal behaviour (Simon, 2014; Du et al., 2017), while across all countries, 60% of transitions from ideation to plan and attempt occur within the first year after ideation onset (Nock et al., 2008). This may be dangerous, especially for people with undiagnosed and untreated OSA. SI may be largely preventable (Stanley and Brown, 2012; Simon, 2014) through early detection. However, sleep disorders including OSA are very rarely assessed on a regular basis in patients suffering from psychological distress. This is of particular importance, as adjunct treatment for symptoms of depression such as sedative-hypnotics may exacerbate OSA (Pagel and Parnes, 2001). Another source of concern is that OSA patients with depressive symptomatology and/or fatigue may suffer from reduced activity and consequently may have poor motivation to visit hospital, get a diagnosis and receive appropriate OSA treatment. Thus, it may be beneficial to detect undiagnosed OSA in psychological and psychiatric care with simple and economical screening tools. Disturbed night-time sleep quality is largely modifiable through medication or behavioural interventions. The education of people with OSA on basic sleep hygiene may improve the quality of sleep and decrease fatigue. With a larger sample and a longitudinal design, the relationships should be further unveiled.

## Conclusion

The prevalence of SI in OSA patients was found to be 20.1%. Poor night-time sleep quality and fatigue were strongly related to SI. Social support was not significantly related to SI. Our findings emphasize the necessity of monitoring SI in OSA patients during clinical care. Longitudinal research is needed as a source of better understanding of the pathways between OSA severity, sleep-related problems social support and SI in OSA patients, as this may contribute to better disease management.

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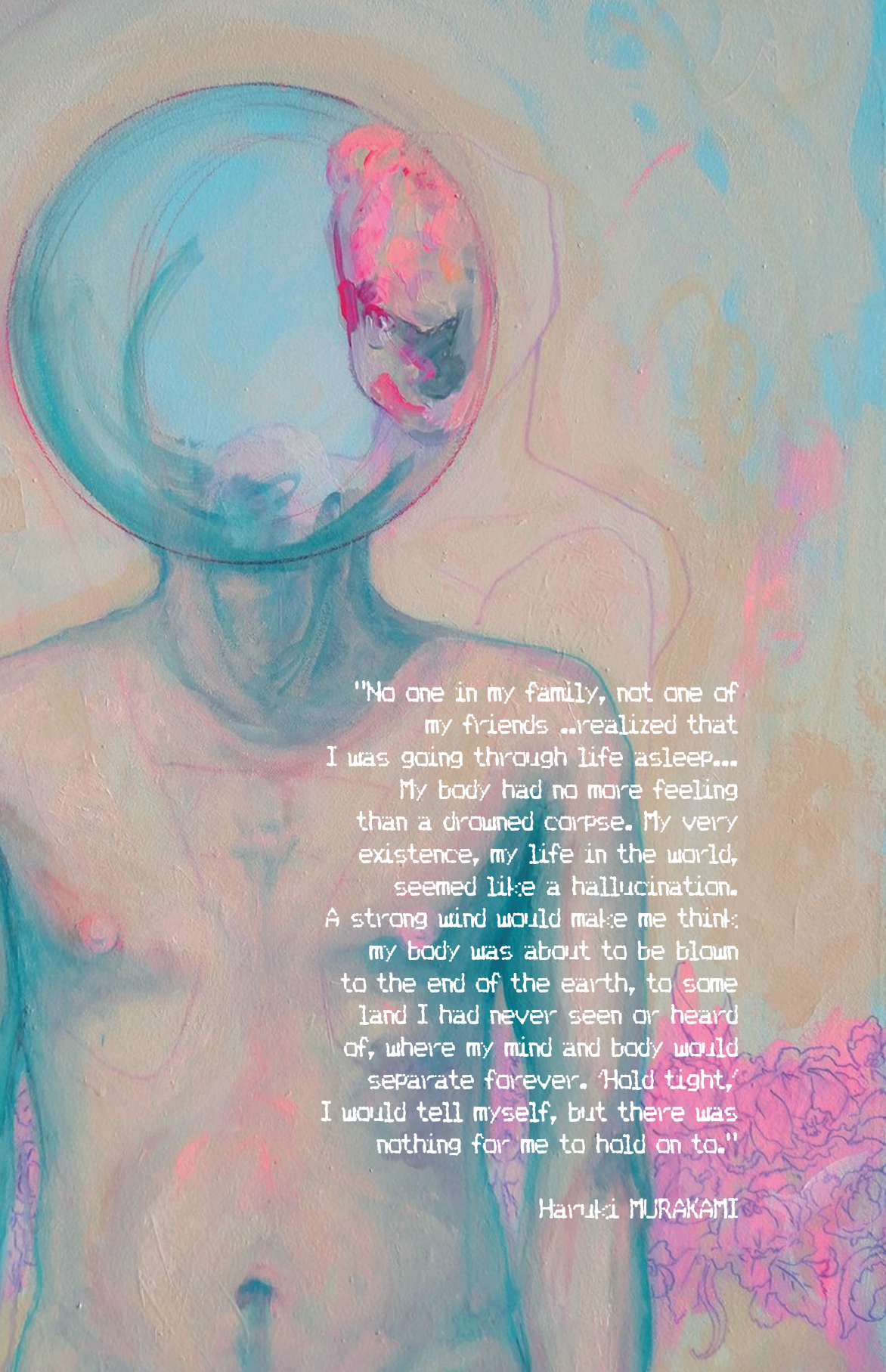
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# Social support, mastery, sleep-related problems and their association with functional status in untreated obstructive sleep apnoea patients

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"No one in my family, not one of
my friends ...realized that
I was going through life asleep...
My body had no more feeling
than a drowned corpse. My very
existence, my life in the world,
seemed like a hallucination.
A strong wind would make me think
my body was about to be blown
to the end of the earth, to some
land I had never seen or heard
of, where my mind and body would
separate forever. 'Hold tight,'
I would tell myself, but there was
nothing for me to hold on to."

Haruki MURAKAMI

## Abstract

### Background and aim

Social support and mastery are important aspects in the treatment of chronic diseases, however their role in connection with Obstructive Sleep Apnoea (OSA) remains unclear. The purpose of this study was to examine the associations between social support, mastery, sleep-related problems and functional status in untreated patients with OSA and to assess the mediating role of social support and mastery in the association between sleep-related problems and functional status in patients with OSA.

### Methods

All patients completed the Multidimensional Scale of Perceived Social Support, the Pearlin Mastery Scale, the Pittsburgh Sleep Quality Index, the Epworth Sleepiness Scale and the Functional Outcomes of Sleep Questionnaire. Multiple linear regression and mediation analyses were used to analyse the data.

### Results

Participants were 150 newly diagnosed OSA patients (Apnoea-Hypopnoea Index–AHI≥5; 68% male; mean age 48.9±9.5 years). Compared with social support, mastery was more strongly associated with functional status. Moreover, mastery mediated the association between sleep-related problems and functional status. The direct effects of sleep-related problems on functional status varied between 76.7% and 82.3%, whereas the indirect effects via mastery varied between 17.7% and 23.3%.

### Conclusions

Supporting OSA patients' sense of mastery over one's life and circumstances may significantly contribute to better disease management.

## Introduction

Obstructive Sleep Apnoea (OSA) is an incapacitating chronic disease caused by pharyngeal collapse during sleep (Manarino et al., 2012). OSA, along with insomnia, is considered to be one of the most common sleep disorders in adults, with an estimated prevalence of 2–10% (Leger et al., 2012), and is related to higher all-cause mortality (Marshall et al., 2008). OSA has been shown to be associated with night-time sleep disturbance (Krakow et al., 2015; Tippin et al., 2016) and daytime sleepiness (Antic et al., 2011). These disabling symptoms pose multiple challenges for functional status in patients with OSA (Weaver et al., 2007), with a larger effect in females (Chervin, 2000; Quintana-Gallego et al., 2004; Silva et al., 2016; Boccabella and Malouf, 2017). Recent studies have also emphasized the importance of studying patients' functional status in sleep medicine research, because of its ability to provide insights which may go beyond the pathophysiology of commonly investigated OSA-related symptoms (Boccabella and Malouf, 2017).

Despite the acceptance of continuous positive airway pressure (CPAP) as a standard OSA treatment, there is a lack of consensus regarding the CPAP treatment effect on functional status in patients with OSA. Several studies have concluded that patients with OSA, even with a good CPAP treatment adherence, do not achieve normal functional status (Weaver et al., 2007; Reishtein et al., 2010; Weaver, 2013; Tippin et al., 2016) when compared to the general population. This suggests that other key factors may play a role (Reishtein et al., 2010). Moreover, personalization of the OSA treatment (Hesselbacher et al., 2014), which includes overall evaluation of functional status and the psychosocial aspects of disease, becomes more important in current clinical practice (Boccabella and Malouf, 2017).

Social support may be one of the essential, though under-investigated, protective factors associated with healthier sleep and better functional status in people with OSA (Günbey and Karabulut, 2014). There are several plausible pathways which may link social support with sleep, including protecting against social isolation, attenuating stress responses, encouraging healthy sleep behaviours, and entraining circadian rhythms (Troxel et al., 2010). Patients with OSA may experience lower levels of social support compared to other populations with chronic diseases. A study by Glenn et al. (2015) revealed an association between a low level of social support and the presence of sleep disordered breathing symptoms. Poor social support was also found to be independently associated with short sleep duration when controlled for sociodemographic variables (Glenn et al., 2015). Moreover, partners of patients with OSA also described their relationship as adversely affected by their partners' OSA symptomatology (Luyster et al., 2016). Lack of social support has a significant impact on health-related behaviour and risk of illness (Reblin and Uchino, 2008; Alemi et al., 2003). Moreover, lack of social support was associated with poorer self-rated health in patients with acute myocardial infarction (Bucholz et al., 2014) chronic arthritis pain (Lee et al., 2016), multiple sclerosis (Krokavcova et al., 2008a) and depression (Liu et al., 2016). Social support also had a positive influence on sleep in people with insomnia (Troxel et al., 2010). Although it has been posited that social support may be a key indicator of how patients with

OSA manage their disease (Günbey and Karabulut, 2014), to date only one study (Choi et al., 2015) has been performed regarding social support in the association with health outcomes in patients with OSA. Social support was also found to have a positive effect on CPAP treatment adherence (Luyster et al., 2016). Insufficient emotional (e.g., encouragement) and instrumental (e.g. help with putting on mask, verbal reminders) support from partners of OSA patients was identified as a barrier for adherence with CPAP treatment (Luyster et al., 2016).

As patients with OSA have very little control over the symptoms of their disease and have to learn how to live with it, mastery may help them to reduce the stress that breathing, and sleep-related symptoms bring about, and may thus improve their functional status (De Ridder and Schreurs, 2001). According to Pearlin and Schooler (1978), mastery is defined as a general sense of control over one's life and circumstances. In line with this, a diminished sense of mastery was associated with a decrease in overall functional ability (Kempen et al., 2006), physical, mental and social functioning (Krokavcova et al., 2008b; Sloan et al., 2009), and with increased mortality rates (Surtees et al., 2006) in patients with various chronic conditions or the general population (Tang, 2009). In older people a greater sense of mastery was found to be associated with seeking treatment at an early stage of disease and more efficient use of healthcare services (Menec and Chipperfield, 1997). In OSA patients with comorbid insomnia, the positive associations between mastery and both physical and mental quality of life remained significant even after adjustment for age, obesity, chronic diseases, erectile dysfunction, sleepiness, mood and financial strain (Lang et al., 2016). It has also been suggested that the relationship between social support and mastery may be reciprocal, and that higher levels of mastery may help to facilitate needed social support, while greater perceived social support may lead to greater feeling of mastery over one's life and circumstances (Green and Rodgers, 2001).

Sleep-related problems are associated with functional status in patients with chronic conditions (Kim et al., 2015), including OSA (Boccabella and Malouf, 2017). Previous studies have shown that sleep disruption (Mermigkis et al., 2009) poor sleep quality and daytime sleepiness (Lau et al., 2013) were associated with impaired functional status in patients with idiopathic pulmonary fibrosis (Mermigkis et al., 2009) and OSA (Lau et al., 2013). Research and clinical practice should therefore focus not only on treating OSA, but also on ensuring that all OSA-related symptoms, including sleep related problems, are managed adequately. To achieve this, we first need to understand how these symptoms and constructs relate to functioning in untreated patients with OSA.

Patients with OSA are known to have a high level of sleep-related problems; in contrast, the role of social support and mastery in the association between poor sleep quality, daytime sleepiness and functional status is less clear. Therefore, the purpose of this study was to examine the associations between social support, mastery, sleep-related problems and functional status in untreated patients with OSA, and to assess the mediating role of social support and mastery in the association between sleep-related problems and functional status in patients with OSA.

## Methods

### Sample and procedure

This cross-sectional study was conducted at the Department of the Department of Pneumology and Phtiseology, L. Pasteur University Hospital and the Medical Faculty of PJ Safarik University in Kosice, Slovak Republic. All patients who visited the Department for one-night polysomnography (PSG) between July 2013 and June 2016 and underwent PSG were eligible for the study. Indication for PSG was based on a general practitioner referral form. OSA was diagnosed based on an overnight sleep examination. Only patients with OSA between 18 and 65 years of age were included due to possible functional changes, increased vulnerability and decline in abilities and performance related to age. The study sample comprised patients with an Apnoea Hypopnoea Index (AHI; number of apnoeas+ hypopnoeas per hour of sleep) score of 5 or more (American Academy of Sleep Medicine, 2005) who had no previous continuous positive airway pressure (CPAP) therapy or other OSA treatment, were Slovak-speaking and had no major comorbidities. Out of 263 eligible patients, 41 patients who underwent PSG refused to participate in the study, yielding a total response of 84.0%. Another 72 were excluded because of major comorbidities. The reasons for exclusion were major comorbidities related to sleep (co-existing sleep disorder such as insomnia, narcolepsy, or circadian rhythm sleep disorder); major cardiovascular diseases (e.g. myocardial infarction, angina pectoris; primary pulmonary hypertension); pulmonary conditions (e.g. chronic obstructive pulmonary disease; Pickwick syndrome); and a history of cancer in the past twelve months. Neurological and psychological comorbidities included neurological condition (e.g. stroke, epilepsy); major psychiatric diagnosis (e.g. psychotic disorders, major depression) in the medical record, and/or current usage of psychiatric medications which may affect cognitive functions (e.g. benzodiazepine, antipsychotics or antidepressants); drug abuse in the past six months, and regular shift work in the past six months. Due to assessment of health outcomes related to sexual functioning, we excluded patients with diabetes and those using hypotensive medication, which may affect sexual functioning (following Hoekema et al., 2007). Screening for comorbidities was based on medical data and an initial clinical interview prior to data collection. The clinical diagnoses were established according to the standard International Classification of Diseases-10 revision Codes. Medical examinations of patients were conducted by a pulmonologist specialized in sleep-disordered breathing. Patients with non-respiratory sleep-related complaints (e.g. narcolepsy, insomnia) were routinely referred to another group of clinical specialists. The invitation letter, the informed consent and the questionnaires were sent to participants by postal mail three weeks before the medical examination. One week before the medical examination, patients were reminded about the questionnaires by phone call. Patients filled in self-report questionnaires at home.

To maintain ethical principles with regard to the participants, we explained the purpose of the study and guaranteed confidentiality. We also explained that the collected data would only be used for the purposes of this research. Each patient

completed and signed an informed consent form prior to their participation in the study, which was fully voluntary and included no incentives for participation. The study was approved by the Ethics Committee of PJ Safarik University in Kosice (approval no. 115/2011).

## Measures
### Functional status
Functional status was assessed using the Functional Outcomes of Sleep Questionnaire (FOSQ). (Weaver et al., 1997). The FOSQ is a 30-item self-report, disease-specific measure designed to assess the impact of sleep disorders or excessive daytime sleepiness on multiple activities of daily living. The FOSQ has five sub-scales: activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcomes. Responses are averaged (excluding missing responses) to create a subscale score of 1 to 4, and then subscale scores are summed for the total score (5-20), with higher scores indicating less effect of sleepiness on daily life (Billings et al., 2014). In our sample, Cronbach's alpha was 0.90 for the total scale, 0.90 for the activity level, 0.84 for vigilance, 0.95 for intimacy and sexual relationships, 0.90 for the general productivity subscale and 0.82 for the social outcomes subscale.

### Social support
The Multidimensional Scale of Perceived Social Support (MSPSS) is a 12-item self-report measure of social support (Zimet et al., 1988). It uses a seven-point Likert-type scale, with scores ranging from 'very strongly disagree' (1) to 'very strongly agree' (7), so the total score ranges from 12 to 84, with higher scores indicating greater social support (Zimet et al., 1988). The MSPSS has three subscales: significant others, family and friends. In our sample, Cronbach's alpha was 0.90 for all three separate subscales. Cronbach's alpha of the total scale was 0.94.

### Mastery
Mastery was measured using the Pearlin Mastery Scale (PMS) (Perlin and Schooler, 1978). The PMS measures an individual's level of mastery, a psychological resource that has been defined as "the extent to which one regards one's life-chances as being under one's own control in contrast to being fatalistically ruled" (Perlin and Schooler, 1978). The scale includes 7 items (five negatively-worded items and two positively-worded items), e.g. "You have little control over the things that happen to you", and "What happens to you in the future mostly depends upon you". The negatively-worded items require reverse coding prior to scoring, resulting in a score range of 7 to 35, with higher scores indicating higher levels of mastery (Perlin and Schooler, 1978). Cronbach's alpha of the total scale was 0.85.

### Sleep-related problems
Sleep-related problems concerned night-time sleep quality and daytime sleepiness. *Night-time sleep quality* was measured using the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI is a self-rated questionnaire to assess sleep quality and disturbances over a one-month time interval. The PSQI consists of 19 self-report questions which cover seven domains: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction. The score ranges from 0 to 21, with higher scores reflecting poor night-time sleep quality. A cut-off score of 5 separates good from poor sleepers (Buysse et al., 1989). Cronbach's alpha in our sample was 0.85.

*Daytime sleepiness* was measured using the self-report Epworth Sleepiness Scale (ESS), an eight-item questionnaire assessing the tendency to fall asleep in various daytime scenarios (Miletin and Hanly, 2003). The score ranges from 0 to 24, with higher scores indicating greater daytime sleepiness. An ESS total score greater than 10 indicates excessive daytime sleepiness (Miletin and Hanly, 2003). Cronbach's alpha in our sample was 0.86.

### Sociodemographic and clinical data
Information on age, gender and marital status was obtained from patient records. The Body Mass Index (BMI; height and weight) was assessed by a physician. BMI was used to sort patients into categories: underweight (<18.50), normal (18.50-24.99), overweight (25.00-29.99) and obese (≥30.00). PSG was used to determine whether the diagnosis of OSA was present and to identify the severity of the disorder. PSG consists of a simultaneous recording of multiple physiological parameters related to sleep and wakefulness, which directly monitor and quantify the number of respiratory events, related hypoxemia and arousals. PSG consisted of the overnight recording of left and right electrooculograms, standard central and occipital electroencephalogram, submental electromyogram (EMG), bilateral tibialis EMG, nasal and oral airflow using a thermistor and thoracic, and abdominal excursions using respiratory inductive plethysmography. OSA severity was determined using PSG and was based on an AHI (number of apnoeas + hypopnoeas per hour of sleep) score of 5 or more, according to standard criteria (American Academy of Sleep Medicine, 2005). According to this, OSA severity is mild (AHI≥5≤15), moderate (AHI>15≤30) or severe (AHI>30).

## Statistical analyses
All analyses were performed using the Statistical Package for the Social Sciences (IBM SPSS 23) and MedGraph. Firstly, we described the background characteristics of the sample and calculated means and standard deviations for functional status (FOSQ), social support (MSPSS), mastery (PMS), night-time sleep quality (PSQI), daytime sleepiness (ESS) and OSA severity (AHI) for the total sample and stratified by gender. T-tests were conducted to assess gender differences in the continuous variables. Differences in the categorical variables were analysed using Chi-square tests. Secondly, we investigated the bivariate correlations between all variables. Thirdly, multiple linear regressions were used to examine the associations between social support, mastery, sleep-related problems and functional status for the total scale and by subscales, controlled for sociodemographic and clinical variables.

Using regression analyses we firstly assessed the crude effects (i.e. associations unadjusted for the number of predictors) of each variable separately on functional status, and then we continued with multiple regression analyses. Multicollinearity was assessed using the variance inflation factor (VIF<2.0). We applied the enter method in linear regression to identify the factors associated with summary score of functional status in the total scale and in the subscales. For each factor, beta coefficients represent the mean variation of functional status for the total scale and by subscales. The first model of the variables included sociodemographic data (age, gender, marital status). A second model included a clinical variable (OSA severity - measured by AHI), and a third model included night-time sleep quality and daytime sleepiness. Finally, in the fourth and fifth models, social support and mastery were included separately to assess the increase in the explained amount of total variance in functional status.

Mediation analyses were used to assess the role of social support and mastery in the association between sleep-related problems and functional status. According to Baron and Kenny (1986), the following conditions must be met to establish mediation: the independent variable must affect the dependent variable; secondly, the independent variable must affect the mediator; and lastly, the mediator must affect the dependent variable. The proportion of the effect which is mediated was calculated as the indirect effect divided by the total effect and multiplied by 100, while the as-advised standardized total effect was at least ±0.2. The Sobel z-test was used to examine the mediating effects of social support and mastery on the association between sleep-related problems and functional status in patients with OSA. We used partial correlation analyses to assess the association between variables under study when controlled for age, gender, marital status and OSA severity.

A p-value of <0.05 was considered statistically significant. Missing data were expressed as percentage of total number of patients for each variable. Power analysis revealed that the statistical power for multivariate analyses exceeded 93%, with medium effect size at α=0.05. The statistical power for univariate analysis was 98%, with medium effect size at α=0.05 (Faul et al., 2009).

## Results

### Sample characteristics

The final sample consisted of 150 patients with OSA (AHI≥5). The mean age of participants was 48.9±9.5 years. The majority of patients were male (68.0%), had secondary education (57.3%) and had a partner (76.0%). A total of 47.7% were obese and 49.3% had severe OSA. The mean score for functional status was 13.68±4.04. Female patients with OSA reported a significantly poorer level of perceived social support, greater sleep-related problems and poorer functional status compared with male patients with OSA (Table 7.1).

*Table 7.1 Baseline characteristics of the patients with OSA with AHI ≥ 5*

| Characteristics | OSA patients (N=150) | Male (N=102) | Female (N=48) | p-values |
|---|---|---|---|---|
| Age in years; mean, sd | 48.9±9.5 | 47.9±9.5 | 51.4±9.3 | **0.04*** |
| Gender; male, N (%) | 102 (68.0%) | 102 (68.0%) | 48 (32.0%) | |
| Education; N (%) | | | | 0.27 |
| Elementary | 8 (5.3%) | 4 (3.9%) | 4 (8.3%) | |
| Secondary | 86 (57.3%) | 56 (54.9%) | 30 (62.5%) | |
| University | 56 (37.3%) | 42 (41.2%) | 14 (29.2%) | |
| Marital status; single, N (%) | 36 (24.0%) | 26 (25.5%) | 10 (20.8%) | 0.53 |
| Body Mass Index; mean, sd | 30.2±7.7 | 30.1±7.4 | 30.6±8.2 | 0.73 |
| Body Mass Index; N (%) | | | | 0.28 |
| Underweight (<18.50) | 9 (6.0%) | 4 (3.9%) | 5 (10.4%) | |
| Normal (18.50-24.99) | 42 (28.0%) | 32 (31.4%) | 10 (20.8%) | |
| Overweight (25.00-29.99) | 32 (21.3%) | 23 (22.5%) | 9 (18.8%) | |
| Obese (>30.00) | 67 (44.7%) | 43 (42.2%) | 24 (50.0%) | |
| Apnoea Hypopnoea index; mean, sd | 36.1±22.3 | 33.9±21.0 | 39.4±24.6 | 0.16 |
| OSA severity; N (%) | | | | 0.41 |
| Mild (AHI≥5≤15) | 23 (15.3%) | 16 (15.7%) | 7 (14.6%) | |
| Moderate (AHI>15≤30) | 52 (34.7%) | 38 (37.2%) | 14 (29.2%) | |
| Severe (AHI>30) | 74 (49.3%) | 47 (46.1%) | 27 (56.2%) | |
| Night-time sleep quality; mean, sd (PSQI; 0-21) | 9.7±4.1 | 9.2±4.0 | 10.7±4.1 | **0.03*** |
| Excessive daytime sleepiness; mean, sd (ESS; 0-24) | 11.0±5.3 | 10.2±4.9 | 12.5±5.8 | **0.01*** |
| Perceived social support; mean, sd (MSPSS; 12-84) | 62.9±13.5 | 63.6±12.6 | 62.0±15.3 | 0.50 |
| Perceived social support; family; mean, sd | 21.2±5.4 | 21.4±5.2 | 20.8±5.8 | 0.50 |
| Perceived social support; friends; mean, sd | 19.9±4.9 | 19.9±4.3 | 19.8±5.5 | 0.92 |
| Perceived social support; signif. other; mean, sd | 22.0±5.1 | 22.3±4.7 | 21.4±5.4 | 0.31 |
| Mastery; mean, sd (PMS; 7-35) | 20.4±4.3 | 20.9±4.5 | 19.4±3.6 | 0.05 |
| Functional status; mean, sd (FOSQ; 5-20) | 13.7±4.0 | 14.5±3.9 | 11.8±4.2 | **0.001**** |
| Activity level | 2.8±0.8 | 2.9±0.9 | 2.5±0.8 | **0.01*** |
| Vigilance | 2.11±0.8 | 2.3±0.8 | 1.7±0.7 | **p<0.001***** |
| Intimacy and sexual relationships | 2.6±1.3 | 2.8±1.1 | 2.1±1.4 | **p<0.001***** |
| General productivity | 3.0±0.8 | 3.2±0.8 | 2.7±0.9 | **p<0.001***** |
| Social outcome | 3.2±1.0 | 3.3±0.9 | 2.9±1.3 | **0.001**** |

OSA – Obstructive Sleep Apnoea; PSQI – Pittsburgh Sleep Quality Index; ESS – Epworth Sleepiness Scale; MSPSS – Multidimensional Scale of Perceived Social Support; SS – Social Support; PMS – Pearlin Mastery Scale; FOSQ – Functional Outcomes of Sleep Questionnaire; *p<0.05; **p<0.01; ***p<0.001. Missing values: OSA severity: (0.7%); age: (1%); ESS, PSQI (1%); MSPSS: (2.0%).

## Correlations between the study variables

Table 7.2 shows the correlations between the study variables. Poor social support, low level of mastery, poor night-time sleep quality and daytime sleepiness were significantly correlated with functional status impairment in patients with OSA.

*Table 7.2 Correlations between age, gender, marital status, OSA severity, social support, mastery, night-time sleep quality and daytime sleepiness*

| | Age | Gender | Marital status | OSA severity | Social support | Mastery | Night-time sleep quality | Daytime sleepiness |
|---|---|---|---|---|---|---|---|---|
| **Gender** | 0.18* | - | | | | | | |
| **Marital status** | -0.13 | | - | | | | | |
| **OSA severity** | 0.13 | 0.11 | 0.13 | - | | | | |
| **Social support** | 0.06 | -0.07 | -0.12 | 0.07 | - | | | |
| **Mastery** | 0.07 | -0.17* | 0.08 | -0.12 | 0.20** | - | | |
| **Night-time sleep quality** | 0.05 | 0.17* | -0.09 | 0.19* | -0.16* | -0.28** | - | |
| **Daytime sleepiness** | -0.00 | 0.21** | 0.10 | 0.24** | -0.14 | -0.29*** | 0.15* | - |
| **Functional status** | -0.05 | -0.34*** | -0.05 | -0.35*** | 0.26** | 0.57*** | -0.43*** | -0.56*** |

## Associations between social support, mastery, sleep-related problems and functional status (total scale)

Significant crude associations on functional status were found for gender (B: -2.68; 95%CI= -4.07;-1.30; p<0.001), OSA severity (B: -0.06; 95%CI= -0.09; -0.03; p<0.001), sleep quality (B: -0.43; 95%CI= -0.58; -0.28; p<0.001), daytime sleepiness (B: -0.43; 95%CI= -0.53; -0.33; p<0.001), social support (B: 0.08; 95%CI= 0.03; 0.13; p<0.01), and mastery (B: 0.54; 95%CI= 0.42; 0.67; p<0.001) (Table 7.3). In the subsequent multivariate models, the effects of gender, OSA severity and sleep-related problems on functional status were statistically significant (Model 1 - Model 3). The association between social support (B: 0.04; 95%CI= 0.01; 0.08; p<0.05) and functional status (Model 4) was no longer statistically significant (B: 0.03; 95%CI= -0.00; 0.06; p=0.06) when mastery was added to the model (Model 5). The association between mastery and functional status was strong (B: 0.33; 95%CI= 0.22; 0.43; p<0.001), and the final model (Model 5) explained 62% of the functional status total variance.

*Table 7.3 Multiple linear regression analyses: associations of social support, mastery and sleep-related problems with total functional status scale*

| Functional status (FOSQ) | Crude | Model 1 | Model 2 | Model 3 | Model 4 | Model 5 |
|---|---|---|---|---|---|---|
| | B (95%CI) | B (95%CI) | B (95%CI) | B (95%CI) | B (95%CI) | B (95%CI) |
| Age | -0.05 (-0.12; 0.02) | -0.01 (-0.08; 0.06) | 0.01 (-0.06; 0.07) | -0.01 (-0.06; 0.04) | -0.01 (-0.06; 0.04) | -0.03 (-0.07; 0.02) |
| Gender | -2.68 (-4.07;-1.30)*** | -2.94 (-4.30;-1.58)*** | -2.67 (-3.97;-1.38)*** | -1.50 (-2.54;-0.46)** | -1.44 (-2.46;-0.41)** | -1.18 (-2.09;-0.27)* |
| Marital status | -0.95 (-2.53; 0.63) | -0.68 (-2.15; 0.80) | -0.24 (-1.66; 1.18) | -0.26 (-1.38; 0.86) | -0.05 (-1.16; 1.05) | -0.46 (-1.45; 0.53) |
| OSA severity | -0.06 (-0.09; -0.03)*** | - | -0.06 (-0.08; -0.03)*** | -0.03 (-0.05; -0.00)* | -0.03 (-0.05; -0.01)** | -0.03 (-0.05; -0.01)** |
| Night-time sleep quality | -0.43 (-0.58; -0.28)*** | - | - | -0.36 (-0.47; -0.24)*** | -0.34 (-0.45; -0.21)*** | -0.26 (-0.37; -0.16)*** |
| Daytime sleepiness | -0.43 (-0.53; -0.33)*** | - | - | -0.33 (-0.42; -0.23)*** | -0.31 (-0.40; -0.22)*** | -0.25 (-0.34; -0.17)*** |
| Social support | 0.08 (0.03; 0.14)** | - | - | - | 0.04 (0.01; 0.08)* | 0.03 (-0.00; 0.06) |
| Mastery | 0.54 (0.42; 0.67)*** | - | - | - | - | 0.33 (0.22; 0.43)*** |
| F Change | | 6.68*** | 16.61*** | 46.63*** | 6.68* | 38.74*** |
| Adjusted R² | | 0.10 | 0.19 | 0.50 | 0.52 | 0.62 |

Crude: effect of each variable separately on functional status; Model 1: effect of age, gender and marital status on FOSQ score; Model 2: effect of age, gender, marital status and disease severity on FOSQ score; Model 3: effect of age, gender, marital status, disease severity and sleep-related problems on FOSQ score; Model 4: effect of age, gender, marital status, disease severity, sleep-related problems and social support on FOSQ score; Model 5: effect of age, gender, marital status, disease severity, sleep-related problems, social support and mastery on FOSQ score; B: unstandardized regression coefficient; CI – confidence interval; Gender – male gender was set as the reference; Marital status: single was set as the reference; OSA – Obstructive Sleep Apnoea; FOSQ – Functional Outcomes of Sleep Questionnaire; F Change – significance of prediction improvement in model fit; Adjusted R² – explained variance adjusted for the number of predictors in the model; FOSQ – higher scores indicating less impaired daily life; *p<0.05; **p<0.01; ***p<0.001.

## Associations between social support, mastery, sleep-related problems and functional status by subscale

Significant crude effects on all functional status subscales were found for social support, mastery, sleep quality and daytime sleepiness. Social support was significantly associated with intimacy-sexual relationships only, while mastery was associated with all functional status subscales in the final models (with an explained total variance of 38% for activity level, 48% for vigilance, 45% for intimacy-sexual relationships, 63% for general productivity and 38% for social outcome). Sleep-related problems were associated with all functional status subscales in the final models, except for the association between night-time sleep quality and vigilance (Table S7.4).

## Mediating effect of social support on the association between sleep-related problems and functional status

No mediating role of social support was observed in the association between night-time sleep quality and functional status (Sobel z-value=-1.55, p=0.12).

## Mediating effect of mastery on the association between sleep-related problems and functional status

A significant partial mediating effect of mastery on the association between night-time sleep quality (Sobel z-value= -3.202; $p<0.001$), daytime sleepiness (Sobel z-value=-3.302; $p<0.001$) and functional status was found. Standardized coefficients showed that 17.7% of the total effect of night-time sleep quality (PSQI) on functional status was mediated by mastery (-0.08), and 82.3% of the total effect was direct (-0.35) (Figure 7.1).

*Figure 7.1 The mediating role of mastery in the association between night-time sleep quality and functional status*
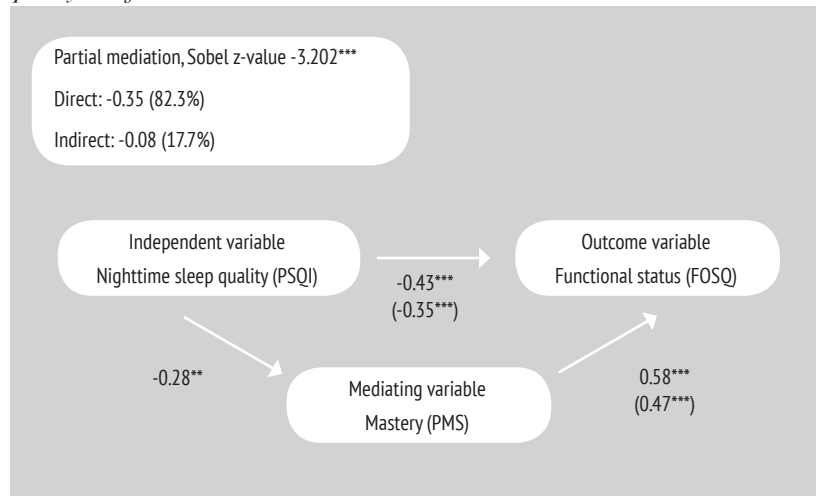


PSQI – Night-time sleep quality; PMS – Pearlin Mastery Scale; FOSQ – Functional Outcomes of Sleep Questionnaire; **p<0.01; ***p<0.001.

Further, standardized coefficients showed that 23.3% of the total effect of daytime sleepiness (ESS) on functional status was mediated by mastery (-0.13), and 76.7% of the total effect was direct (-0.43) (Figure 7.2).

*Figure 7.2 The mediating role of mastery in the association between daytime sleepiness and functional status*
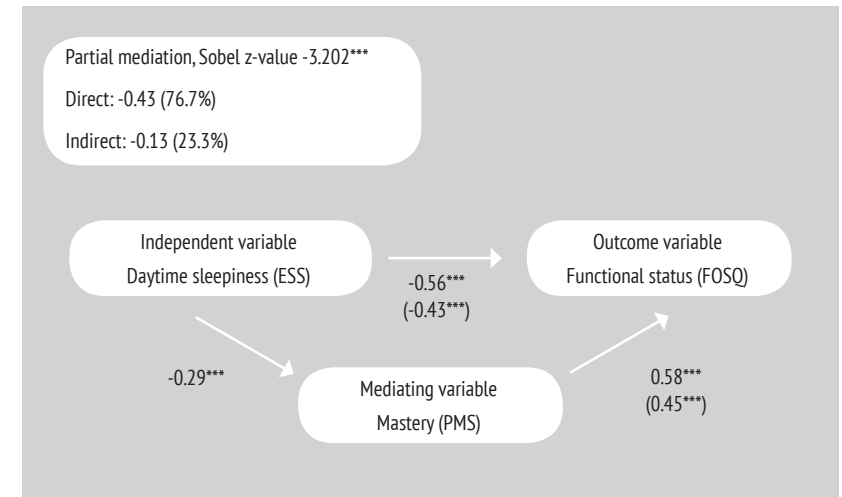


ESS – Epworth Sleepiness Scale; PMS – Pearlin Mastery Scale; FOSQ – Functional Outcomes of Sleep Questionnaire; ***p<0.001.

## Discussion

Our results provide evidence that suggests that poor social support, low levels of mastery, poor night-time sleep quality and daytime sleepiness were associated with impaired functional status in patients with OSA. The association between social support and functional status was weak, and no longer significant when mastery was added to the model. Mastery was strongly associated with functional status. Furthermore, mastery mediated the association between sleep-related problems and functional status.

We found a small but significant association between social support and functional status in patients with OSA. Given the evidence that sleep disturbances may represent an important predictor of daytime functioning, including engagement in social activities (Dew et al., 1994), it may be hypothesized that in cases of extreme daytime sleepiness, the sources of social support may not be adequately utilized and thus may be of less importance. Furthermore, it is also plausible recent studies have suggested that sleep disturbances may lead to more negative perceptions of the social environment (Troxel et al., 2010). Previous research has shown that disturbed sleep in people with OSA and their partners was associated with mood swings and aggression which affected relationships in a negative way. Patients with OSA also had difficulties initiating new intimate relationships or friendships (Broström et al.,

2007). In line with these assumptions, OSA symptoms were also associated with reduced social participation (Liu et al., 2016). Nevertheless, the subscale analyses in our study showed that social support was significantly associated only with one functional status subscale, i.e. intimacy-sexual relationships, while mastery was strongly associated with all functional status subscales. Thus, it may be assumed that mastery, together with social support, may improve intimate and sexual functioning in patients with OSA. This may be crucial as better relationship quality was identified as being the most important need expressed by untreated patients with OSA (Broström et al., 2007).

Mastery was strongly associated with overall functional status and explained an additional 10% of the variance in functional status beyond the variance explained by sociodemographic, clinical, sleep-related variables and social support. Moreover, the association between social support and functional status was attenuated and no longer significant when mastery was added to the model. These results are in line with findings from studies of other incapacitating diseases (Krokavcova et al., 2008b; Sloan et al., 2009; Raaijkmakers et al., 2014), including one preliminary study involving OSA patients with comorbid insomnia (Lang et al., 2016), where higher levels of mastery were associated with better self-rated health and quality of life. As expected, our study identified a significant association between poor sleep quality, daytime sleepiness and consequent functional impairment in patients with OSA. Furthermore, mastery mediated the association between sleep-related problems and functional status. The associations between mastery, sleep-related problems, and functional status were statistically significant after controlling for sociodemographic variables and OSA severity.

Our results suggest that adequate mastery may have the potential to diminish the negative effects of sleep-related problems on functional status. As patients with OSA were found to have reduced energy and activity levels (measured with the Functional Outcomes of Sleep Questionnaire-FOSQ) even after treatment with continuous positive airway pressure treatment (CPAP) (Lau et al., 2013), mastery may help in diminishing the negative effects of sleep-related symptoms on functional status. The establishment of new strategies for functional status improvement may be crucial in patients with OSA, as reduced general productivity, poor energy and impaired vigilance lead to work-related and vehicle accidents (Karimi et al., 2013; Allen et al., 2016) and impaired work functioning in these patients (Mulgrew et al., 2007). Thus, greater levels of mastery may contribute to better functional status and better OSA management and treatment.

Since OSA is diagnosed according to a cut-off score in the Apnoea-Hypopnoea Index (AHI), a logical assumption is that higher AHI indicates higher sleep-related problems. Previous research has shown that AHI does not correlate well with the presence or degree of daytime sleepiness (Bixler et al., 2005; Roure et al., 2008; Macey et al., 2010; Dündar et al., 2015), poor sleep quality (Kezirian et al., 2009; Macey et al., 2010), psychological symptomatology (Macey et al., 2010; Lau et al., 2013; Rezaeitalab et al., 2014) or female sexuality (Hoekema et al., 2007). Moreover, contrary to the common belief, sleepy patients showed longer sleep duration and

increased slow-wave sleep compared to non-sleepy patients with OSA (Roure at al., 2008). In contrast, we found significant associations between AHI, sleep-related problems and functional status both in univariate as well as multivariate analyses. This profound role of OSA severity revealed in our study may occur due to lack of major comorbidities which are expected to influence sleep and affective symptoms (Macey et al., 2010). Also, unlike previous research, participants with regular shift works in the past six months were excluded from our study, which may strengthen the role of AHI.

Additionally, our results reveal possible gender differences in the impact of OSA on functional status. We found that despite the absence of a significant difference in age, marital status, body mass index and AHI, newly-diagnosed female patients with OSA reported significantly greater sleep-related problems and functional status impairment when compared with male OSA patients. In previous studies, functional status and sleep quality were also more impaired in female OSA patients compared with male patients (Chervin, 2000; Quintana-Gallego et al., 2004; Ye et al., 2009; Silva et al., 2016) despite similarity in sociodemographic and clinical variables (Ye et al., 2009). This larger impact of OSA severity on health outcomes cannot be explained only by female gender per se (Chervin, 2000; Quintana-Gallego et al., 2004); there are other attendant factors, for instance that women may be more often underdiagnosed regarding OSA when compared with men due to circumstances related to family lifestyle, sociocultural factors and different OSA clinical expressions (Chervin, 2000; Quintana-Gallego et al., 2004).

### Strengths and limitations

The strength of our study lies in the objective assessment of OSA using PSG. To our knowledge, this is the first study examining the ways in which social support and mastery are associated with functional status in patients with OSA. Some limitations should be noted, however. Due to the cross-sectional design of our study, causal relationships cannot be established. In addition, in our sample 68% of the patients with OSA were men; thus, our results may be less generalizable to female patients with OSA. However, the number of participants in our study is consistent with the man-to-woman ratio in OSA (3:1). Another limitation is the length of the questionnaires used, which may influence the data quality, especially in patients with sleep-related problems. This limitation was mitigated by our sending the questionnaires to the patients three weeks in advance by postal mail, so they had enough time to fill them in.

### Implications for practice and future research

This study shows that social support, mastery and sleep-related problems are associated with functional status in patients with OSA, and that mastery may contribute to functional status improvement. As elimination of OSA symptoms with CPAP does not lead to complete restoration of daytime energy, subjective and objective sleepiness (Pack et al., 2001; Lau et al., 2013), and overall functional status (Weaver et al., 2007; Weaver, 2013; Tippin et al., 2016) in many adherent patients, present

research and clinical practice should focus not just on standard treatment of OSA, but also on functional status in these patients. In line with this, health care professionals should be aware of the possibility that interventions focusing on mastery enhancement may help improve functional status in patients with OSA. Mastery as a part of patient empowerment (Aujoulat et al., 2008) was also found to be associated with individuals' capacity to make decisions about their health behaviour and to have or to take control over aspects of their lives that are related to health (McAllister et al., 2012). Moreover, as psychological resources associated with control over one's life, such as self-efficacy (Baron et al., 2011) or internality (Wild et al., 2004), were found to contribute to CPAP treatment adherence, the role of mastery may have a similar effect.

As mastery is not considered as a fixed personality trait but as an adaptive self-concept born of pivotal experience (Pearlin et al., 2007), education of patients with OSA, provided by psychologists or trained nurses focusing on personal empowerment for maintaining an adequate level of mastery in people affected by OSA, may be important. Mastery may also be improved by relaxation techniques (O'Brien et al., 2012), or by chronic disease management programmes which have been found to be effective in patients with pulmonary disease (Rea et al., 2004). Thus, health practitioners' education about the role of mastery and counselling supporting mastery for patients with OSA may be one of the important components of effective patient management. Additionally, we found that these interventions should be aimed especially at the group of female patients with a severe condition, who have higher probability of experiencing significant impairment in functional status.

Research advancing our knowledge of protective factors to enhance functional status in patients with OSA may help to develop comprehensive multidisciplinary strategies designed to improve self-management skills in patients with OSA. Further research should identify risk groups of patients with low mastery levels, so that counselling and interventions can be tailored to these patients. Future longitudinal intervention studies targeting patients with OSA should be designed to cast more light on the causality in the associations between social support, mastery and functional status. We recommend that our study should be replicated with a larger sample and in a longitudinal setting. As mastery may reflect components of negative affectivity or neuroticism (Surtees et al., 2006), future studies should examine the associations between mastery and psychological symptomatology. Finally, future studies may verify the association between mastery and CPAP treatment adherence. General CPAP treatment adherence has been found to be poor (Aloia et al., 2004; Haniffa et al., 2004; Weaver and Grunstein, 2008) due to various reasons including discomfort and feelings of claustrophobia due to the mask (Aloia et al., 2004), as well as other unspecified reasons (Haniffa et al., 2004). However, interventions to increase patients' autonomous motivation (e.g self-efficacy) have demonstrated increased nightly use (Richards et al., 2007). Similarly, mastery is likely to increase patients' autonomous motivation to manage their condition (Raaijmakers et al., 2014), so it may be useful for improvement of CPAP treatment adherence.

## Conclusion

While poor social support was weakly associated with impaired functional status in patients with OSA, we found a strong association between low mastery and impaired functional status. Mediation analysis showed that mastery may have the potential to diminish the negative effect of sleep-related problems on functional status. As supporting mastery of patients with OSA may play an important role in management of the condition, patients and health care professionals should learn more about the concept of mastery in connection with sleep-related problems and functional status.

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# General discussion, implications, and conclusions

"I've always loathed the necessity of sleep. Like death, it puts even the most powerful men on their backs."

Frank UNDERWOOD

Obstructive sleep apnoea (OSA) has been linked with the exacerbation of physiological and psychological disturbances that not only contribute to decreased quality of life (QoL) (Bishop et al., 2018), and poor daytime functioning (Sharkey et al., 2013; Aaronson et al., 2016), but also may be associated with increased suicide risk (Bishop, et al., 2018; Gupta and Jarosz, 2018). Therefore, OSA is recommended to be approached as a chronic disease requiring multidisciplinary managerial and treatment implications, including behavioural treatments (Epstein et al., 2009). The burden of this long-term chronic condition poses a challenge for health-care professionals, and for a successful management of OSA, bio-psycho-social factors need to be taken into consideration (Weaver, 2013; Vaske et al., 2017; Hilbert and Yaggi, 2018). This thesis seeks to address the psycho-social factors that have been identified as key determinants in the adaptation to various chronic diseases but are less known in OSA yet. The thesis further aims to contribute to the understanding of the associations between biomedical factors and self-reported health outcomes in OSA patients that have been identified as ambivalent in previous research. Section 8.1 summarizes the main findings of Chapters 3-7. The next section 8.2 provides a general overview and discussion of the main findings. The methodological considerations of the study are addressed in section 8.3. Finally, implications of the study for practice along with opportunities for future research are discussed in section 8.4.

## 8.1   Main findings

**Research question 1** (Chapter 3)
Has continuous positive airway pressure (CPAP) treatment a positive effect on quality of life (QoL) in OSA patients when compared to sham CPAP, placebo pills, and conservative treatment?
Meta-analysis of 13 randomised controlled trials showed no significant differences in overall (0.18; 95%CI = 0.10, 0.26) and psychological QoL (0.25; 95%CI = -0.23, 0.72) comparing values of CPAP treated patients with controls; however, physical QoL improved (0.20; 95%CI = 0.04, 0.35). Subgroup analyses and sensitivity analyses showed that CPAP significantly affected the overall QoL in studies with controls receiving sham CPAP, parallel design, low risk of bias, and mild OSA patients.

**Research question 2a** (Chapter 4)
*Are OSA severity, sleep-related problems, and anxiety associated with work functioning in OSA patients when controlled for age, gender, and type of occupation?*
Impaired work functioning was reported by 82% of the OSA patients. A weak association between OSA severity and impaired work functioning was found in the crude model that was no longer significant in the adjusted models. Multivariate analyses revealed that poor perceived sleep quality was more strongly associated with impaired work functioning than sleep efficiency and daily disturbances. We found no significant association between daytime sleepiness and work functioning. Anxiety was strongly associated with impaired work functioning (-0.61; 95%CI = -1.10, -0.15). After adding anxiety to age, gender, OSA severity, and night-time sleep quality, the explained variance of work functioning increased from 20% to 25%.

**Research question 2b** (Chapter 4)
Does anxiety moderate the associations between sleep-related problems and work functioning?
The moderating effect of anxiety on the association between overall night-time sleep quality and work functioning was especially strong in patients with better sleep quality, while the effect of anxiety on the association between overall night-time sleep quality and work functioning was negligible in case of high sleep quality problems. Separate analyses of the three night-time sleep quality factors showed that anxiety moderated the associations between low and medium levels of perceived sleep quality problems, daily disturbances and work functioning. No moderating effect of anxiety on the association of sleep efficiency with work functioning was found.

**Research question 3a** (Chapter 5)
*Are hostility and coping self-efficacy associated with psychological distress in OSA patients when controlled for sociodemographic, clinical, and sleep-related variables?*
A high level of hostility and poor coping self-efficacy were strongly associated with psychological distress in OSA patients. In the regression models, hostility and the three coping self-efficacy dimensions, a) the ability to get support from family and friends, b) problem-focused coping self-efficacy, and c) coping self-efficacy for stopping unpleasant emotions and thoughts explained 5%, 4%, 8%, and 11% of the variance of psychological distress, respectively.

**Research question 3b** (Chapter 5)
*Does coping self-efficacy mediate the association between hostility and psychological distress?*
All coping self-efficacy dimensions mediated the associations between hostility and psychological distress. The indirect effects of all three coping self-efficacy dimensions were significant. They accounted for 10% of coping self-efficacy for getting support from family and friends, 15% of problem-focused coping self-efficacy, and 17% of coping self-efficacy for stopping unpleasant emotions and thoughts.

**Research question 4** (Chapter 6)
*What is the prevalence of suicidal ideation in OSA patients? Are OSA severity, sleep-related problems, and social support related to suicidal ideation in OSA patients?*
The prevalence of suicidal ideation in OSA patients was 20.1%. Patients reporting suicidal ideation scored higher on sleep-related problems compared to non-suicidal ideation patients. OSA severity was not directly related to suicidal ideation but the association was mediated by night-time sleep quality. Poor night-time sleep quality and fatigue were directly related to suicidal ideation; with fatigue most strongly related to suicidal ideation. Unexpectedly, the relationships between daytime sleepiness, social support and suicidal ideation were not significant. Adjustment for age, gender, and marital status did not change the associations between social support, daytime sleepiness and suicidal ideation.

**Research question 5a** (Chapter 7)

*Is there an association between social support, mastery, sleep-related problems and functional status in OSA patients when controlled for sociodemographic and clinical variables?*

Social support was weakly associated with functional status in OSA patients and this association was no longer significant when mastery was added to the model. Mastery was strongly associated with functional status in OSA patients. We also identified significant associations between poor night-time sleep quality, daytime sleepiness and functional impairment.

**Research question 5b** (Chapter 7)

*Do social support and mastery mediate the association between sleep-related problems and functional status?*

No mediating role of social support was observed in the association between sleep-related problems and functional status. Mastery, however, mediated the association between sleep-related problems and functional status. The direct effects of sleep-related problems on functional status varied between 76.7% and 82.3%, whereas the indirect effects via mastery varied between 17.7% and 23.3%.

## 8.2   Discussion of the main findings

This thesis focuses on the associations between bio-psycho-social factors and selected aspects of self-reported health outcomes in OSA patients, i.e. quality of life, functional status, work functioning, and overall psychological distress — with particular interest in suicidal ideation. Our health model, the choice of examined constructs, and related measures were partially inspired by Wilson and Cleary (1995) and the bio-psycho-social approach as proposed by Engel (1978). The chosen health model stresses the presence of interactive, causal, and complex relationships between symptoms of the disease, functional status, general health perceptions, and overall QoL, as experienced by individuals (Wilson and Cleary 1995; Krabbe, 2017). More detailed information about the used health model can be found in Chapter 1.

*Figure 8.1. Conceptual model of the associations between constructs examined in the thesis*
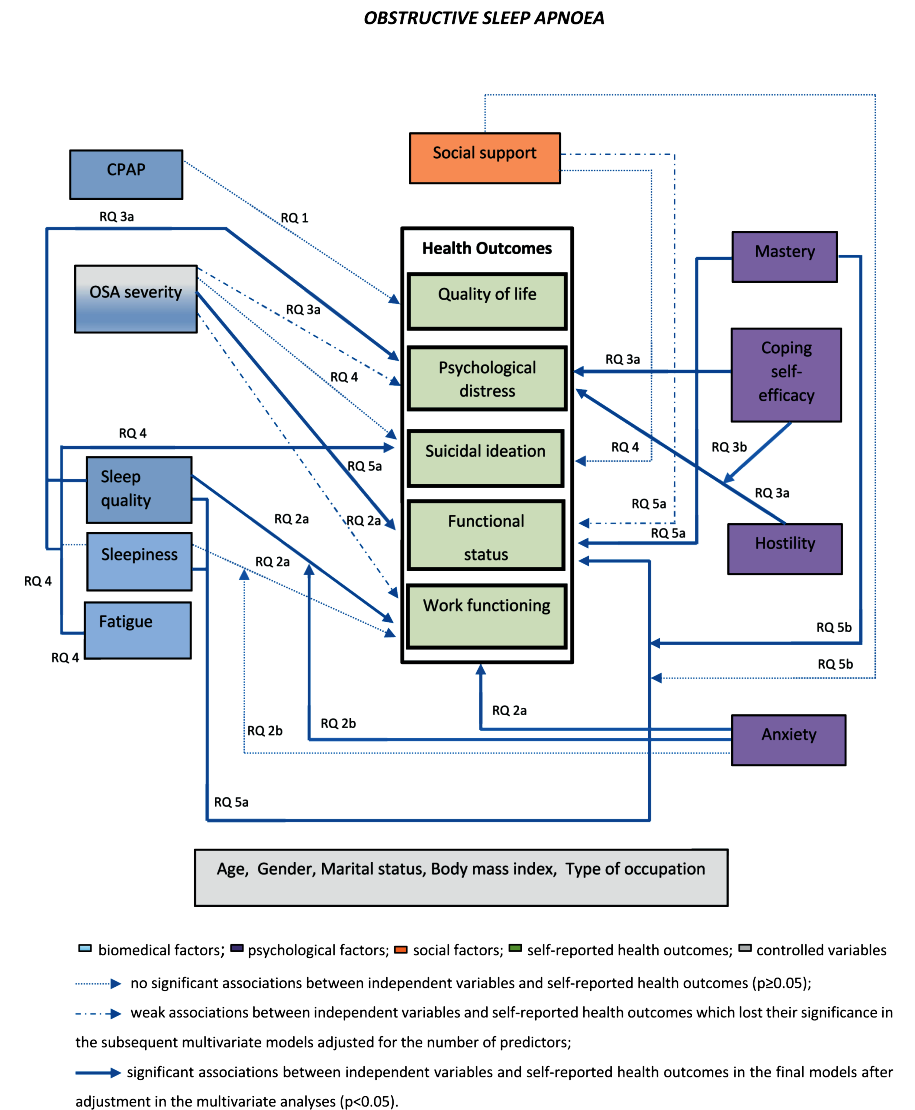
## 8.2.1 Biomedical and psychological factors and their association with self-reported health outcomes in obstructive sleep apnoea patients

The examined OSA-related biomedical factors in this thesis concerned CPAP treatment, OSA severity, and sleep-related problems – measured as night-time sleep quality, daytime sleepiness, and fatigue. Psychological factors in this thesis were operationalized as anxiety and hostility. Other important intra-individual psychological resources, considered as major features within the process of coping with chronic disease (Kempen et al., 1997), were defined as coping self-efficacy and sense of mastery over one's life and circumstances.

**Continuous positive airway pressure treatment and quality of life**
We identified no CPAP treatment effect on overall QoL in studies with a crossover design compared to a small but significant effect found in studies with a parallel design. This finding supports the results of prior research, as parallel-group trials were found to be more efficient at capturing the persistence of benefits from CPAP treatment (Richens, 2001; Jing et al., 2008). Subgroup analyses further showed that CPAP led to a small but significant improvement in overall QoL in studies with controls undergoing sham CPAP treatment, compared to negligible overall QoL improvement revealed in controls receiving placebo pills. This result is unexpected, as sham CPAP treatment is supposed to worsen both sleep quality and gas exchange (Engleman et al., 1999; Sanner et al., 2000). A possible explanation may be that most studies that used placebo pills as control condition also had very small study samples. Moreover, all studies with placebo pills as control condition had a crossover design – identified as less sensitive in capturing the effect of CPAP treatment due to short wash-out periods which are not able to eliminate the effects of the first treatment (Richens, 2001). We also found significant QoL improvement in studies with mild OSA patients and low risk of bias. Thus, disease severity and level of low risk of bias may also be relevant when measuring the effect of CPAP treatment on QoL in OSA patients.

In line with previous meta-analyses by Jing et al. (2008), we have further confirmed that CPAP treatment may help to improve physical symptoms of OSA, whereas impaired psychological QoL still cannot be alleviated. The suboptimal effect of CPAP treatment on psychological QoL may be explained by irreversible OSA-related brain injuries, confirmed by recent histopathological investigations of brain tissue autopsy in OSA patients (Owen et al., 2018). These neural alterations in OSA patients may contribute to the development of psychological symptomatology (Huang et al., 2019), including mood (Peiffer et al., 2001), anxiety disorders (Milad 2007), and disturbed social functioning (Jack and Pelphrey, 2015). Owen and colleagues (2018) further suggest that myelin in OSA patients is impacted and not protected by CPAP treatment. Moreover, poor neuropsychological function and psychological symptoms may diminish adherence with CPAP treatment (Kushida, 2007; Hussain et al., 2014; Jackson et al., 2018). Thus, if the hypothesis

on irreversible brain injuries and their contribution to psychological impairment in OSA patients can be confirmed, the next step is to better understand OSA-related psychological symptoms and to adopt appropriate psycho-social interventions in disease management. Another possible explanation for the lack of a CPAP treatment effect on QoL is that there is no "perfect placebo" for CPAP and each approach has limitations and difficulties in blinding. For example, even a patient on sham CPAP treatment may be made aware of persisting snoring or observed apnoeas by a bed partner (Kushida et al., 2007).

Finally, the results of our meta-analyses may also be explained by the relatively low CPAP compliance level (with the highest value of 5.0 hours per night) in the included studies. It is well known that CPAP adherence is often suboptimal and remains persistently low over twenty years of reported data (Rotenberg et al., 2016b). Due to problematic adherence, the real effectiveness of CPAP may be poor, with a large proportion of users abandoning the machine within one year of prescription (Rotenberg et al., 2016a). These low rates of adherence consequently call into question the status of CPAP as first line treatment for OSA (Rotenberg et al., 2016b). Moreover, the question of what level of CPAP yields optimal health outcomes and defines adherence has not yet been clearly established and varies between 4 and 7.5 hours per night (Zimmerman et al., 2006; Weaver et al., 2007; Masa and Corral-Peñafiel, 2014), while some patients are not able to achieve normal daily functioning or remain excessively sleepy despite optimal CPAP treatment (Weaver et al., 2007; Antic et al., 2011; Jackson et al., 2018). The aforementioned findings may serve as a reminder that a "one size fits all" approach may not be appropriate in OSA and that decisions concerning the effectiveness of evaluation of CPAP treatment and its management need to be more individualized (Hilbert and Yaggi, 2018).

**OSA severity and self-reported health outcomes**
Mostly weak and inconsistent associations between OSA severity and self-reported health outcomes were found. The missing association between OSA severity and subjective health outcomes may be related to the lack of adaptation to the hospital environment and the recording equipment during the first night of polysomnography (PSG) assessment (Choi et al., 2015). We may further assume that this lack of adaptation may be especially significant in patients experiencing psychological distress. Therefore, issues such as abbreviated PSG monitoring, night-to-night variability, or the "first-night effect" of the PSG may partly explain the variability of OSA severity across different studies and outcomes (Punjabi, 2008). Furthermore, the Apnoea-Hypopnoea Index (AHI) does not capture the range of physiological variability related to adverse health outcomes of OSA, such as sleep fragmentation, degree of hypoxemia, or arousal threshold (Butler et al., 2019). All in all, considering the aforementioned problems, we believe that many controversies in the field of OSA may be caused due to the inability of AHI to measure the exact severity of the disease in a reliable and valid way (e.g. Asghari et al., 2012; Asghari and Mohammadi; 2013; Ryu et al., 2016).

**Daytime sleepiness and work functioning**
No significant association between daytime sleepiness and work functioning was found. We assume that the perception of subjective daytime sleepiness may be confounded by the patients´ habituation to the increased sleep fragmentation that may occur with the long duration of the untreated disease. Perhaps, daytime napping could also be a confounding factor in the expression of the symptoms of sleepiness, e.g. people with more flexible working hours may have more nap opportunities, when compared to people with fixed working hours. Sleepiness, further, represents an interaction of physiological systems that increase sleep tendency and other systems opposing sleep drive. These complemantary factors provide a dynamic equilibrium that oscilates over the course of a day depending on homeostatis between sleep debt and circadian phase. Thus, it may be difficult to objectively assess the level of daytime sleepiness as it may inevitably vary during the day (Kushida, 2007; Hurdiel et al., 2018). Moreover, the levels of daytime sleepiness were found to be significantly influenced by a deterioration of the circadian rhythm, especially in OSA patients with poor sleep quality (Burioka et al., 2008; More et al., 2019).

Other observations indicate that the Epworth Sleepiness Scale may be an unreliable screening tool for OSA (Al Houqani and Arora, 2019). Sleepiness is a subjective, physiological, and behavioural construct and this may lead to a certain amount of confusion in the discussion of its prevalence, mechanisms, and societal implications (Cappuccio et al., 2010). The subjective evaluation of daytime sleepiness is often complicated by the fact that patients may complain about a lack of energy, exhaustion, and tiredness, rather than sleepiness itself (Chervin, 2000; Sharkey et al., 2013). Therefore, if OSA patients underestimate these symptoms, we recommend health care professionals to accompany self-reported measures of daytime sleepiness by clinical judgement and objective assessment – using technological devices to monitor sleepiness and alertness with documented validity (e.g. Cappuccio et al., 2010; Kaplan et al., 2018).

Finally, the lack of an association between daytime sleepiness and work functioning may be attributed to the hyperarousal theory, which links the symptoms of poor sleep quality and anxiety (Perlis et al., 2005). More specifically, both sleep-disordered breathing and anxiety may be associated with waking or sleeping hyperarousal activity (Krakow, 2015). Thus, anxiety in OSA patients may develop into a chronic state of hypervigilance, which refers to being on high alert much more than normal. This arousal may ultimately lead to a state of chronic anxiety and may eventually obliterate the natural daytime sleepiness or cause sleeplessness (Perlis et al., 2005; Krakow, 2015).

**Night-time sleep quality and work functioning: the moderating role of anxiety**
One of the most interesting findings of the moderation analysis was that the role of anxiety in the association between sleep quality and work functioning was weakest in OSA patients with the highest levels of sleep quality problems. Moderation analyses revealed that high sleep quality problems may become more significant in the association with poor work functioning than anxiety, while the moderating

effect of anxiety on work functioning may be especially profound in patients with better sleep quality. Thus, it can be assumed that in case of very poor night-time sleep quality, anxiety symptoms in OSA patients may become less dominant. An explanation may be that very poor sleep quality may cause fatigue, which may decrease the levels of (work-related) anxiety. Due to fatigue, OSA patients may have a lack of energy and may thus avoid work-related social interactions (e.g. Haack and Mullington, 2005), which are perceived by OSA-patients as stressful (Reishtein et al., 2006). Prior research showed that OSA patients may have difficulties to complete work tasks and that they perceived a lack of trust from coworkers which led to embarrassment (Reishtein et al., 2006). Thus, it should be considered that an increased prevalence of anxiety as identified in our study may also be social or work-related (e.g. adverse work environment, poor relationships at work) and not solely OSA-related.

Although the Beck Anxiety Inventory (BAI) represents a reliable indicator of anxiety in primary care (Wetherell and Gatz, 2005; Muntingh et al., 2011), its focus on psychophysiological symptoms linked to panic disorder such as a racing heart or dizziness (Julian, 2011), should be considered when interpreting our results (Beck and Steer, 1991; Cox et al., 1996), including the relatively high prevalence of anxiety identified in our study. It seems that the mechanism of the association between sleep and anxiety in OSA is complicated, e.g. a previous study reported a higher anxiety dream incidence in OSA patients (Carrasco et al., 2006) and OSA-related snoring when compared to controls (de Groen et al., 1993). OSA also appears to confer a higher risk for future development of nocturnal panic attacks due to breathing-related OSA symptoms (Edlund et al., 1991; Su et al., 2015), as well as somatic symptoms of anxiety such as excessive sweating, or nightmares (Wiersema et al., 2018). In light of these findings, it can be assumed that anxiety as measured in our study may be associated with psychophysiological symptomatology related to panic attacks, rather than with anxiety in general. As the BAI does not assess other aspects of anxiety, such as cognitive symptomatology, further research should include additional anxiety measures to distinguish between symptoms linked to panic disorder and other anxiety disorders (e.g. generalized anxiety disorder) in OSA patients.

**Sleep-related problems and suicidal ideation**
We found that disturbed night-time sleep quality and fatigue were directly related to suicidal ideation. There is a large body of evidence showing that disrupted night-time sleep quality may directly affect mental functioning in several ways including increased impulsivity, decreased executive functioning, and emotional exhaustion (Krakow et al., 2000; Weaver and George, 2011; Bernert et al., 2014) all of which may consequently diminish the capacity to inhibit suicidal ideation or behaviour (e.g. Malik et al., 2014). Notable is also the recent study by Bishop et al. (2018) which described that self-reported OSA was significantly associated with suicidal ideation and suicide planning, after controlling for key covariates such as depression, substance use disorders, and comorbid physical diseases. Nonetheless, sleep disturbances were not included in the recent suicide risk factor lists compiled by

the World Health Organization (2012). Therefore, the associations between disturbed night-time sleep quality, fatigue, and suicidal ideation revealed in our study may provide an additional support for the importance of sleep-related problems in the course and development of suicidal ideation in OSA patients beyond major depression (Krakow et al., 2011; Bishop et al., 2018), when confirmed in longitudinal studies.

Several mechanisms may explain our findings. First, it seems that repeated OSA-related arousal during sleep may exacerbate suicidality through the effects on night-time sleep quality (e.g. Krakow et al., 2000; Tseng et al., 2018). Second, the theory of entrapment may apply. Entrapment represents a core component of the psychological mechanisms underlying suicidal ideation. The term entrapment is derived from the concept of ''arrested flight,'' whereby a powerful motivation to escape from a situation, driven by threat-related psychobiological systems, is blocked (Gilbert and Allan, 1998). As poor sleep quality was found to alter the association between pre-sleep entrapment and awakening suicidal ideation (Littlewood et al., 2019), OSA patients may represent a group endangerd by suicide. Moreover, OSA may lead to a low perception of control over the disease and its symptoms, which may potentiate the feeling of entrapment. Sleep may further be seen as an alternative way to escape these perceptions of entrapment. The potential downside to this occurs when people start 'escaping' via daytime napping, because this can disrupt night-time sleep. Subsequently, this behaviour may reinforce the disturbed sleep patterns, which in turn contribute to increased suicidal ideation and behaviours (Littlewood et al., 2016). Furthermore, if the hypothesis on the 'escaping' via sleep in the daytime is valid, it may be used as a possible explanation for the lack of the significant association between daytime sleepiness and suicidal ideation. Finally, the lack of an association between daytime sleepiness and suicidal ideation can be explained by the conceptual difference between fatigue and sleepiness. More specifically, daytime sleepiness can be defined as drive for sleep while fatigue can be described as drive for rest. Fatigue was also found to be strongly associated with psychological symptoms (Harvey et al., 2009) and involves neurastenic qualities (Kushida, 2007) and thus may better reflect the presence of psychological distress, including SI, when compared to daytime sleepiness.

**Hostility and psychological distress: the mediating effect of coping self-efficacy**
All assessed coping self-efficacy dimensions mediated the association between hostility and psychological distress. The coping self-efficacy for stopping unpleasant emotions and thoughts was the most adaptive strategy in attenuating the association between hostility and psychological distress. An explanation why coping self-efficacy for stopping unpleasant emotions and thoughts may be most adaptive in OSA patients is that they have very little control over the symptoms of their disease. When patients lack the ability to control disease-related symptoms and need to learn how to manage them, the avoidance-oriented coping strategies may help them to diminish the level of psychological distress (e.g. De Ridder and Schreurs 2001; Mikula et al., 2014). Furthermore, our results corroborate with previous studies showing that

hostile individuals were more likely to employ escape-avoidance coping styles to handle psychological distress (Vandervoort, 2006). All in all, our findings support the hypothesis that healthy emotion-regulation may not merely be about using the "right" problem focused strategies (Haines et al. 2016) and that coping can diminish psychological distress only when used in appropriate contexts (Bonanno and Burton, 2013; Haines et al. 2016).

However, our findings coincide with previous research among OSA patients. Two former studies (Bardwell et al., 2001; Gassara et al., 2017) concluded that the more active coping strategies reported by OSA patients, the lower the level of depressive symptoms they experienced. A possible explanation for the inconsistency with our findings may be the difference in OSA diagnosis criteria (Bardwell et al., 2001) and different measurements of coping and psychological symptomatology (Bardwell et al., 2001; Gassara et al., 2017). Recent studies also identified active coping processes as potential behavioural intervention targets to promote CPAP use (Dieltjens et al., 2013; Saconi et al., 2018), while passive coping was significantly associated with poor adherence with treatment. Thus, it may be assumed that during the solution-oriented CPAP treatment process, active coping strategies may become more useful when compared with passive-oriented coping. Therefore, an important issue to resolve in future research is the role of the different coping self-efficacy dimensions in the management of CPAP treatment.

**Sleep-related problems and functional status: the mediating role of mastery**
Mastery over one's life and circumstances was significantly associated with all functional status subscales in terms of activity level, vigilance, general productivity, social outcomes, and intimate and sexual relationships. Our findings are in line with previous studies showing that mastery was found to facilitate QoL, psychological well-being, and adaptation under stressful situations, including medical events (Kempen et al., 1997; Lang et al., 2016). Furthermore, when looking at the mediating effect of mastery on the association between sleep-related problems and functional status, we found that mastery mediated the association between night-time sleep quality, daytime sleepiness and functional status. As OSA patients were found to experience reduced energy and activity levels even after treatment with CPAP (Lau et al. 2013; Weaver, 2013) with optimal compliance (Antic et al., 2011; Jackson et al., 2018), adequate mastery may help in diminishing the negative effects of sleep-related symptoms on functional status. As mastery is not considered a stable element of personality but is understood as a personal resource that may evolve and change over the lifespan in response to circumstances and interventions (Pearlin et al., 2007; Zautra et al., 2012), the development of new strategies for the improvement of mastery may be beneficial.

## 8.2.2 Social factors and self-reported health outcomes
It is now generally accepted that health and illness are not only the result of an interaction between biological and psychological factors, but also social factors (Haslam et al., 2018). The impact of OSA is significant and the disease does not only affect

physical and psychological health but the whole person in the context of his or her social life. OSA itself may cause changes in the social envinronment which may inevitably affect health outcomes of the individual. In this thesis, we were particularly interested in the associations between social support (measured as perceived social support) and health-related outcomes (assessed as functional status and suicidal ideation).

**Social support and functional status**
We identified only a weak association between social support and overall functional status in OSA patients. Still, we found that social support was strongly associated with one functional status subscale, i.e. intimacy-sexual relationships. Beyond the increasing interest in the associations between sleep disorders and a couple's intimate relationships, some specific consequences of OSA such as the high incidence of erectile dysfunction (Schulz et al., 2019), or experienced sexual dysfunction in female OSA patients (Yilmaz et al., 2017) make the investigation of intimate relationships worthwhile. The role of social support in couples may be significant, since relationship satisfaction represents a relevant variable in enhancing the QoL and helps to diminish psychological distress in OSA patients (Baron et al., 2009). Moreover, improving intimate relationships may be crucial as better relationship quality was identified as being the most important need expressed by untreated OSA patients (Broström et al., 2007).

**Social support and suicidal ideation**
The importance of social support was consistently described across multiple theories of suicidal behaviour. The sociological theory of suicide (Durkheim and Simpson, 1951), the psychache theory of suicide (Shneidman, 1993), the arrested flight model (Williams, 2001), and the interpersonal-psychological theory of suicide (Joiner, 2007; Mars et al., 2019) suggest that inadequate social support, lack of strong interpersonal relationships, and perception of low belonginess may increase the risk for suicidal ideation and suicidal attempts. Perception of social support was found to represent a protective factor for suicidal ideation and behaviours (Rowe et al., 2006). Surprisingly, we found only a weak, non-significant association between perceived social support and suicidal ideation in OSA patients. The lack of the association between social support and suicidal ideation in our study may be explained by the presence of severe sleep-related problems in OSA patients. In line with this hypothesis, individuals with severe sleep deprivation report being less sociable (Haack and Mullington, 2005). Previous research also showed that the association between perceived and received social support may be reciprocal and people who reported giving less social support also reported getting less support (Piferi et al., 2006). Families of OSA patients also described their relationships and their overall QoL as negatively affected by OSA of their relatives or partners (Parish and Lyng 2003; Brown, 2005; Luyster et al., 2016; Bergeron et al., 2017). Moreover, people may be less willing to interact with an extremely sleep-deprived person (Sundelin et al., 2017). Thus, it should be considered that in case of extreme sleep-related OSA

symptoms, the sources of social support may be of less importance as well as of less adequacy, which may reduce resilience and increase the risk of suicidal behaviour when difficulties are encountered.

### 8.2.3 Towards a bio-psycho-social approach for OSA

*"Macbeth does murder sleep, the innocent sleep,*
*Sleep that knits up the ravell'd sleeve of care,*
*The death of each day' s life, sore labour's bath,*
*Balm of hurt minds, great nature's second course,*
*Chief nourisher in life's feast"*

William Shakespeare, Macbeth

The aforementioned findings of the lack of the CPAP treatment effect on overall and psychological QoL call into question the identification of factors that may help to improve impaired health outcomes in OSA patients. All in all, the studies presented in this thesis revealed that sleep-related problems, including night-time sleep quality, dayime sleepiness, and fatigue explained more variance in health outcomes, when compared to psychological or social factors. Thus, the treatment of sleep-related problems should be recommended as a main practical tool for promoting mental health and daily functioning in OSA patients.

This thesis also revealed that factors related to external resources such as self-perceived social support and coping self-efficacy for the ability to get support from family and friends explained less variance in health outcomes when compared to intra-individual psychological resources such as mastery and coping-self-efficacy for the ability to stop unpleasant emotions and thoughts and problem-focused coping.

A possible explanation may be that sleep-related problems hamper social interactions (Haack and Mullington, 2005; Cappuccio et al., 2010). Moreover, because of the tendency to disengage from stressful situations (e.g. Reishtein et al., 2006; Kang et al, 2018), interpersonal sensitivity (Kang et al, 2018), or negative feedback provided from patients´ relatives, partners (Parish and Lyng 2003; Brown, 2005; Schwarzer, 2014; Luyster et al., 2016; Bergeron et al., 2017; Sundelin et al., 2017), or co-workers (Reishtein et al., 2006), OSA patients may do little to improve their social interactions. Another reason why the social support may be insufficient is that the person is not able to cope in an adaptive manner. Paradoxically, those individuals who have valuable personal resources such as competence, high self-esteem, internal locus of control, and optimism were found to elicit a stronger tendency in others to provide social support. The expression of too much distress strains the social network, evokes negative reactions, and turns away those who would have been supportive (Schwarzer, 2014).

Negative feedback from others may further booster social inhibition and serve as precursor to social isolation and loneliness. Neuroimaging techniques also showed that loneliness may consequently lead to an increased level of hypervigilance to hostile

cues and a negative attitude towards others (Cacioppo et al., 2016). Moreover, higher levels of anxiety or hostility identified in OSA patients (Lau et al., 2014; Unal et al., 2017; Wiersema et al., 2018) may be associated with a lack of ability to communicate with others (Perfect et al., 2013), social inhibition, social dysfunction (Sasaki and Yamasaki, 2002), and oppositional orientation towards others (Houston and Vavak, 1991). Thus, it may be assumed that patients with OSA, identified as hostility-prone, may have even poorer motivation to participate in social activities.

Nevertheless, we should also consider the ways in which the bio-psycho-social factors have the capacity to influence and restructure each other over time (Jull, 2017; Haslam et al., 2018). Moreover, if the hypothesis based on the hyperarousal theory and the theory of entrapment can be confirmed, then the next step is to reveal whether a decrease in psychological distress with adequate treatment induces daytime sleepiness in OSA patients (Krakow et al., 2015).

We may also ask: "Are sleep problems only symptoms or also causes and consequences of other OSA-related problems?" Shakespeare says it rather well: it may be all three. First, lack of sleep is a cause of distress and ill health. If we miss sleep, we miss the balm of hurt minds. Second, Macbeth's distress murders sleep. Sleep disturbance is a consequence of the circumstances of people´s life. Third, Lady Macbeth's heart is sorely charged and her sleep is disturbed. Sleep disturbance is a symptom of psychological distress or perhaps other disease. Moreover, these three domains – causes, consequences, and symptoms, can all interact. Sleep-related problems can not only be a result of disorder, but can in turn, cause other problems (Marmot, 2010).

The abovementioned examples illustrate that the possibility of interaction between causes, consequences, and symptoms in the bio-psycho-social model must always be considered, as it is important to sort out which of the three is dominant, as interventions might differ (Marmot, 2010). All in all, failure to recognise the 'fluidity' in the bio-psycho-social model lessens the appreciation of the variety within, as well as the associations between its domains, and the relative importance of each factor in the individual patient at initial and progressive time points could have negative impact on disease management. Thus, the graphical presentation of the bio-psycho-social factors as three mainly symmetrical areas can cause misleading information or errors in the clinical reasoning (Haslam et al., 2018). Therefore, when interpreting our results, we need to consider the relative and variable contributions of each domain of the bio-psycho-social model to individual patients' presentations over time (Jull, 2017; Haslam et al., 2018).

Although the bio-psycho-social model has been successfully applied to obtain a better theoretical understanding of the causes of the disease and its processes, or for public health purposes (Alonso, 2004), unfortunately, it has not yet been included in a model of medical practice (Wade and Halligan, 2017; Hadi et al., 2017). Nevertheless, as Engel (1978) pointed out, even though both patient and doctor may culturally adhere to the biomedical model, the patient's needs and ultimate criteria for defining disease are always psycho-social, even when the health complaints are physical. Thus, despite many drawbacks related to greater knowledge, personnel,

and time investment, which will probably continue to relegate the bio-psycho-social model to a secondary position in clinical practice (Wade and Halligan, 2017), the broadening of the health-care professionals' knowledge of the importance of psychological and social aspects may be beneficial for the patient (Alonso, 2004). Moreover, if the findings of OSA-related biological mechanisms involved in the spread of brain injuries resistent to CPAP treatment (Owen et al., 2018) and their consequent contribution to psychological symptomatology in OSA patients (Huang et al., 2019) can be confirmed, the next step should definitely include the adoption of appropriate psycho-social interventions in disease management.

## 8.3   Methodological considerations

The strenghts and limitations of the studies are described in more detail in the separate chapters of this thesis. A short synopsis of the main methodological considerations is presented below. First, the quality of the study sample will be discussed. Second, the quality of the measuring instruments will be described. Finally, causality and confounding will be considered.

### 8.3.1  Quality of the sample

A strength of the study is that it was based on a sample with a wide age range (25-65 years) and a man-to-woman ratio of 3:1. Next, patients were diagnosed using PSG, which is considered the criterion standard for diagnosing OSA and determining disease severity. The indication for PSG was based on a general practitioner referral form while OSA was diagnosed based on an overnight sleep study carried out at a clinical laboratory. Medical examinations were carried out by a pulmonologist specialized in sleep-disordered breathing. To ensure that health outcomes were not influenced by major comorbidities such as stroke, comorbid sleep-disorders or diseases associated with the use of sedatives or hypnotics, we studied recently-diagnosed, mild to severe OSA patients with minimal comorbidities, who had not started treatment. Only OSA patients between 18 and 65 years of age were included due to possible increased vulnerability, functional changes and a decline in abilities and/or performance related to age. We also excluded participants in shift work, due to the negative impact of shift work on QoL (Kaliterna et al., 2004), well-being (Nezamodini et al., 2014), mood, alertness (Cori et al., 2018), and quality of sleep (Nezamodini et al., 2014). Thus, the findings are not generalizable to the general working population including shift workers, only to workers with regular working time arrangements. It may be assumed that the results may be even worse when shift workers are included. It should further be noted, that our sample with minimal co-morbidities and recent diagnosis may be not fully representative of the general OSA population. Another major limitation concerns the small sample size. Finally, in our sample, the majority of OSA patients was male. Thus, the results may be less generalizable to female OSA patients.

### 8.3.2 Quality of the measuring instruments

Patients' reported outcome measures (PROMS) increasingly accompany the traditional clinical way of measuring health and the effect of treatment in various chronic diseases (Weldring and Smith, 2013; Appleby et al., 2016), including OSA (Tam et al., 2014). A clear strenght of this thesis is that it aimed to get more insight into less known factors underlying adaptive functioning of OSA patients. To our best knowledge, this is the first time that the Work Role Functioning Questionnaire has been used in a sample of OSA patients. It is also the first study using the Pittsburgh Sleep Quality Inventory factor structure in an OSA population. Although we used valid and reliable measures of the relevant constructs, some limitations should be noted. A major limitation concerns that we used self-reported measures and no formal psychiatric diagnosis of suicidal ideation or anxiety was established. Another limitation is that the OSA diagnosis was based on a single sleepover. Although a one-night PSG is sufficient for the diagnosis of OSA (Scholle et al., 2003; Gouveris et al., 2010), significant variability in the AHIs taken from two nights was revealed in OSA patients (Gouveris et al., 2010). Many studies have further shown that AHI may not be able to quantify the disease severity (e.g. Ryu et al., 2016) and complications such as clinical impact of OSA on self-reported health outcomes, including QoL (Moyer et al., 2001), or psychological distress (Asghari et al., 2012). Another source of concern may be the length of the used questionnaires, which may have influenced the data quality, especially in patients with sleep-related problems. To overcome this methodological limitation, the questionnaires were sent to the patients three weeks before the PSG examination by postal mail, so they had enough time to fill them in at home.

### 8.3.3 Causality and confounding

Due to the cross-sectional design of the study, causal inferences cannot be made. Although we adjusted for key covariates that have consistently been associated with health outcomes in OSA patients, including sociodemographic and clinical variables; we did not adjust for all possible confounders. Thus, we cannot rule out the possibility of residual confounding that may account for the associations between the examined variables.

## 8.4  Implications

In clinical sleep medicine, the focus has shifted from OSA diagnosis to OSA management, with the emergence of new, integrated models of care (Heatley et al., 2013). Multidisciplinary OSA treatment can help to minimize fragmentation of care (Shelgikar et al., 2014), to improve the risk assessment for the consequences of untreated OSA, and can lead to better treatment strategies (Kapur, 2018). Results of this study may be helpful in identifying bio-psycho-social factors associated with poor health outcomes that can be modified by health care professionals and by the patients themselves.

### 8.4.1 Implications for clinical practice

We found that medical treatment of OSA may help to improve physical symptoms of the disease, whereas existing psychological impairment still cannot be successfully alleviated. Therefore, the current research and clinical practice should focus not only on the standard treatment of OSA, but also on ensuring that psychological symptoms are efficiently managed.

As impaired work functioning was reported by 82% of the OSA patients, employee assessment of their work functioning may be an important proxy for the health burden of OSA. There is also a need for workplace strategies that encourage behaviours and practices that may be helpful in reducing OSA-related symptoms and improve work functioning in OSA patients. Occupational health professionals may together with OSA patients find ways to address the specific work demands that are difficult to conduct. Management of unsatisfactory sleep through a variety of proven strategies, including naps, better management of work demands, regular exercise, duty hour considerations, and instruction on the basics of sleep hygiene including stimulating activities prior to bedtime, ingestions, and bedtime rituals (Jansson and Linton, 2006; Kushida, 2007) may be helpful.

Further, our findings may enhance health care professionals' understanding of the mental health problems in OSA patients. Health care professionals should keep in mind that OSA may not be immediately apparent but might present in an atypical fashion. The presence of some atypical psychological OSA-related symptoms revealed in this study, was also identified in previous research (Krakow et al., 2015; Choi et al., 2015; Unal et al., 2017) and may include anxiety, hostility, or suicidal ideation. A lack of knowledge regarding the heterogeneity of OSA's clinical presentation may pose critical challenges to its clinical recognition, resulting in missed or delayed diagnosis. Moreover, the lag time between initial OSA symptoms and OSA diagnosis can vary widely, with the average duration from seven to ten years (Guilleminault et al., 1995; Rahaghi and Basner, 1999). People with atypical or less known OSA symptomatology may have had a longer lag time, leading to a longer duration of exposure to untreated OSA and, thus, a higher probability of developing comorbidities. All in all, primary care providers represent the key to successful case finding. Therefore, it is essential to promote an understanding of the signs and symptoms of OSA. Simple questions about key OSA symptoms such as snoring, witnessed nocturnal apnoeas, and sleep-related problems, together with questions about atypical psychological symptoms should become a routine component of the medical interview.

Health care professionals also have to be informed about the alarming prevalence's of overall psychological distress (56.0%) and suicidal ideation (20.1%) in OSA patients. As suicidal ideation and behaviour may be largely preventable (Stanley and Brown, 2012; Simon, 2014) by early detection, preventive education of caregivers and relatives about the high prevalence of suicidal ideation in OSA patients may be important. Based on the strong relationship between poor sleep quality, fatigue and suicidal ideation, we recommend health care professionals to

consider investigating and monitoring suicidal ideation in people with sleep-related disorders. Sleep problems are a modifiable risk factor for suicidal thoughts and behaviours (Littlewood et al., 2019). Thus, the education of OSA patients on basic sleep hygiene may improve the quality of sleep and decrease fatigue. OSA patients with psychological symptoms and/or sleep-related problems may suffer from decreased activity and reduced social participation (e.g. Haack and Mullington, 2005), and consequently may have poor motivation to seek health care. Therefore, an OSA diagnosis may represent an early opportunity for health care providers to discuss mental health with their patients. Health care professionals' communication skills, particularly related to a frank and clear discussion of suicidality, should be developed through training courses. Because assessing suicidality in medical settings may be challenging, the use of self-administered screening questionnaires that identify patients at risk of suicidality could be a promising strategy (Kye and Park, 2017). Our results further indicated that anxiety was strongly associated with poor-nighttime sleep quality and impaired work functioning. Anxiety, especially at severe and panic levels, has a major impact on night-time sleep and breathing, which may in turn exacerbate OSA symptoms and contribute to difficulties with CPAP adaptation (Shapiro, 2014). Therefore, screening for anxiety at the time of OSA diagnosis with a simple, cost-effective self-rating tool may improve reporting of anxiety symptoms among OSA patients, and in turn, may help to improve assessment of OSA in primary care settings.

Another source of concern is that sleep disorders along with OSA are rarely assessed on a regular basis by mental health professionals in patients suffering from psychological distress. The presence of the sleep-wake complaints in a patient's profile, and the onset of those complaints prior to the development of the psychological symptomatology, should draw the mental health professional's attention to a potential concurrent or underlying OSA. Screening for symptoms associated with OSA can easily be integrated in symptom screening in a psychiatric interview (Braitman, 2018). Additionally, it is important for mental health professionals to understand that the routinely prescribed psychiatric medications may affect OSA. Thus, identifying patients with overlapping diagnoses of mental disorders and OSA may help to improve their treatment outcomes through more careful dosing of pharmacotherapy and CPAP treatment. Especially, sedation medications should be used with caution, as they were found to exacerbate OSA (Weatherspoon et al., 2016). Notably benzodiazepines are considered to be inappropriate due to potential adverse effects, such as increased risk for adverse respiratory events, decrease in wakefulness and airway muscle tone, as well as weak response to hypoxemia (Hanly and Powles, 1993; Kushida, 2007; Zhang, et al., 2014; Kao et al., 2018). Benzodiazepines have the potential to cause next-day hangover and may contribute to fatigue and cognitive impairment already experienced by individuals with OSA (Kushida, 2007). Furthermore, patients with coexisting OSA and mental disorders may respond less well to antipsychotic medications than psychiatric patients without OSA (Gupta and Simpson, 2015).

Targeted psychological interventions, such as psychotherapy which starts early in the OSA disease trajectory, may help to prevent serious problems later on. Our study revealed that both high hostility and poor coping self-efficacy may result in a higher level of psychological distress in OSA patients. Considering our findings, we may conclude that the use of adaptive coping self-efficacy may be used as a gateway to improve overall psychological well-being and to diminish the negative effect of hostility on psychological well-being in OSA patients. Although hostility is a relatively stable personality trait, coping self-efficacy can be actively modified, e.g. by cognitive behavioural therapy. Given that sense of mastery was found to represent a skill of importance to daily functioning, interventions focused on mastery enhancement may be a part of an integrated OSA care model. Specifically, brief interventions may be applied for the improvement of the functional status, as mastery seems to be responsive to short-term psychological treatment (Zautra et al., 2012).

### 8.4.2 Implications for future research

Clearly, more high-quality studies with larger study populations and with longer treatment duration are needed to better understand the effect of CPAP treatment on QoL in OSA patients. Yet, further longitudinal research is required to reveal how and to what extent social and psychological resources are relevant and effective in ameliorating the impact of OSA-related symptomatology and whether they can be of use in targeting interventions. The lack of widely acknowledged, tested and proven explanatory models of the pathophysiological mechanisms to understand the relationships between anxiety, suicidal ideation, sleep-related problems and OSA may be a barrier for understanding the clinical relevance of these conditions. Therefore, examining these factors over time may help to properly address the revealed associations in a more comprehensive way. Next, since major comorbidities may influence sleep and affective symptoms, a detailed assessment of OSA patients with various categories of major comorbidities will further extend our knowledge.

Another key challenge of future research is our limited knowledge of the factors that determine suicidal behaviour, i.e., which individual with suicidal ideation will act on this ideation (O'Connor, 2017). Thus, it is important to examine the inter-relationships between sleep disturbances, suicidal ideation, and other symptoms of OSA, which will provide novel insights into the specific pathways by which sleep-related symptoms contribute to the occurrence of suicidal ideation. Future research should include both objective and subjective assessments of key sleep parameters to ascertain suicide risk among OSA patients. Because suicidality can reflect a wide range of factors that can have various effects in different sociocultural contexts, more research is needed to explore the long-term effects of OSA on suicidality, while considering comprehensive psycho-social factors.

Our findings indicate that coping self-efficacy for the ability to stop unpleasant emotions and thoughts may be the most closely associated with diminishing of psychological distress in OSA out of the three studied coping strategies. Previous

research demonstrated that emotional suppression may be less adaptive in reducing psychological distress and symptoms over a longer time span (Wenzlaff and Wegner, 2000; Gross and Thompson, 2007). Thus, longitudinal studies are needed to verify the role of coping self-efficacy for the ability to stop unpleasant emotions and thoughts in diminishing the negative effect of OSA-related symptoms on psychological well-being in OSA patients. Finally, as social support was strongly associated with one functional status subscale, i.e. intimacy-sexual relationships, another area that merits further attention is the patient-partner dyad. With respect to the clinical importance of our study, the revealed significance of sources of social support in intimate relationships should be addressed as previous research identified poor health-related outcomes not only in OSA patients, but also in their bed-partners (Parish and Lyng 2003; Luyster et al., 2016).

## Conclusion

The results of this thesis confirmed the previous findings of a very small improvement in self-reported health outcomes with CPAP treatment in OSA patients. Based on the results of our meta-analysis, we may assume that medical treatment of OSA may help to improve physical symptoms of OSA, whereas existing psychological impairment still cannot be successfully alleviated. We further found that psychological factors, together with some biological and social factors, are associated with health-related outcomes in OSA patients. As we found strong associations between sleep-related problems and self-reported health outcomes, we recommend health care professionals to intervene on sleep to reduce psychological distress and impaired daytime functioning in OSA patients. Our findings indicate that factors related to external resources such as social support and coping self-efficacy for the ability to get support from family and friends, may be of less importance in influencing health outcomes when compared with patients' intra-individual psychological factors such as coping self-efficacy for stopping unpleasant emotions and thoughts, problem focused coping, and mastery. Based on these results we may further assume that helping OSA patients to strengthen their intra-individual psychological resources may be an important strategy to attenuate the negative impact of OSA-related symptoms. However, longitudinal research is needed to confirm our results.

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"Unlike stories, real life, when it has passed, inclines toward obscurity, not clarity."

Elena FERRANTE

# Summary

This thesis studied patients with obstructive sleep apnoea (OSA) who face the burden of this chronic disease in their everyday lives. OSA represents one of the most widespread sleep disorders that requires lifetime care. It has serious consequences, not only for patients and their families, but also for society as a whole. Thus, regarding clinical care, one of the main goals is to improve patients' daily functioning and well-being. While medical treatment of OSA may help to improve physical symptoms of the disease, existing psychological impairment still cannot be successfully cured. Therefore, in clinical sleep medicine, the main focus has shifted from OSA diagnosis to OSA management, with the emergence of new, integrated models of care. Thus, this thesis seeks to address the psycho-social factors that have been identified as one of the key factors in the adaptation to various chronic diseases, but less are known in OSA yet. This thesis further aims to contribute to the understanding of the associations between biomedical factors and self-reported health outcomes in OSA patients that have been identified as ambivalent in previous research.

*Chapter 1* provides a general introduction of OSA. It further describes the key theoretical constructs of the thesis: continous positive airway pressure (CPAP) treatment, sleep-related problems, anxiety, hostility, coping self-efficacy, mastery over one's life and circumstances, and social support. Health-related outcomes were identified as quality of life (QoL), functional status, work functioning, and psychological distress, including suicidal ideation. This chapter also introduces the conceptual model of the associations between constructs examined in the thesis.

*Chapter 2* presents information about the study design. It describes the sample and procedure of the data collection, and settings used in the thesis. It also provides a description of the measures and used statistical analyses.

*Chapter 3* examines the effect of CPAP treatment on QoL, when compared to placebo pills, sham CPAP, and conservative treatment. We found no significant differences in overall and psychological QoL between CPAP treated patients and controls. However, physical QoL improved in CPAP treated patients compared with control treatments. Furthermore, subgroup analyses and sensitivity analyses showed that the type of control group, the study design, OSA severity, and risk of bias may be relevant in capturing the effect of CPAP on QoL. However, high-quality trials with low risk of bias and more participants are needed for further investigation of the effect of CPAP treatment on QoL improvement.

*Chapter 4* examines whether OSA-severity, sleep-related problems, and anxiety are associated with work functioning in OSA patients when controlled for age, gender, and type of occupation. It also investigates whether anxiety moderates the associations between sleep-related problems and work functioning. We found that the majority of working OSA patients was anxious and had impaired work functioning. The results of our study further showed that poor night-time sleep quality and anxiety
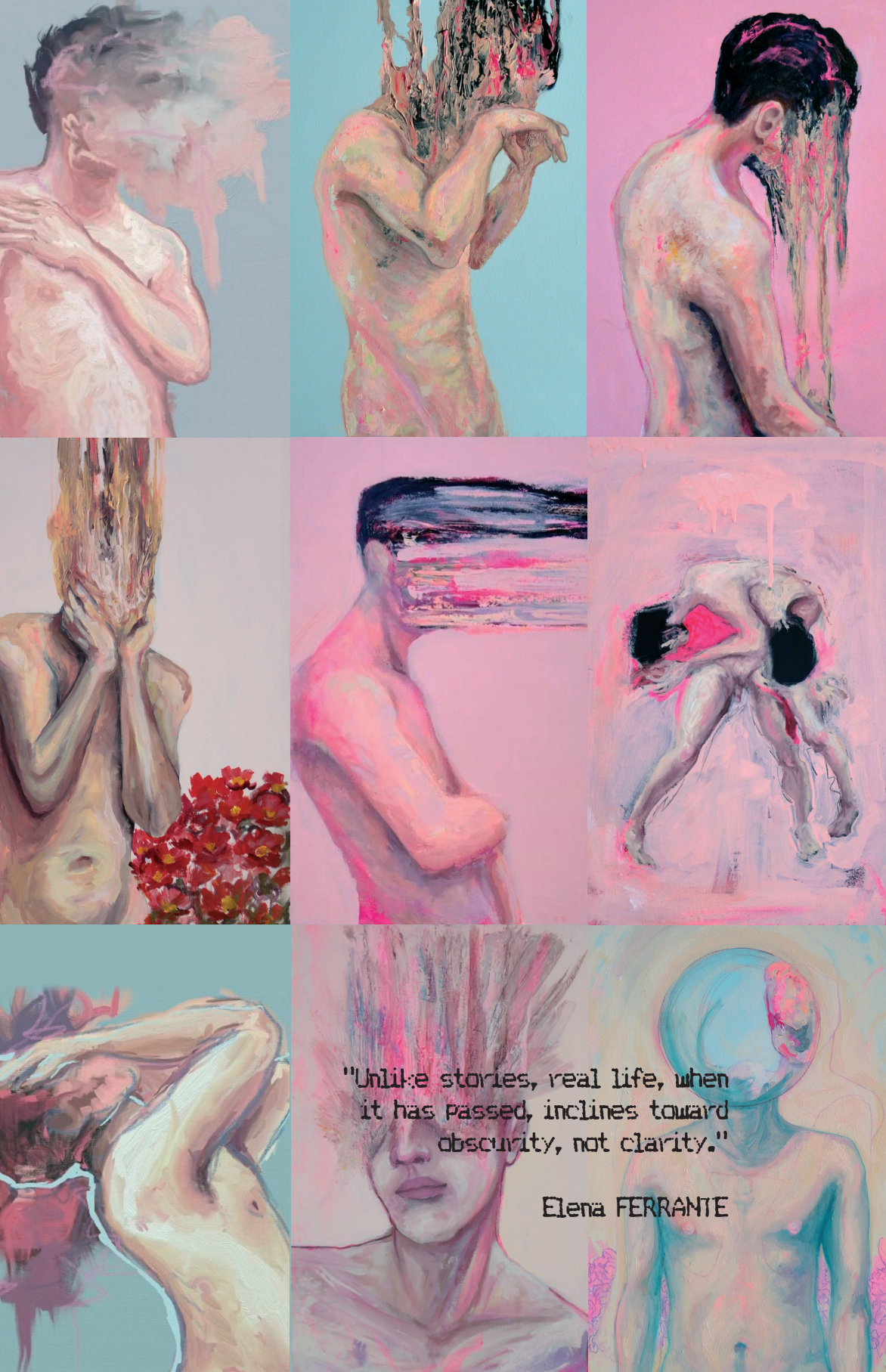
were associated with impaired work functioning. The moderating effect of anxiety on the association between night-time sleep quality and work functioning was especially strong in patients with better sleep quality, while the effect of anxiety on the association between night-time sleep quality and work functioning was negligible in case of worse sleep quality.

*Chapter 5* examines the associations between hostility, coping self-efficacy and psychological distress in OSA patients when controlled for sociodemographic, clinical, and sleep-related variables. It further explores whether coping self-efficacy dimensions mediate the association between hostility and psychological distress. Our study revealed that hostility and poor coping self-efficacy were strongly associated with psychological distress in OSA patients. We also found that all coping self-efficacy dimensions mediated the association between hostility and psychological distress. Our sudy further provided the evidence that coping self-efficacy for stopping unpleasant emotions and thoughts was found to be the most adaptive strategy in OSA patients.

*Chapter 6* describes the prevalence of suicidal ideation in patients with OSA. It also examines the associations between OSA severity, sleep-related problems, social support and suicidal ideation in OSA patients. Our findings suggest that suicidal ideation is highly prevalent among OSA patients (20.1%). Poor night-time sleep quality and fatigue were directly related to suicidal ideation, however OSA severity and social support were not. The adjustment for sociodemographic variables did not change the association between social support and suicidal ideation either. Sleep quality mediated the effect of OSA severity on suicidal ideation.

*Chapter 7* examines the associations between social support, mastery, sleep-related problems and functional status in patients with OSA when controlled for sociodemographic and clinical variables. It also investigates the mediating role of social support and mastery in the association between sleep-related problems and functional status. Our results provided suggestive evidence that low level of social support, poor mastery, disturbed night-time sleep quality, and daytime sleepiness were associated with an impairment in functional status in OSA patients. While social support was weakly associated with functional status, we found a strong association between mastery and overall functional status in OSA patients. The subscale analyses showed that social support was strongly associated with one functional status subscale, i.e. intimacy-sexual relationships, while mastery was associated with all functional status subscales in the final models. We found that mastery mediated the association between sleep-related problems and functional status. However, no mediating role of social support in the association between sleep-related problems and functional status was observed.

Finally, in *Chapter 8* we summarise the key findings as presented in the Chapters 3-7, discussed them in the context of contemporary scientific research and provided implications. In line with previous studies, the results of our meta-analysis confirmed that CPAP treatment may help to improve physical symptoms of OSA, whereas existing psychological impairment still cannot be successfully cured. Therefore, the current research and clinical practice should focus not only on the standard treatment of OSA, but also on ensuring that psychological symptoms are efficiently managed.

Our findings may also enhance health care professionals' understanding of the mental health problems in OSA patients. Next, our study provided evidence for high prevalence of overall psychological distress in OSA patients including suicidal ideation and anxiety. Thus, the necessity of monitoring psychological symptoms in OSA patients during clinical care should be highlighted. The education of people with OSA on basic sleep hygiene and application of behavioural interventions may improve the quality of sleep and decrease fatigue strongly associated with self-reported health outcomes. Health care professionals may also directly recommend targeted psychological care, which starts early in the OSA trajectory and may help to prevent serious problems later on. Moreover, identifying patients with overlapping symptoms of mental disorders and OSA may help to improve the diagnostic process and treatment outcomes through careful dosing of pharmacotherapy and use of CPAP treatment.

Another interesting observation to emerge from our study was that the external resources related to social support explained less variance in health outcomes when compared to intra-individual psychological resources such as mastery and coping-self-efficacy focused on stopping unpleasant emotions and thoughts or problem focused coping self-efficacy. Based on these results we may conclude that helping OSA patients to strengthen their intra-individual resources may be one of the important protective strategies, attenuating the negative impact of OSA-related symptoms. Therefore, encouraging mastery over ones' life and circumstances, and dispelling coping self-efficacy may be paramount in improving functional status and handling the psychological distress in OSA patients. Still, we found that social support was strongly associated with one functional status subscale, i.e. intimacy-sexual relationships. Thus, the revealed significance of sources of social support in intimate relationships should be addressed as previous studies identified poor health-related outcomes not only in OSA patients, but also in their bed-partners.

Chapter 8 also addresses the methodological considerations and future research implications of the study. Strengths of this study include OSA diagnosis stated using polysomnography. Results of our study may be helpful in identifying bio-psycho-social risk factors of poor health outcomes that can be modified by health care professionals or by the patients themselves. Multidisciplinary OSA care can help to reduce effort duplication, minimize fragmentation of care, control costs, improve risk assessment for the consequences of untreated OSA, and lead to better treatment strategies. All in all, our study has led us to conclude that impairment of health outcomes in OSA patients may not be solely due to biomedical factors or the effect of OSA itself. Rather, psychological factors such as anxiety, hostility, the choice of coping strategies, or mastery, may play a key role in determining the experience of poor health. However, further longitudinal confirmation of our results is needed.

# Sammenvattig

Dit proefschrift bestudeert patiënten met obstructieve slaapapneu (OSA) die in hun dagelijks leven geconfronteerd worden met de last van deze chronische ziekte. OSA is een van de meest voorkomende slaapstoornissen waarvoor levenslang zorg nodig is. Het heeft ernstige gevolgen, niet alleen voor patiënten en hun families, maar ook voor de samenleving als geheel. Wat klinische zorg betreft, is één van de hoofddoelen het verbeteren van het dagelijks functioneren en welzijn van patiënten. Hoewel medische behandeling van OSA kan helpen de fysieke symptomen van de ziekte te verbeteren, kunnen bestaande psychische klachten nog steeds niet met succes worden genezen. In de klinische slaapgeneeskunde is met de opkomst van nieuwe, geïntegreerde zorg-modellen de nadruk verschoven van de OSA-diagnose naar het omgaan met OSA. Dit proefschrift zal ingaan op de psychosociale factoren die zijn geïdentificeerd als sleutelfactoren bij de aanpassing aan verschillende chronische ziekten, maar bij OSA zijn er minder zulke factoren bekend. Dit proefschrift beoogt verder bij te dragen aan het begrip van de associaties tussen biomedische factoren en zelfgerapporteerde gezondheid bij OSA-patiënten die in eerder onderzoek als niet-doorslaggevend zijn geïdentificeerd.

In *Hoofdstuk 1* wordt een algemene introductie van OSA gegeven. De belangrijk-ste theoretische constructen van het proefschrift worden beschreven: continue posi-tieve luchtweg-druk (CPAP), slaapgerelateerde problemen, angst, vijandigheid, zel-fredzaamheid, eigen effectiviteit, beheersing van iemands leven en omstandigheden, en sociale steun. De gezondheidsgerelateerde uitkomstmaten die zijn gebruikt zijn kwaliteit van leven (KvL), functionele status, functioneren in het werk en psychische klachten, inclusief zelfmoordgedachten. Dit hoofdstuk introduceert ook het concep-tuele model van de verbanden tussen de constructen die in het proefschrift zijn onder-zocht.

*Hoofdstuk 2* geeft informatie over de onderzoeksopzet. Het beschrijft de steekproef en de procedure van de gegevensverzameling die in het proefschrift zijn gebruikt. Het geeft ook een beschrijving van de meetinstrumenten en gebruikte statistische analyses.

In *Hoofdstuk 3* wordt het effect van CPAP-behandeling op KvL onderzocht, in vergelijking met placebo-pillen, schijn-CPAP en conservatieve behandeling. We vonden geen significante verschillen in de totale en psychologische KvL tussen met CPAP behandelde patiënten en controles. De fysieke KvL verbeterde echter bij met CPAP behandelde patiënten in vergelijking met de controlebehandelingen. Verder toonden subgroepanalyses en sensitiviteitsanalyses aan dat het type controlegroep, de onderzoeksopzet, de ernst van OSA en het risico op bias relevant kunnen zijn bij het bepalen van het effect van CPAP op de KvL. Kwalitatief hoogwaardige onderzoeken met een laag risico op bias en meer deelnemers zijn nodig voor verder onderzoek naar het effect van CPAP-behandeling op KvL verbetering.

In *Hoofdstuk 4* wordt onderzocht of de ernst van OSA, slaapgerelateerde problemen en angst geassocieerd zijn met het functioneren in het werk bij OSA-patiënten als gecontroleerd wordt voor leeftijd, geslacht en type beroep. Ook wordt onderzocht of angst de verbanden tussen slaapgerelateerde problemen en functioneren in het werk beinvloedt. We vonden dat de meerderheid van de werkende OSA-patiënten angstig was en dat het functioneren in het werk belemmerd was. De resultaten van onze studie toonden verder aan dat slechte nachtelijke slaapkwaliteit en angst geassocieerd waren met een verminderd functioneren in het werk. Het modererende effect van angst op het verband tussen nachtelijke slaapkwaliteit en functioneren in het werk was vooral sterk bij patiënten met een betere slaapkwaliteit, terwijl het effect van angst op het verband tussen nachtelijke slaapkwaliteit en functioneren in het werk te verwaarlozen was in het geval van slechte slaapkwaliteit.

In *Hoofdstuk 5* worden de verbanden onderzocht tussen vijandigheid, eigen effectiviteit en psychische klachten bij OSA-patiënten als deze gecontroleerd worden voor sociodemografische, klinische en slaapgerelateerde variabelen. Verder wordt onderzocht of dimensies van eigen effectiviteit het verband tussen vijandigheid en psychische klachten mediëren. Onze studie toonde aan dat vijandigheid en lage eigen effectiviteit sterk geassocieerd waren met psychische klachten bij OSA-patiënten. We ontdekten ook dat alle dimensies van eigen effectiviteit het verband mediëerden tussen vijandigheid en psychische klachten. Ons onderzoek leverde verder op dat eigen effectiviteit in de zin van het stoppen van onaangename emoties en gedachten de meest adaptieve strategie bleek te zijn bij OSA-patiënten.

In *Hoofdstuk 6* wordt de prevalentie beschreven van suïcidale gedachten bij patiënten met OSA. Ook worden de verbanden onderzocht tussen de ernst van OSA, de slaapgerelateerde problemen, de sociale steun en de suïcidale ideeën bij OSA-patiënten. Onze bevindingen suggereren dat suïcidale ideeën zeer gangbaar zijn bij OSA-patiënten (20,1%). Slechte nachtelijke slaapkwaliteit en vermoeidheid waren direct gerelateerd aan suïcidale ideeën, maar de ernst van OSA en sociale steun waren dat niet. De controle voor sociodemografische variabelen veranderde ook het verband tussen sociale steun en suïcidale ideeën niet. Slaapkwaliteit mediëerde het effect van OSA-ernst op suïcidale gedachten.

In *Hoofdstuk 7* worden de verbanden onderzocht tussen sociale steun, beheersing, slaapgerelateerde problemen en functionele status bij patiënten met OSA die gecontroleerd werden voor sociodemografische en klinische variabelen. Ook wordt de mediërende rol van sociale steun en beheersing in het verband tussen slaapgerelateerde problemen en functionele status onderzocht. Onze resultaten leverden suggestief bewijs op dat een laag niveau van sociale steun, een slechte beheersing, verstoorde nachtelijke slaapkwaliteit en slaperigheid overdag een verband hebben met een verslechtering van de functionele status bij OSA-patiënten. Hoewel er tussen sociale steun en functionele status een zwak verband was, vonden we een sterk verband tussen beheersing en functionele status bij OSA-patiënten. De subschaalanalyses toonden aan dat sociale steun sterk geassocieerd was met één subschaal van functionele status, te weten die van intimiteit-seksuele relaties, terwijl beheersing geassocieerd was met alle subschalen van functionele status in de uiteindelijke modellen. We ontdekten

dat beheersing het verband tussen slaapgerelateerde problemen en functionele status mediëerde. Zo een mediërende rol werd niet van sociale steun waargenomen met betrekking tot het verband tussen slaapgerelateerde problemen en functionele status.

Tenslotte vatten we in *hoofdstuk 8* de belangrijkste bevindingen samen zoals gepresenteerd in de hoofdstukken 3-7, we bespreken de bevindingen in de context van het hedendaags wetenschappelijk onderzoek en geven implicaties aan. In overeenstemming met eerdere studies, bevestigden de resultaten van onze meta-analyse dat CPAP-behandeling kan helpen om fysieke symptomen van OSA te verbeteren, terwijl bestaande psychische klachten nog steeds niet met succes kunnen worden behandeld. Daarom moet het huidige onderzoek en de klinische praktijk niet alleen gericht zijn op de standaardbehandeling van OSA, maar ook op het waarborgen van een efficiënte behandeling van psychische problemen. Onze bevindingen kunnen ook de kennis van zorgverleners over psychische problemen bij OSA-patiënten verbeteren. Vervolgens liet ons onderzoek een hoge prevalentie van algemene psychische klachten bij OSA-patiënten zien, inclusief zelfmoordgedachten en angst. Daarom is het uitermate belangrijk deze psychische klachten bij OSA-patiënten tijdens de klinische zorg te monitoren. Het kennisniveau van OSA-patiënten over elementaire slaaphygiëne en de toepassing van gedragsinterventies kan de slaapkwaliteit verbeteren en vermoeidheid verminderen, en is sterk verbonden met de zelfgerapporteerde gezondheid. Gezondheidszorgprofessionals kunnen ook direct psychologische zorg op maat aanbevelen, die vroeg in het OSA-traject begint en later kan helpen ernstige problemen te voorkomen. Bovendien kan het identificeren van patiënten met symptomen van zowel psychische problemen en OSA helpen het diagnostische proces en de behandelresultaten door zorgvuldige dosering van farmacotherapie en het gebruik van de CPAP-behandeling te verbeteren.

Een andere interessante observatie die uit onze studie naar voren kwam, was dat de externe bronnen met betrekking tot sociale steun minder variantie in gezondheidsuitkomsten verklaarden in vergelijking met intra-individuele psychologische bronnen zoals beheersing en eigen effectiviteit die gericht is op het stoppen van onaangename emoties en gedachten of probleemgericht omgaan met zelfredzaamheid. Op basis van deze resultaten kunnen we concluderen dat het helpen versterken van intra-individuele bronnen bij OSA-patiënten één van de belangrijke beschermende strategieën kan zijn, waardoor de negatieve impact van OSA-gerelateerde symptomen wordt verzacht. Het aanmoedigen van beheersing van iemands leven en omstandigheden en eigen effectiviteit kunnen van groot belang zijn bij het verbeteren van de functionele status en het omgaan met de psychische klachten bij OSA-patiënten. Ook vonden we een sterk verband tussen sociale steun en één subschaal van functionele status, te weten de subschaal intimiteit-seksuele relaties. Daarom zou sociale steun in intieme relaties moeten worden aangepakt, ook omdat eerdere studies slechte gezondheidsgerelateerde uitkomsten rapporteerden, niet alleen bij OSA-patiënten zelf, maar ook bij hun bedpartners.

Hoofdstuk 8 behandelt ook de methodologische overwegingen en toekomstige implicaties van het onderzoek voor verder onderzoek en de praktijk. Sterke punten van deze studie zijn dat de diagnose OSA gesteld is met behulp van polysomnografie.

Resultaten van ons onderzoek kunnen helpen bij het identificeren van bio-psycho-sociale risicofactoren voor slechte gezondheidsuitkomsten, die kunnen worden aangepast door gezondheidszorgprofessionals of door de patiënten zelf. Multidisciplinaire OSA-zorg kan helpen een verdubbeling van inspanningen te verminderen, versnippering van zorg te minimaliseren, kosten te beheersen, risicobeoordeling voor de gevolgen van onbehandelde OSA te verbeteren en kan tot betere behandelstrategieën leiden. Al met al heeft ons onderzoek ons ertoe gebracht te concluderen dat een verslechtering van de gezondheidsuitkomsten bij OSA-patiënten mogelijk niet alleen te wijten is aan biomedische factoren of aan het effect van OSA zelf. Integendeel, psychologische factoren zoals angst, vijandigheid, de keuze van strategieën met betrekking tot eigen effectiviteit of beheersing kunnen een belangrijke rol spelen bij het bepalen van de ervaring van slechte gezondheid. Een bevestiging van onze resultaten in longitudinaal onderzoek is echter nodig.

# Zhrnutie

Obštrukčné spánkové apnoe (OSA) predstavuje jednu z najrozšírenejších porúch spánku, ktorá si vyžaduje celoživotnú liečbu. Toto ochorenie má vážne dôsledky nielen pre pacientov a ich rodiny, ale aj pre spoločnosť ako celok. Jedným z hlavných cieľov klinickej starostlivosti je zlepšiť každodenné fungovanie pacientov a ich well-being. Medicínska starostlivosť môže pomôcť zlepšiť fyzické príznaky ochorenia ale existujúce psychologické symptómy však stále nie je možné u pacientov s OSA úspešne vyliečiť. Vzhľadom na to presúva súčasná spánková medicína primárny dôraz z diagnostiky OSA na manažment ochorenia s využitím nových, integrovaných modelov starostlivosti. Cieľom tejto štúdie je popísanie úlohy psycho-sociálnych faktorov, ktoré boli identifikované ako jeden z kľúčových aspektov pri adaptácii na rôzne chronické ochorenia, ale sú menej známe v oblasti OSA. Táto práca sa ďalej snaží prispieť k pochopeniu asociácií medzi biomedicínskymi faktormi a seba-posudzovaným zdravím u pacientov s OSA, ktoré boli v predchádzajúcom výskume identifikované ako ambivalentné.

*Prvá kapitola* poskytuje všeobecný úvod do problematiky OSA. Ďalej opisuje kľúčové teoretické konštrukty tejto práce: liečbu kontinuálnym pozitívnym tlakom v dýchacích cestách (CPAP), problémy súvisiace so spánkom, anxietu, hostilitu, copingovú seba-účinnosť, schopnosť zvládania životných okolností a sociálnu oporu. Výstupy súvisiace so seba-posudzovaným zdravím boli identifikované ako kvalita života, funkčný stav, úroveň pracovnej funkčnosti a psychologické symptómy vrátane samovražedných myšlienok. Táto kapitola ďalej definuje konceptuálny model asociácií medzi konštruktmi skúmanými v tejto štúdii a jednotlivé výskumné otázky.

*V druhej kapitole* poskytujeme informácie o dizajne štúdie. V tejto kapitole popisujeme výskumnú vzorku, postup zberu údajov, použité nástroje merania a štatistické analýzy.

*Tretia kapitola* skúma efekt CPAP liečby na kvalitu života v porovnaní s placebo tabletami, simulovanou CPAP a konzervatívnou liečbou. U pacientov liečených CPAP sme nezistili významné rozdiely v celkovej a psychologickej kvalite života v porovnaní so skupinou pacientov podstupujúcou kontrolnú liečbu. Na druhej strane sme zistili, že fyzická kvalita života sa u pacientov liečených CPAP sa v porovnaní s kontrolnou skupinou signifikantne zlepšila. Analýzy ďalej ukázali, že typ kontrolnej skupiny, dizajn štúdie, závažnosť ochorenia a risk of bias môžu zohrávať relevantnú úlohu pri meraní účinku CPAP na kvalitu života. Na presnejšie stanovenie úrovne účinku CPAP liečby na kvalitu života pacientov s OSA je však potrebné väčšie množstvo kvalitných štúdií s nízkou úrovňou risk of bias a väčšou výskumnou vzorkou.

*Štvrtá kapitola* skúma či závažnosť OSA, problémy súvisiace so spánkom a anxieta súvisia s úrovňou pracovnej funkčnosti u pacientov s OSA. Pri overovaní našej výskumnej otázky sme uplatnili kontrolu asociácií vzhľadom na vek, pohlavie a typ zamestnania. Ďalším predmetom skúmania bolo posúdenie moderačného efektu

anxiety na asociácie medzi problémami súvisiacimi so spánkom a úrovňou pracovnej funkčnosti. Zistili sme, že väčšina pracujúcich pacientov s OSA vykazovala zvýšenú úroveň anxiety a zníženú úroveň pracovnej funkčnosti. Výsledky našej štúdie ďalej ukázali, že nízka kvalita nočného spánku a zvýšená úroveň anxiety súviseli so zníženou úrovňou pracovnej funkčnosti. Moderačný efekt anxiety na asociáciu medzi kvalitou nočného spánku a úrovňou pracovnej funkčnosti bol obzvlášť signifikantný u pacientov s lepšou kvalitou spánku, zatiaľ čo moderačný vplyv anxiety na asociáciu medzi kvalitou nočného spánku a úrovňou pracovnej funkčnosti bol zanedbateľný v prípade nízkej kvality spánku.

*Piata kapitola* skúma asociácie medzi hostilitou, copingovou seba-účinnosťou a psychologickým distresom u pacientov s OSA. Skúmané asociácie boli kontrolované berúc do úvahy sociodemografické, klinické a spánkové premenné. Táto kapitola ďalej skúma, či jednotlivé dimenzie copingovej seba-účinnosti mediujú asociáciu medzi hostilitou a psychologickým distresom. Naša štúdia ukázala, že hostilita a nízka úroveň copingovej seba-účinnosti boli u pacientov s OSA silne spojené s psychologickým distresom. Taktiež sme zistili, že všetky posudzované dimenzie copingovej seba-účinnosti mali mediačný efekt na asociáciu medzi hostilitou a psychologickým distresom. Táto štúdia ďalej poskytla dôkazy o tom, že najúčinnejšiu copingovú stratégiu u pacientov s OSA predstavuje seba-účinnosť zameraná na zastavenie nepríjemných emócií a myšlienok.

*Šiesta kapitola* opisuje výskyt samovražedných myšlienok u pacientov s OSA. Skúma tiež súvislosť medzi závažnosťou OSA, problémami súvisiacimi so spánkom, sociálnou oporou a samovražednými myšlienkami u pacientov s OSA. Naše zistenia naznačujú, že suicidálne myšlienky sú u pacientov s OSA alarmujúco prevalentné (20.1%). Nízka kvalita nočného spánku a únava vykazovali priamu súvislosť so samovražednými myšlienkami, avšak naša štúdia nenašla signifikantný vzťah medzi závažnosťou OSA, ospalosťou počas dňa, sociálnou oporou a suicidálnymi myšlienkami. Kontrola pre sociodemografické premenné neovplyvnila absentujúcu signifikanciu vzťahu medzi ospalosťou počas dňa, sociálnou oporou a samovražednými myšlienkami. Kvalita spánku mala mediačný efekt na vzťah medzi závažnosťou OSA a samovražednými myšlienkami.

*Siedma kapitola* skúma asociácie medzi sociálnou oporou, úrovňou zvládania životných okolností, problémami súvisiacimi so spánkom a funkčným stavom u pacientov s OSA. Skúmané asociácie boli kontrolované berúc do úvahy sociodemografické a klinické premenné. Táto kapitola zároveň skúma mediačný efekt sociálnej opory a úrovne zvládania životných okolností na asociáciu medzi problémami súvisiacimi so spánkom a funkčným stavom. Naše výsledky poskytli sugestívne dôkazy o tom, že nízka úroveň sociálnej opory, nízka schopnosť zvládania, narušená kvalita nočného spánku a denná ospalosť boli u pacientov s OSA spojené s nízkou úrovňou funkčného stavu. Zatiaľ čo sociálna opora bola len nevýrazne asociovaná s celkovým funkčným stavom, zistili sme signifikantnú asociáciu medzi schopnosťou zvládania a celkovým funkčným stavom. Analýzy subškál ukázali, že sociálna opora bola signifikantne asociovaná s jednou subškálou funkčného statusu, t. j. intimita-sexuálne vzťahy, zatiaľ čo schopnosť zvládania bola asociovaná so všetkými subškálami funkčného stavu. Zistili

sme, že schopnosť zvládania mala mediačný efekt na asociáciu medzi problémami súvisiacimi so spánkom a funkčným stavom. Nepozorovali sme však mediačný efekt sociálnej opory na asociáciu medzi problémami súvisiacimi so spánkom a funkčným stavom.

*Ôsma kapitola* sumarizuje kľúčové zistenia prezentované v kapitolách 3-7, obsahuje diskusiu našich zistení v kontexte súčasných vedeckých poznatkov a poskytuje implikácie pre prax a ďalší výskum. V súlade s predchádzajúcimi štúdiami, výsledky našej metaanalýzy potvrdili, že liečba CPAP môže pomôcť zlepšiť fyzické príznaky OSA, zatiaľ čo existujúce psychologické poškodenia často nie je možné úspešne minimalizovať. Súčasný výskum a klinická prax by sa preto mali zamerať nielen na štandardnú liečbu OSA, ale aj na zabezpečenie efektívneho manažmentu psychologických symptómov. Naše zistenia môžu tiež zlepšiť pochopenie problematiky duševného zdravia u pacientov s OSA. Naša štúdia poskytla dôkazy o zvýšenej prevalencii celkového psychologického distresu u pacientov s OSA, vrátane samovražedných myšlienok a anxiety. Preto je následne potrebné zdôrazniť adekvátnosť monitorovania psychologických symptómov u pacientov s OSA počas klinickej starostlivosti. Vzdelávanie ľudí s OSA v oblasti základnej spánkovej hygieny a aplikácie behaviorálnych intervencií môže zlepšiť kvalitu spánku a znížiť únavu, ktorá je u týchto pacientov významne spojená so seba-posudzovaným zdravím. Zdravotnícki pracovníci môžu pacientom priamo odporučiť cielenú a včasnú psychologickú starostlivosť, ktorá môže zamedziť neskoršiemu vzniku vážnych problémov. Identifikácia pacientov s prekrývajúcimi sa príznakmi duševných porúch a OSA môže naviac pomôcť k zlepšeniu diagnostických procesov a výsledkov liečby prostredníctvom starostlivého dávkovania farmakoterapie a aplikácie CPAP liečby.

Ďalším zaujímavým pozorovaním, ktoré vyplynulo z našej štúdie, bolo, že externé zdroje súvisiace so sociálnou oporou boli menej signifikantne asociované so seba-posudzovaným zdravím v porovnaní s inter-individuálnymi psychologickými zdrojmi, ako je celková úroveň zvládania životných okolností a coping zameraný na zastavenie nepríjemných emócií a myšlienok. Na základe týchto výsledkov predpokladáme, že facilitácia inter-individuálnych zdrojov môže predstavovať jednu z dôležitých ochranných stratégií, pri zmierňovaní negatívneho vplyvu symptómov OSA na seba-posudzované zdravie. Podpora schopnosti zvládania a copingovej seba-účinnosti môže preto predstavovať jeden z rozhodujúcich faktorov v rámci zlepšovania funkčného stavu a zvládania psychologického distresu u pacientov s OSA. Nesmieme však zabudnúť na naše zistenie, že sociálna opora bola významne spojená s jednou funkčnou subškálou, t.j. intímne-sexuálne vzťahy. Vzhľadom na skutočnosť, že predchádzajúce štúdie identifikovali negatívne zdravotné dôsledky OSA nielen u pacientov s týmto ochorením, ale u ich partnerov, význam sociálnej opory v partnerských vzťahoch by mal byť ďalším predmetom skúmania.

*Ôsma kapitola* následne popisuje limity tejto štúdie a sumarizuje odporúčania pre klinickú prax a ďalší výskum. Silné stránky tejto štúdie zahŕňajú diagnostiku OSA s využitím polysomnografie. Výsledky našej štúdie môžu byť užitočné pri identifikácii bio-psycho-sociálnych faktorov, ktoré môžu ovplyvniť zdravie pacientov s OSA, a ktoré môžu byť následne manažované zdravotníckymi pracovníkmi a v neposlednom

rade aj samotnými pacientmi. Multidisciplinárna starostlivosť o pacientov s OSA môže zamedziť duplikovaniu úkonov, minimalizovať fragmentáciu starostlivosti, znížiť náklady na kontrolu, zlepšiť posúdenie rizika následkov neliečeného OSA a viesť k efektívnejším stratégiám liečby. Naša štúdia viedla k záveru, že zhoršenie seba-posudzovaného zdravia u pacientov s OSA nemusí byť spôsobené len biomedicínskymi faktormi alebo samotným ochorením. Psychologické faktory ako sú anxieta, hostilita, typ copingovej seba-účinnosti alebo celková schopnosť zvládať životné okolnosti môžu zohrávať kľúčovú úlohu pri určovaní úrovne seba-posudzovaného zdravia u pacientov s OSA. Výsledky našej štúdie je však potrebné potvrdiť longitudinálnymi štúdiami.

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*"We are such stuff as dreams are made on,*
*and our little life is rounded with a sleep."*

William Shakespeare, The Tempest

Getting a PhD can be challenging and isolating. As my favourite novelist Haruki Murakami says; sometimes I just felt like like being in a *"sandstorm that keeps changing directions. You change direction but the sandstorm chases you. You turn again, but the storm adjusts. And you really will have to make it through that metaphysical, symbolic storm. And once the storm is over you won't remember how you made it through.... You won't even be sure, in fact, whether the storm is really over. But one thing is certain. When you come out of the storm you won't be the same person who walked in. That's what this storm's all about."* Thankfully, I was not alone and there were many people who were willing to give me helping hand, supported me, cheered me and helped me to not give up, and for that, I am grateful. The range of people I intrinsically would like to thank is broad.

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# About the author

Vladimira Timkova was born on 15 November, 1987 in Kosice, Slovakia. She completed her bachelor´s degree in psychology in June 2010 and her master´s degree in psychology in June 2012, both at the Pavol Jozef Safarik University in Kosice, Faculty of Arts. Her qualifying area is clinical psychology and her master thesis was focused on problematic internet use. After her masters study her interest in the clinical area of psychology encouraged her to seek experience in working with patients suffering from mental illness. Therefore, she started her clinical internship at the Department of Psychiatry. Due to her interest in the field of research she started to work as researcher at the Pavol Jozef Safarik University in Kosice, Medical Faculty and also began her PhD program at the University of Groningen, The Netherlands. In her PhD project she explored the associations between bio-psycho-social factors and self-reported health outcomes in patients with obstructive sleep apnoea. While doing her research, she acquired skills in methodology, data analyses, dissemination of scientific results, including publishing. She currently participates in projects on integrated care, social care, and health-related behaviour change. In addition to scientific and research activities, she is also involved in teaching. She delivered lectures and practicals on Social Medicine, Behavioral Medicine and Qualitative and Quantitative Methods in Research.

*Supplement 3.1: TableS3.2 Search strings*

**Web of Knowledge:** ("Sleep apnea" OR "sleep apnoea" OR OSA) AND ("quality of life" OR " health status" OR "functional status" OR "self-perceived health" OR "self-perceived health" OR "self-rated health" OR "self-rated health") AND (CPAP OR "continuous positive airway pressure").

**Pubmed:** ("Sleep Apnea Syndromes"(Mesh) OR sleep apnea(tiab) OR sleep apnoea(tiab) OR OSA(tiab)) AND ("Continuous Positive Airway Pressure"(Mesh) OR CPAP(tiab) OR continuous positive airway pressure(tiab)) AND ("Quality of Life"(Mesh) OR "Health Status"(Mesh) OR quality of life(tiab) OR health status(tiab) OR functional status(tiab) OR self-rated health(tiab) OR self-perceived health(tiab)).

**PsycINFO:** (DE "Sleep Apnea" OR TI („sleep apnea" OR "sleep apnoea" OR OSA) OR AB („sleep apnea" OR "sleep apnoea" OR OSA)) AND ( TI ( "continuous positive airway pressure" OR CPAP ) OR AB ( "continuous positive airway pressure" OR CPAP ) ) AND ( DE "Quality of Life" OR TI ( "quality of life" OR "health status" OR "functional status" OR "self-rated health" OR "self-perceived health" ) OR AB ( "quality of life" OR "health status" OR "functional status" OR "self-rated health" OR "self-perceived health" ) ).

**The Cochrane Library:** ("sleep apnea" or "sleep apnoea" or OSA:ti,ab,kw) and ("continuous positive airway pressure" or CPAP:ti,ab,kw) and ("quality of life" or "health status" or "functional status" or "self-rated health" or "self-perceived health":ti,ab,kw)

**EMBASE:** ((('sleep apnea':ti,ab,kw OR 'sleep apnoea':ti,ab,kw OR 'osa':ti,ab,kw) AND 'continuous positive airway pressure':ti,ab,kw OR 'cpap':ti,ab,kw) AND 'quality of life':ti,ab,kw OR 'health status':ti,ab,kw OR 'self-rated health':ti,ab,kw OR 'self-perceived health':ti,ab,kw OR 'functional status':ti,ab,kw)).

**CINAHL:** "sleep apnea OR sleep apnoea OR OSA AND continuous positive airway pressure OR CPAP AND quality of life OR health status OR functional status OR self-rated health OR self-perceived health on 2019-03-03 09:15 AM"

*Supplement 3.2: Overview of the included studies: exclusion criteria, sociodemographic and clinical data, level of compliance with CPAP*

*Table S3.4 Overview of the included studies*

| Study | Exclusion criteria | Sociodemographic and clinical data Mean (SD/SE, range) | CPAP compliance, Mean (SD/ SE, range) |
|---|---|---|---|
| Engleman 1997, Scotland | neurological disorder; co-existing sleep disorder | Age: 52±2.0 years<br>Gender: 12 men, 4 women<br>AHI: 12.5±0.5 events/h<br>BMI: 29.8±1.8 kg/m$^2$<br>ESS: 14±1.0 | 8 patients: 5.00.6± h/per night |
| Engleman 1998, Scotland | lung disease; neurological disorder; co-existing sleep disorder | Age: 47±12.0 years<br>Gender: 21 men, 2 women<br>AHI: 43.0±12.0 events/h<br>BMI: 30.0±7.0 kg/m$^2$<br>ESS: 12.04.0± | 2.8±2.0 h/per night |
| Engleman 1999, Scotland | shift workers; co-existing sleep disorder; neurological disease; lung disease | Age: 44.0±8.0 years<br>Gender: 21 men, 13 women<br>AHI: 10.0±3.0 events/h<br>BMI: 30.0±5 kg/m$^2$<br>ESS: 13.0±3.0 | 2.8±2.1 h/per night |
| Jenkinson 1999, UK | mental impairment; major psychoses; alcohol dependence; learning difficulties | Age: real CPAP: 50.0 (33-71) years<br>Age: sham CPAP: 48.0 (36-68) years<br>Gender: 101 men, 0 women<br>AHI: NA<br>Oximeter: >4% SaO2 (dips/h)<br>Sham CPAP: 28·5 (10.7–68.7)<br>Real CPAP: 32·9 (15.5–63.4)<br>BMI: real CPAP: 35.1 (25.8-44.3) kg/m$^2$<br>BMI: sham CPAP: 35.0 (26.9-51.4) kg/m$^2$<br>ESS: real CPAP: 16.0<br>ESS: Sham CPAP: 17.0 | controls: 4.6 h/per night<br>real CPAP: 5.4 h/per night |
| Barbé 2001, Spain | cognitive deterioration; chronic underlying disease; cardiac disease; less than 8 years of formal education<br>Illicit drugs; alcohol abuse | Age: real CPAP: 54±2.0 years<br>Age: sham CPAP: 52±2.0 years<br>Gender: 5 female, 49 male<br>AHI: real CPAP: 54±2.0 events/h<br>AHI: sham CPAP: 52±2.0 events/h<br>BMI: 29.0±1.0 (26.9-51.4) kg/m$^2$<br>BMI: sham CPAP: (29±0.4) kg/m$^2$<br>ESS: real CPAP: 7.0±0.4<br>ESS: sham CPAP: 7.0±0.4<br>multicentre; 6 hospitals | controls: 4.0±0.5 h/per night<br>real CPAP: 5.0±0.4 h/per night |

*Table S3.4 Overview of the included studies - continued*

| Study | Exclusion criteria | Sociodemographic data and clinical data Mean (SD/SE, range) | CPAP compliance, mean (SD, SE, range) |
|---|---|---|---|
| Faccenda 2001, UK | shift workers; diabetes; taking medication which may alter blood pressure | Age: 50.0 (29-72) years<br>Gender: 55 males, 13 females<br>AHI: 35.0 (15-129) events/h<br>BMI: 30.0 (21-53) kg/m$^2$<br>ESS: 15.0 (16-24) | 3.3±0.8 h/per night |
| Montserrat 2001, Spain | severe cardiovascular disease; hazardous job coincidentally with OSA | Age: 54.0±10.0 years<br>Gender: 41 male, 4 female<br>AHI: 54.0±19.0 events/h<br>BMI: 32.0±6.0 kg/m$^2$<br>ESS: 16.0±5.0 | not specified |
| Chakravorty 2002, UK | neuromuscular disorders; hypothyroidism; associated respiratory diseases; acute abdomen; chest infection; visual impairment | Age: 50.0±11.0 years<br>Gender: not specified<br>AHI: 49.0±28.0 events/h<br>BMI: 37.0±12.0 kg/m$^2$<br>ESS: 14.0±5.0 | not specified |
| Barnes 2004, Australia | not specified | Age: 46.6±1.1 years<br>Gender: 64 male, 16 female<br>AHI: 5-30 events/h<br>BMI: 31.0±0.6 kg/m$^2$<br>ESS: 10.0±0.5 | 3.6± 0.3 h/per night |
| Marshall 2005, New Zealand | history of somnolence requiring immediate treatment; shift work; chronic sleep restriction; currently taking sedatives, antidepressants, psychotropics or stimulants; an alcohol intake of 0.3 standard units/24 hours or caffeine dependency (unable to forego caffeine on testing days); had undergone upper airway surgery; or had any clinically significant co-existing disease or additional sleep disorders | Age: 50.5 (25-67) years<br>Gender: 23 male, 6 female<br>AHI: 21.67.5± events/h<br>BMI: 3.5 (6.0) kg/m$^2$<br>ESS: 12.5 (0.8) | 4.9 (0-8.4) h/per night |
| Siccoli 2008, UK | respiratory failure | Age: real CPAP: 48.1±9.5 years<br>Age: sham CPAP: 48.7±10.6 years<br>Gender: 102 male; 0 female<br>BMI: real CPAP:  35.8±7.3 kg/m$^2$<br>BMI: sham CPAP: 34.5±5.0 kg/m$^2$<br>ESS: real CPAP: 15.8±4.0<br>ESS: sham CPAP: 15.2±4.0 | controls: 3.9±2.5 h/per night<br>real CPAP: 4.7±2.1 h/per night |

*Table S3.4 Overview of the included studies - continued*

| Study | Exclusion criteria | Sociodemographic data and clinical data Mean (SD/SE, range) | CPAP compliance, mean (SD, SE, range) |
|---|---|---|---|
| Weaver, 2012 USA | unstable medical condition in the past 3 months; greater than fifth grade reading level; and no history of other sleep disorder, current pregnancy, substance abuse, sleepiness-related driving accident, or sleepi-ness-sensitive occupation | Age: real CPAP: 49.5±10.9 years<br>Age: sham CPAP: 51.7±11.9 years<br>Gender: 223 patients; 140 male; 122 female<br>Black: 79.3%; whites: 76.3%<br>AHI: real CPAP: 12.8±6.4 events/h<br>AHI: sham CPAP: 12.5±6.5 events/h<br>BMI: real CPAP: 33.2±6.3 kg/m²<br>BMI: sham CPAP: 34.2±7.8 kg/m²<br>ESS: real CPAP: 15.0±3.4<br>ESS: sham CPAP: 14.7±3.0 | controls: 3.1±2.1 h/per night<br><br>real CPAP: 4.0±2.0 h/per night |
| Batool-Anwar, 2016 USA | previous treatment for OSA with CPAP or surgery, oxygen saturation on baseline PSG < 75% for > 10% of the recording time, history of motor vehicle accident related to sleep-iness within the past 12 months, chronic medical conditions, use of various medications known to affect sleep or neurocog-nitive function, health and social factors that may impact testing procedures (e.g. shift work) | Age: real CPAP: 52.0±12.0 years<br>Age: sham CPAP: 51.0±12.0 years<br>Gender: male; female<br>AHI: real CPAP: 40.0±24.0 events/h<br>AHI: sham CPAP: 41.0±25.0 events/h<br>BMI: real CPAP: NA<br>BMI: sham CPAP: NA<br>ESS: real CPAP: 10.3±4.5<br>ESS: sham CPAP: 14.7±3.0<br>multi-centre study | controls: 2.922.92± h/per night<br><br>real CPAP: 3.69±3.10 h/per night |

CPAP: continuous positive airway pressure

*Supplement 4.1*
*Supplementary Table S4.1 Multiple linear regression analysis: associations of OSA severity, perceived sleep quality, daytime sleepiness and anxiety with work functioning*

**Work functioning (WRFQ)**

| | Crude B (95%CI) | Model 1 B (95%CI) | Model 2 B (95%CI) | Model 3 B (95%CI) | Model 4 B (95%CI) | Model 5 B (95%CI) |
|---|---|---|---|---|---|---|
| Age | -0.22 (-0.79; 0.36) | -0.10 (-0.67; 0.47) | -0.10 (-0.48; 0.68) | -0.12 (-0.64; 0.40) | -0.19 (-0.71; 0.32) | -0.19 (-0.69; 0.31) |
| Gender | 14.70 (2.56; 26.84)* | 14.36 (1.97; 26.74)* | 12.56 (-0.74; 25.10) | 7.86 (-3.61; 17.38) | 6.15 (-5.08; 17.38) | 4.88 (-6.22; 15.78) |
| Occupation | -4.03 (-15.40; 7.34) | - | - | - | - | - |
| OSA severity | -0.27 (-0.53; -0.01)* | - | -0.21 (-0.48; 0.06) | -0.13 (-0.37; 0.11) | -0.10 (-0.34; 0.13) | -0.10 (-0.33; 0.13) |
| Perceived sleep quality | -5.76 (-7.90; -3.61)*** | - | - | -5.28 (-7.48; -3.08)*** | -3.41 (-5.99; -0.85)* | -9.76 (-16.25; -3.27)** |
| Daytime sleepiness | -0.61 (-1.70; 0.48) | - | - | - | - | - |
| Anxiety | -1.02 (-1.40; -0.63)*** | - | - | - | -0.60 (-1.06; -0.14)* | -1.49 (-2.44; -0.54)** |
| Perceived sleep quality x Anxiety | -0.05 (-0.07; -0.03)*** | - | - | - | - | 0.18 (0.10; 0.35)* |
| F Change | - | 2.93 | 2.47 | 22.76*** | 6.58* | 4.45* |
| Adjusted R² | - | 0.04 | 0.05 | 0.23 | 0.27 | 0.29 |

Crude effects: effect of each variable separately on work functioning; Model 1: effect of age and gender on work functioning; Model 2: effect of age, gender and OSA severity on work functioning; Model 3: effect of age, gender, OSA severity and perceived sleep quality on work functioning; Model 4: effect of age, gender, OSA severity, perceived sleep quality and anxiety on work functioning; Model 5: interaction between perceived sleep quality and anxiety; B: unstandardized regression coefficient; CI – confidence interval; Gender – male gender was set as the reference; Blue-white collar – white collar was set as the reference; OSA – Obstructive Sleep Apnoea; F Change – significance of prediction improvement in the model fit; Adjusted R2 – explained variance adjusted for the number of predictors in the model; *p<0.05; **p<0.01; ***p<0.001.

*Supplementary Table S4.2 Multiple linear regression analysis: associations of OSA severity, sleep efficiency, daytime sleepiness and anxiety with work functioning*

**Work functioning (WRFQ)**

| | Crude B (95%CI) | Model 1 B (95%CI) | Model 2 B (95%CI) | Model 3 B (95%CI) | Model 4 B (95%CI) | Model 5 B (95%CI) |
|---|---|---|---|---|---|---|
| Age | -0.22 (-0.79; 0.36) | -0.06 (-0.62; 0.51) | 0.01 (-0.56; 0.58) | -0.09 (-0.65; 0.46) | -0.21 (-0.74; 0.32) | -0.28 (-0.79; 0.23) |
| Gender | 14.70 (2.56; 26.84)* | 16.15 (3.71; 28.59)* | 14.41 (1.76; 27.05)* | 8.58 (-4.26; 21.42) | 5.58 (-6.64; 17.80) | 2.20 (-9.62; 14.01) |
| Occupation | -4.03 (-15.40; 7.34) | - | - | - | - | - |
| OSA severity | -0.27 (-0.53; -0.01)* | | -0.18 (-0.45; 0.08) | -0.09 (-0.35; 0.18) | -0.08 (-0.33; 0.17) | -0.07 (-0.31; 0.17) |
| Daily disturbances | -7.88 (-11.93; -3.84)*** | | | -6.45 (-10.92; -1.99)** | -3.49 (-8.00; 1.03) | -21.78 (-33.67; -9.89)** |
| Daytime sleepiness | -0.61 (-1.70; 0.48) | | | | | - |
| Anxiety | -1.02 (-1.40; -0.63)*** | | | | -0.80 (-1.24; -0.36)** | -3.18 (-4.68; -1.68)** |
| Daily disturbances x Anxiety | -0.05 (-0.07; -0.03)*** | | | | | 0.56 (0.22; 0.90)** |
| F Change | - | 3.55* | 1.88 | 8.24** | 12.90** | 10.75** |
| Adjusted R² | - | 0.05 | 0.06 | 0.16 | 0.22 | 0.29 |

Crude effects: effect of each variable separately on work functioning; Model 1: effect of age and gender on work functioning; Model 2: effect of age, gender and OSA severity on work functioning; Model 3: effect of age, gender, OSA severity and daily disturbances on work functioning; Model 4: effect of age, gender, OSA severity, daily disturbances and anxiety on work functioning; Model 5: interaction between daily disturbances and anxiety; B: unstandardized regression coefficient; CI – confidence interval; Gender – male gender was set as the reference; Blue-white collar – white collar was set as the reference; OSA – Obstructive Sleep Apnoea; F Change – significance of prediction improvement in the model fit; Adjusted R2 – explained variance adjusted for the number of predictors in the model; *p<0.05; **p<0.01; ***p<0.001.

*Supplementary Table S4.3 Multiple linear regression analysis: associations of OSA severity, daily disturbances, daytime sleepiness and anxiety with work functioning*

**Work functioning (WRFQ)**

| | Crude B (95%CI) | Model 1 B (95%CI) | Model 2 B (95%CI) | Model 3 B (95%CI) | Model 4 B (95%CI) | Model 5 B (95%CI) |
|---|---|---|---|---|---|---|
| Age | -0.22 (-0.79; 0.36) | -0.10 (-0.67; 0.47) | -0.02 (-0.59; 0.56) | 0.07 (-0.50; 0.64) | -0.15 (-0.69; 0.39) | -0.16 (-0.70; 0.38) |
| Gender | 14.70 (2.56; 26.84)* | 14.36 (1.96; 26.74)* | 12.58 (0.07; 25.08)* | 13.27 (0.98; 25.56)* | 7.81 (-3.84; 19.46) | 7.34 (-4.40; 19.09) |
| Occupation | -4.03 (-15.40; 7.34) | - | - | - | - | - |
| OSA severity | -0.27 (-0.53; -0.01)* | | -0.21 (-0.48; 0.06) | -0.17 (-0.44; 0.09) | -0.12 (-0.36; 0.13) | -0.13 (-0.37; 0.12) |
| Sleep efficiency | -3.55 (-6.60; -0.51)* | | | -3.31 (-6.35; -0.27)* | -1.14 (-4.14; 1.85) | -4.33 (-13.26; 4.60) |
| Daytime sleepiness | -0.61 (-1.70; 0.48) | | | | | - |
| Anxiety | -1.02 (-1.40; -0.63)*** | | | | -0.89 (-1.31; -0.47)*** | -1.03 (-1.60; -0.46)*** |
| Sleep efficiency x Anxiety | -0.05 (-0.07; -0.03)*** | | | | | 0.09 (-0.14; 0.32) |
| F Change | - | 2.93 | 2.47 | 4.66* | 17.40*** | 0.57 |
| Adjusted R² | - | 0.04 | 0.05 | 0.09 | 0.22 | 0.22 |

Crude effects: effect of each variable separately on work functioning; Model 1: effect of age and gender on work functioning; Model 2: effect of age, gender and OSA severity on work functioning; Model 3: effect of age, gender, OSA severity and daily disturbances on work functioning; Model 4: effect of age, gender, OSA severity, daily disturbances and anxiety on work functioning; Model 5: interaction between daily disturbances and anxiety; B: unstandardized regression coefficient; CI – confidence interval; Gender – male gender was set as the reference; Blue-white collar – white collar was set as the reference; OSA – Obstructive Sleep Apnoea; F Change – significance of prediction improvement in the model fit; Adjusted R2 – explained variance adjusted for the number of predictors in the model; *p<0.05; **p<0.01; ***p<0.001.

*Supplementary Table S4.4 Multiple linear regression analyses: associations of OSA severity, sleep-related problems and anxiety with WRFQ subscales*

**Crude effects**

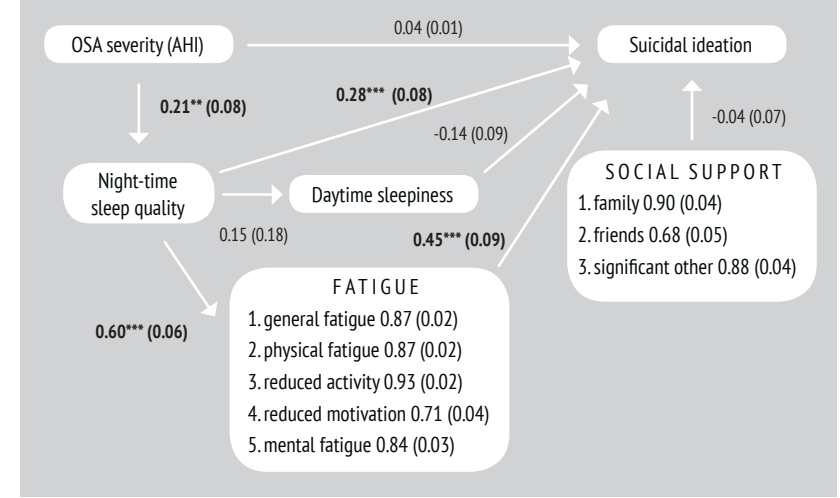| | Work Scheduling and Output demands | Physical demands | Flexibility demands | Mental and Social demands |
|---|---|---|---|---|
| | B (95%CI) | B (95%CI) | B (95%CI) | B (95%CI) |
| Age | -0.15 (-0.78; 0.48) | -0.17 (-0.85; 0.51) | -0.22 (-0.82; 0.39) | -0.29 (-0.92; 0.33) |
| Gender | 10.75 (-2.84; 24.34) | 20.60 (6.95; 34.25)** | 20.35 (7.40; 33.31)* | 17.70 (4.35; 31.05)* |
| Occupation | -0.74 (-13.34; 11.86) | -2.03 (-15.38; 11.33) | -3.99 (-1.45; 1.04) | -5.04 (-17.34; 7.27) |
| OSA severity | -0.19 (-0.48; 0.11) | -0.36 (-0.66; -0.05)* | -0.22 (-0.50; 0.08) | -0.26 (-0.54; 0.03) |
| Night-time sleep quality | -3.43 (-4.69; -2.16)*** | -2.02 (-3.47; -0.56)** | -2.82 (-4.08; -1.57)*** | -2.73 (-3.70; -1.05)** |
| Daytime sleepiness | -0.12 (-1.34; 1.11) | -0.99 (-2.22; 0.24) | -0.20 (-1.46; 1.05) | -0.29 (-1.51; 0.94) |
| Anxiety | -1.17 (-1.81; -0.93)*** | -0.93 (-1.44; -0.42)*** | -0.93 (-1.35; -0.51)** | -0.82 (-1.26; -0.38)*** |
| Night-time sleep quality x Anxiety | -0.06 (-0.08; -0.04)*** | -0.04 (-0.06; -0.01)** | -0.04 (-0.06; -0.02)*** | -0.04 (-0.06; -0.01)** |

**Adjusted models**

| | Work Scheduling and Output demands | Physical demands | Flexibility demands | Mental and Social demands |
|---|---|---|---|---|
| | B (95%CI) | B (95%CI) | B (95%CI) | B (95%CI) |
| Age | -0.16 (-0.67; 0.46) | 0.04 (-0.62; 0.71) | -0.11 (-0.66; 0.44) | -0.20 (-0.79; 0.39) |
| Gender | 2.72 (-9.83; 15.27) | 15.43 (1.60; 29.26)* | 14.40 (1.58; 27.22)* | 13.18 (0.30; 26.65)* |
| OSA severity | - | -0.17 (-0.48; 0.14) | - | - |
| Night-time sleep quality | -2.13 (-3.66; -0.61)** | -0.51 (-2.23; 1.20) | -1.64 (-3.16; -0.12) | -1.31 (-2.92; 0.31) |
| Anxiety | -1.79 (-3.06; -0.52)** | -0.65 (-1.27; -0.03)* | -0.48 (-1.00; 0.05) | -0.45 (-1.01; 0.11) |
| F Change | 7.34** | 4.32* | 3.26 | 2.58 |
| Adjusted R² | 0.26 | 0.16 | 0.23 | 0.15 |

Crude effects: effect of each variable separately on work functioning subscales; Model Work Scheduling and Output demands: effect of age, gender, night-time sleep quality and anxiety on work scheduling and output demands level score; Model Physical demands: effect of age, gender, disease severity, night-time sleep quality and anxiety on physical demands, Model Flexibility demands: effect of age, gender, night-time sleep quality and anxiety on flexibility demands; Model Mental and Social demands: effect of age, gender, night-time sleep quality and anxiety on mental and social demands score; B: unstandardized regression coefficient; CI – confidence interval; Gender – male gender was set as reference; Blue-white collar – white collar was set as a reference; OSA – Obstructive Sleep Apnoea; F Change – significance of prediction improvement in the model fit; Adjusted R2 – explained variance adjusted for the number of predictors in the model. *p<0.05; **p<0.01; ***p<0.001.

*Supplement 6.1*

*Figure S6.1: Hypothesized model of the relationships among OSA severity, night-time sleep quality, daytime sleepiness, fatigue, social support and SI: beta (standard error)*



AHI – Apnoea-Hypopnoea Index; OSA – Obstructive Sleep Apnoea; **p<0.01; ***p<0.001.

*Supplement 7.1*

*Table S7.4 Multiple linear regression analyses: associations of social support, mastery and sleep-related problems with functional status subscales (N=150)*

**Crude effects**

| | Activity level B (95%CI) | Vigilance B (95%CI) | Intimacy-sexuality B (95%CI) | General productivity B (95%CI) | Social outcome B (95%CI) |
|---|---|---|---|---|---|
| Age | 0.01 (-0.02; 0.01) | -0.01 (-0.02; 0.00) | -0.02 (-0.04; 0.00) | -0.01 (-0.02; 0.01) | -0.02 (-0.03; -0.00)* |
| Gender | -0.41 (-0.70; -0.11)*** | -0.60 (-0.87; -0.33)*** | -0.78 (-1.20; -0.36)*** | -0.49 (-0.78; -0.20)** | -0.41 (-0.71; -0.10)* |
| Marital status | -0.23 (-0.52; 0.13) | -0.10 (-0.41; 0.21) | -0.44 (-0.91; 0.04) | -0.13 (-0.45; 0.20) | -0.09 (-0.44; 0.25) |
| OSA severity | -0.01 (-0.02; -0.00)** | -0.01 (-0.01; -0.00)** | -0.02 (-0.03; -0.01)*** | -0.01 (-0.02; -0.01)*** | -0.01 (-0.02; -0.01)*** |
| Nighttime sleep quality | -0.09 (-0.12; -0.05)*** | -0.05 (-0.08; -0.02)** | -0.12 (-0.16; -0.07)*** | -0.09 (-0.12; -0.05)*** | -0.09 (-0.12; -0.05)*** |
| Daytime sleepiness | -0.08 (-0.10; -0.06)*** | -0.09 (-0.11; -0.07)*** | -0.11 (-0.14; -0.07)*** | -0.09 (-0.11; -0.07)*** | -0.06 (-0.09; -0.04)*** |
| Social support | 0.02 (0.01; 0.03)** | 0.01 (0.00; 0.03)* | 0.03 (0.01; 0.04)*** | 0.01 (0.00; 0.02)** | 0.01 (0.00; 0.02)** |
| Mastery | 0.11 (0.01; 0.14)*** | 0.10 (0.07; 0.12)*** | 0.14 (0.09; 0.18)*** | 0.12 (0.09; 0.14)*** | 0.08 (0.05; 0.11)*** |

**Adjusted models**

| | Activity level B (95%CI) | Vigilance B (95%CI) | Intimacy-sexuality B (95%CI) | General productivity B (95%CI) | Social outcome B (95%CI) |
|---|---|---|---|---|---|
| Age | 0.00 (-0.01; 0.01) | -0.00 (-0.01; 0.00) | -0.01 (-0.03; 0.00) | -0.00 (-0.01; 0.01) | -0.01 (-0.02; 0.00) |
| Gender | -0.13 (-0.34; 0.07) | -0.37 (-0.58; -0.15)*** | -0.38 (-0.72; -0.03)* | -0.17 (-0.36; 0.02) | -0.14 (-0.39; 0.12) |
| Marital status | -0.10 (-0.33; 0.12) | -0.01 (-0.24; 0.22) | -0.34 (-0.71; 0.03) | -0.03 (-0.23; 0.17) | 0.02 (-0.26; 0.30) |
| OSA severity | -0.00 (-0.01; 0.00) | -0.00 (-0.01; 0.00) | -0.01 (-0.01; 0.00) | -0.01 (-0.01; -0.00)* | -0.01 (-0.01; -0.00)** |
| Nighttime sleep quality | -0.06 (-0.08; -0.03)*** | -0.02 (-0.04; 0.01) | -0.07 (-0.11; -0.03)** | -0.06 (-0.08; -0.04)*** | -0.06 (-0.09; -0.03)*** |
| Daytime sleepiness | -0.05 (-0.07; -0.03)*** | -0.06 (-0.08; -0.04)*** | -0.06 (-0.09; -0.03)*** | -0.05 (-0.07; -0.04)*** | -0.03 (-0.06; -0.01)** |
| Social support | 0.01 (-0.00; 0.01) | 0.00 (-0.01; 0.01) | 0.01 (0.00; 0.03)* | 0.00 (-0.00; 0.01) | 0.01 (-0.00; 0.02) |
| Mastery | 0.07 (0.05; 0.10)*** | 0.06 (0.04; 0.09)*** | 0.08 (0.04; 0.12)*** | 0.07 (0.05; 0.09)*** | 0.04 (0.01; 0.07)** |
| **F** | 24.49*** | 18.41*** | 16.25*** | 32.42*** | 12.53*** |
| **Adjusted R²** | 0.38 | 0.48 | 0.45 | 0.63 | 0.38 |

Crude effects: effect of each variable separately on functional status subscales; Model Activity level: effect of age, gender, marital status, disease severity, sleep-related problems, social support and mastery on activity level score; Model Vigilance: effect of age, gender, marital status, disease severity,sleep-related problems, social support and mastery on vigilance score; Model Intimacy-sexuality: effect of age, gender, marital status, disease severity, sleep-related problems, social support and mastery on intimacy and sexual relationships score; Model General productivity: effect of age, gender, marital status, disease severity, sleep-related problems,social support and mastery on general productivity score; Model Social outcome: effect of age, gender,marital status,disease severity,sleep-related problems, social support and mastery on social outcome score; B: unstandardized regression coefficient; CI – confidence interval; Gender – male gender was set as the reference; Marital status: single was set as the reference; OSA – Obstructive Sleep Apnoea; F – significance of prediction in model fit; Adjusted R² – explained variance adjusted for the number of predictors in the model; FOSQ – higher scores indicating less impaired daily life; *p<0.05; **p<0.01; ***p<0.001

# Graduate School Kosice Institute for Society and Health (KISH) and previous dissertations

The Graduate School Kosice Institute for Society and Health (KISH) was established in 2004 and is hosted by the Medical Faculty of the Pavol Jozef Safarik University in Kosice, Slovakia. Its interdisciplinary research programs focus on Youth and Health and on Chronic Disease. The Graduate School KISH is collaborating closely with the Department of Community and Occupational Medicine, University Medical Center Groningen, University of Groningen, The Netherlands.

**Previous dissertations from the Graduate School Institute for Society and Health (KISH)**

**Belak A (2019)**
*The health of segregated Roma: first-line views and practices*
Supervisors: Prof. S.A. Reijneveld Prof. A. Geckova
Co-supervisors: Assoc. Prof. Dr. JP van Dijk

**Kopcakova Rondosova J (2018)**
*Physical activity, screen-based activities and their potential determinants: Active living during adolescence*
Supervisors: Prof. Dr. SA Reijneveld, Prof. Dr. A Madarasova Geckova
Co-supervisors: Assoc. Prof. Dr. JP van Dijk, Assoc. Prof. Dr. Z Dankulincova

**Husarova D (2017)**
*Barriers to active participation of school-aged children*
Supervisors: Prof. Dr. SA Reijneveld, Prof. Dr. A Madarasova Geckova
Co-supervisor: Assoc. Prof. Dr. JP van Dijk

**Holubcikova J (2016)**
*Eating habits, body image and health and behavioural problems of adolescents. The role of school and family context*
Supervisors: Prof. Dr. SA Reijneveld, Prof. Dr. A Madarasova Geckova
Co-supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. P Kolarcik

**Vitkova M (2015)**
*Poor sleep quality and other symptoms affecting quality of life in patients with multiple sclerosis*

Supervisors: Prof. Dr. SA Reijneveld, Prof. Dr. Z Gdovinova
Co-supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. J Rosenberger

**Sudzinova A (2015)**
*Roma ethnicity and outcomes of Coronary Artery Disease: Mortality, clinical status and self-rated health*
Supervisor: Prof. Dr. SA Reijneveld
Co-supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. J Rosenberger

**Skorvanek M (2014)**
*Apathy, fatigue and quality of life in patients with Parkinson's disease*
Supervisors: Prof. Dr. JW Groothoff, Prof. Dr. Z Gdovinova
Co-supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. J Rosenberger

**Kolvek G (2014)**
*Etiology and prognosis of chronic kidney disease in children: Roma ethnicity and other risk factors*
Supervisors: Prof. Dr. SA Reijneveld, Prof. Dr. L Podracka
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**Mikula P (2014)**
*Health related quality of life in people with multiple sclerosis : the role of coping, social participation and self-esteem*
Supervisors: Prof. Dr. JW Groothoff, Prof. Dr. Z Gdovinova
Co-supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. I Nagyova

**Prihodova L (2014)**
*Psychosocial and medical determinants of long-term patient outcomes. A specific focus on patients after kidney transplantation and with haemophilia*
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Co-supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. I Nagyova, Dr. J Rosenberger

**Behanova M (2014)**
*Area- and individual-level socioeconomic differences in health and health-risk behaviours*
Supervisor: Prof. Dr. SA Reijneveld
Co-supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. I Nagyova, Dr. Z Katreniakova

**Silarova B (2014)**
*Unraveling the role of sense of coherence in coronary heart disease patients*
Supervisor: Prof. Dr. SA Reijneveld
Co-supervisors: Assoc. Prof. Dr. JP van Dijk, Dr. I Nagyova

**Pitel L (2013)**
*Sociocultural determinants, gender and health-related behaviour in adolescence*
Supervisor: Prof. Dr. SA Reijneveld
Co-supervisors: Assoc. Prof. Dr. JP van Dijk, Assoc. Prof. Dr. A. Geckova

**Majernikova M (2013)**
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**Geckova A (2002)**
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