Insomnia, depression and quality of life among patients with obstructive sleep apnea

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Thesis for the degree of Philosophiae Doctor

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UNIVERSITY OF ICELAND
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Svefnleysi, þunglyndi og lífsgæði sjúklinga með kæfisvefn

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To my dad

-For your support, motivation and sincere interest

throughout all my studies-

Ágrip

Inngangur: Sjúklingar með kæfisvefn sofa gjarnan óvært, þjást af svefnleysi og mögulega þunglyndi. Allir þessir þættir hafa áhrif á lífsgæði og því getur verið erfitt að átta sig á hverjar eru mikilvægustu orsakir lélegrar heilsu og lakra lífsgæða hjá þessum sjúklingum. Því er nauðsynlegt að skoða þessa þætti og kanna hvort hægt sé að bæta meðferð og auka meðferðarheldni við kæfisvefni hjá ákveðnum undirhópum sem þurfa á frekari inngripum að halda samhliða notkun svefnöndunartækis eða áður en slík meðferð hefst.

Tilgangur: Megin tilgangur þessarar rannsóknar var að kanna svefnleysi, þunglyndi og lífsgæði sjúklinga með kæfisvefn.

Aðferðir: Svefnleysi og lífsgæði voru metin með samanburði á 822 sjúklingum með ómeðhöndlaðan kæfisvefn (Íslenska kæfisvefnsrannsóknin, 666 karlar og 156 konur) og 762 þátttakendum úr almennu þýði (404 karlar og 358 konur). Kæfisvefnssjúklingarnir voru endurmetnir tveimur árum eftir upphaf meðferðar með svefnöndunartæki. Að lokum var þunglyndi metið hjá 284 sjúklingum með ómeðhöndlaðan kæfisvefn (223 karlar og 61 kona). Allir kæfisvefnssjúklingarnir fóru í svefnmælingu og svöruðu stöðluðum spurningalistum um svefnvenjur og heilsu. Svefnleysi var metið með The Basic Nordic Sleep Questionnaire og þeir sem upplifðu einkenni svefnleysis ≥3 sinnum í viku töldust vera með svefnleysi. Þrjár gerðir svefnleysis voru skoðaðar: erfiðleikar með að sofna, tíðar uppvaknanir á nóttunni og að vakna of snemma á morgnana. Líkamleg og geðræn lífsgæði voru metin með spurningalistanum The short form 12. Þunglyndi var metið með stöðluðu sálfræðiviðtali (The Mini International Neuropsychiatric Interview).

Niðurstöður: Samtals voru 68.3% ómeðhöndlaðra kæfisvefnssjúklinga með einkenni svefnleysis en töluverð skörun var milli ólíkra gerða svefnleysis. Alls áttu 15.5% sjúklinga erfitt með að sofna á kvöldin, 59.3% vöknuðu oft á nóttunni og 27.7% vöknuðu of snemma á morgnana. Að vakna oft á nóttunni var mun algengara hjá sjúklingum með kæfisvefn samanborið við þátttakendur úr almennu þýði (32% á móti 59.3% hjá kæfisvefnssjúklingum, $p<0.001$). Ekki var marktækur munur á tíðni þess að eiga erfitt með að sofna á kvöldin milli þessara hópa. Sjúklingar með ómeðhöndlaðan kæfisvefn höfðu lakari lífsgæði samanborið við þátttakendur úr

almennu þýði. Bæði líkamleg og geðræn lífsgæði voru marktækt lakari hjá sjúklingum með kæfisvefn eftir að leiðrétt hafði verið fyrir aldur, líkamsþyngdarstuðul (LÞS), kyn, háþrýsting, sykursýki, svefnleysi og dagssyfju. Að meðaltali voru kæfisvefnssjúklingar með 9.48 færri stig líkamlegra lífsgæða (95% CI: -10.53, -8.44; p<0.0001) og 3.35 færri stig geðrænna lífsgæða (95% CI: -4.35, -2.35; p<0.0001) samanborið við þátttakendur úr almennu þýði. Samtals greindust 15.5% sjúklinga með ómeðhöndlaðan kæfisvefn með einkenni óyndis en tíðnin var hærri meðal kvenna (29.5% á móti 11.7% meðal karla, p<0.001). Alvarleg geðlægð greindist hjá 6% sjúklinga en þar var einginn kynjamunur. Samanlögð tíðni þunglyndis (óyndi og alvarleg geðlægð) var 20.8%. Konur voru með hærri tíðni; 36.1% á móti 16.6% hjá körlum, (p<0.001) en kynjamunurinn skýrist af mun á algengi óyndis. Svefnlyfjanotkun var sterkasti skýringarþáttur þunglyndis en dagssyfja og að eiga erfitt með að sofna á kvöldin tengdust einnig hærri tíðni þunglyndis. Líkamsþyngdarstuðull og alvarleiki kæfisvefns voru ekki sjálfstæðir skýringarþættir þunglyndis.

Við tveggja ára eftirfylgd kom í ljós að það að eiga erfitt með að sofna og að vakna of snemma á morgnana lagaðist ekki þrátt fyrir að kæfisvefn væri vel meðhöndlaður. Sjúklingar með slík einkenni svefnleysis voru líklegri til að gefast upp á meðferð með svefnöndunartæki, jafnvel eftir að leiðrétt hafði verið fyrir aldur, kyn, LÞS, reykingar og alvarleika kæfisvefns. Tíðar uppvaknanir á nóttunni löguðust hins vegar þegar kæfisvefn var vel meðhöndlaður og þessi einkenni höfðu ekki áhrif á meðferðarheldni.

Bæði líkamleg (2.6 ± 0.4; p<0.0001) og geðræn (1.9 ± 0.5; p<0.001) lífsgæði bötnuðu tveimur árum eftir að meðferð við kæfisvefni hófst en voru þó áfram lakari samanborið við þátttakendur úr almennu þýði (43.9 ± 0.5 á móti 50.9 ± 0.5, p<0.0001). Lífsgæði bötnuðu (p<0.05) bæði hjá þeim sem notuðu svefnöndunartæki og þeim sem hættu meðferð. Líkamleg lífsgæði voru nálægt því að batna meira hjá þeim sem notuðu svefnöndunartæki samanborið við þá sem hættu meðferð (p = 0.06) en enginn munur var á breytingu á geðrænum lífsgæðum (p = 0.80). Þegar einungis voru skoðaðir einstaklingar með LÞS >35 kom í ljós að líkamleg lífsgæði jukust marktækt meira hjá þeim sem notuðu svefnöndunartæki samanborið við þá sem hættu meðferð (p = 0.02). Enginn munur var á breytingu á geðrænum lífsgæðum milli þessara hópa. Hjá þeim sem notuðu svefnöndunartæki og áttu ekki

erfitt með að sofna (p = 0.02), vöknuðu ekki oft á nóttunni (p = 0.01) og vöknuðu ekki of snemma á morgnana (p = 0.02) fannst marktækur munur á líkamlegum lífsgæðum samanborið við þá sem hættu meðferð.

Ályktanir: Meirihluti sjúklinga með ómeðhöndlaðan kæfisvefn er með einkenni svefnleysis, lífsgæði þeirra eru slök og um fimmtungur þeirra er með þunglyndi. Það að eiga erfitt með að sofna á kvöldin og að vakna of snemma á morgnana lagast ekki þó svo að kæfisvefn sé vel meðhöndlaður og þessi einkenni svefnleysis hafa neikvæð áhrif á meðferðarheldni. Að vakna oft á nóttunni lagast hjá þeim sjúklingum sem nota svefnöndunartæki og virðist því einkenni ómeðhöndlaðs kæfisvefns frekar en raunverulegt svefnleysi. Þeir sem nota svefnöndunartæki bæta lífsgæði sín ekki meira en þeir sem hætta notkun svefnöndunartækis. Þó má sjá marktækan bata líkamlegra lífsgæða hjá þeim sem hafa hæstan LÞS, eru án einkenna svefnleysis og nota svefnöndunartæki. Kæfisvefn hefur í för með sér margvíslega fylgikvilla, eins og svefnleysi og þunglyndi, sem hafa neikvæð áhrif á lífsgæði sjúklinga. Þessa þætti þarf að taka til greina og meðhöndla frekar þegar þörf er á.

Lykilorð: Kæfisvefn, svefnleysi, lífsgæði, þunglyndi

Abstract

Introduction: Patients with obstructive sleep apnea (OSA) often sleep poorly, have a high co-morbidity of insomnia and evidence suggests elevated levels of depression among this patient population. All of these conditions affect quality of life and accordingly it can be difficult to identify the most important contributors for poor health and life qualities among these patients. It is important to look at all of these factors in combination and figure out whether some subgroups of OSA patients require additional interventions prior to or simultaneously with positive airway pressure (PAP) treatment to maximize treatment effects

Objectives: The overall aim of this study was to investigate insomnia, depression and quality of life among patients with OSA: firstly, their prevalence among untreated OSA patients and the relationship with OSA severity, secondly, how these factors change with long term PAP treatment of OSA and thirdly if they have some impact on treatment outcome and adherence.

Methods: The relationship between insomnia, quality of life and OSA was assessed by comparing 822 untreated OSA patients from the Icelandic Sleep Apnea Cohort (ISAC, 666 males, 156 females) to 762 controls from the general population in Iceland (404 males, 358 females). Changes in both insomnia and quality of life were subsequently assessed among ISAC subjects 2 years after initiating PAP treatment. Furthermore, depression was assessed among 284 untreated OSA patients (223 males, 61 females) waiting to initiate PAP treatment. All OSA patients underwent a sleep study and answered standardized questionnaires about their sleep and health. Insomnia was assessed with the Basic Nordic Sleep Questionnaire and those who reported insomnia symptoms ≥3x week were considered to have insomnia. Three subtypes of insomnia were defined: difficulty initiating sleep (initial insomnia), difficulty maintaining sleep (middle insomnia) and early morning awakenings (late insomnia). The Short Form 12 (SF-12) questionnaire was used to assess quality of life. Two summary component scores are derived from the SF-12, the physical component score (PCS) and mental component score (MCS). Depression was assessed with the Mini International Neuropsychiatric Interview (MINI).

Results: The prevalence of having some symptoms of insomnia among untreated ISAC subjects was 68.3%, but there was a considerable overlap between the three different subtypes of insomnia. Symptoms of initial insomnia were reported by 15.5% of patients, 59.3% had symptoms of middle insomnia, and 27.7% exhibited symptoms of late insomnia. Middle insomnia was less prevalent among the general population subjects compared to the untreated ISAC subject (32% vs. 59.3%; $p<0.001$). However, there was no significant difference in the prevalence of initial insomnia between subjects from these two cohorts. Untreated ISAC subjects had a worse quality of life as compared to subjects from the general population. Both MCS and PCS remained significantly lower among untreated ISAC subjects after adjusting for age, body mass index (BMI), gender, smoking, hypertension, diabetes, insomnia and daytime sleepiness; on average, OSA patients had PCS scores 9.48 points lower (95% CI: -10.53, -8.44; $p<0.0001$) and MCS scores 3.35 points lower (95% CI: -4.35, -2.35; $p<0.0001$) than the general population. Overall, 15.5% of subjects in the untreated OSA cohort met the diagnosis for dysthymia, but women had a significantly higher prevalence than men (29.5% vs. 11.7%, $p<0.001$). The prevalence of major depression was 6% in the overall sample and there was no difference between genders. The prevalence of depression overall (dysthymia or major depression) was 20.8% with women showing a significantly higher prevalence, 36.1% vs. 16.6% among men, ($p<0.001$) but this difference was driven by the dysthymia results. Those who suffered from depression reported lower quality of life and were more likely to report symptoms of insomnia and use sleep medication. Sleep medication use, daytime sleepiness and symptoms of initial insomnia were independently related to depression but BMI and OSA severity were not.

At the two-year follow-up, symptoms of initial and late insomnia tended to persist regardless of successful PAP treatment and those presenting with these subtypes of insomnia at baseline were less likely to adhere to PAP treatment, this difference remained significant after adjusting for age, sex, BMI, smoking, and OSA severity. Symptoms of middle insomnia improved after successful OSA treatment and did not affect PAP adherence. Both PCS (mean ± SE change: 2.6 ± 0.4; $p<0.0001$) and MCS (1.9 ± 0.5; $p<0.001$) increased significantly two years after treatment initiation. Despite these significant increases, PCS values in ISAC

subjects at the follow-up remained significantly lower than the values seen in the general population at baseline (mean ± SE after two years: 43.9 ± 0.5 vs. 50.9 ± 0.5, $p<0.0001$). Significant two-year increases ($p<0.05$) in both quality of life measures were observed for full and non-users, separately. Comparison of the changes in physical and mental quality of life between PAP groups showed only a marginal difference between full and non-users for change in PCS ($p = 0.06$) and no differences in the change in MCS ($p = 0.80$). While significant evidence for a PAP by BMI group interaction was not found, a significant difference for PCS was reported when restricting analysis to BMI>35 ($p = 0.02$) such that more obese subjects adherent to PAP had a significantly greater improvement in PCS than non-users. No differences in PAP full and non-users related to BMI groups were found for MCS. Significant differences in PCS change between full users and PAP non-users for those who did not have initial ($p = 0.02$), middle ($p = 0.01$) or late ($p = 0.02$) insomnia at baseline were found; full users had greater increases in PCS.

Conclusions: The majority of untreated OSA patients have symptoms of insomnia, almost a quarter of these patients have depression and their life qualities are poor. Both initial and late insomnia tend to persist regardless of successful PAP treatment and negatively affect treatment adherence. Middle insomnia improves if OSA is successfully treated and seems to be a symptom of untreated OSA rather than a traditional insomnia condition. Full users of PAP in general do not improve their quality of life more than non-users. However, the most obese full users and those without insomnia showed more improvement in physical quality of life compared to non-users. The various co-morbidities of OSA, such as insomnia and depression, have a profound impact on quality of life and affect treatment adherence. This needs to be taken into account and addressed with additional treatment interventions when needed.

Keywords: obstructive sleep apnea, insomnia, quality of life, depression

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Contents

List of abbreviations

AHI	Apnea-hypopnea index
ATC	Anatomical Therapeutic Chemical
biPAP	Bilevel positive airway pressure
BMI	Body mass index
BNSQ	Basic Nordic Sleep Questionnaire
BOLD	Burden of Lung Disease
BzRAs	Benzodiazepine receptor agonists
CBT	Cognitive behavioral treatment
CBT-I	Cognitive behavioral treatment of insomnia
CES-D	Centre for Epidemiological Studies Depression Scale
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CVD	Cardiovascular disease
DIS	Difficulties initiating sleep
DMS	Difficulties maintaining sleep
DSM	Diagnostic and Statistical Manual
EMA	Early morning awakenings
EEG	Electroencephalogram
ESS	Epworth Sleepiness Scale
GER	Gastroesophageal reflux
HADS	Hospital Anxiety and Depression Scale
ICC	The intraclass correlation coefficient
ICSD	The International Classification of Sleep Disorders
ISAC	The Icelandic Sleep Apnea Cohort

MAP	Multivariable Apnea Prediction
MCS	Mental component score
MINI	Mini International Neuropsychiatric Interview
MMPI	Minnesota Multiphasic Personality Inventory
ODI	Oxygen desaturation index
OR	Odds ratio
OSA	Obstructive sleep apnea
PAP	Positive airway pressure
PCS	Physical component score
PS	Propensity scoring
RCT	Randomized controlled study
RDI	Respiratory disturbance index
REM	Rapid eye movement
RIP	respiratory inductance plethysmography
RLS	Restless legs syndrome
SaO_2	Oxygen saturation
SD	Standard deviation

List of figures

List of tables

This thesis is based on the following original publications, which are referred to in the text by their Roman numerals (I-IV):

I. Björnsdottir E, Janson C, Gíslason T, Sigurðsson JF, Pack AI, Gehrman P, Benediktsdottir B. Insomnia in untreated sleep apnea patients compared to controls. *Journal of Sleep Research.* 2011; 2:131-138.

II. Björnsdóttir E, Janson C, Sigurdsson JF, Gehrman P, Perlis M, Juliusson S, Arnardottir ES, Kuna ST, Pack AI, Gislason T, Benediktsdóttir B. Symptoms of insomnia among patients with obstructive sleep apnea before and after two years of positive airway pressure treatment. *SLEEP*. 2013; 36(12): 1901-1909.

III. Björnsdóttir E, Keenan B, Eysteinsdottir B, Arnardottir ES, Janson C, Benediktsdottir B, Sigurdsson JF, Kuna ST, Pack AI, Gislason T. Quality of life among untreated sleep apnea patients compared to the general population and changes after treatment with positive airway pressure. *Journal of Sleep Research*. 2014. In press.

IV. Björnsdóttir E, Benediktsdottir B, Gislason T, Arnardottir ES, Kuna ST, Pack AI, Sigurdsson JF. Assessing depression among untreated OSA patients using a semi-structured standardized psychiatric interview. *Journal of Clinical Sleep Medicine* 2014. Submitted.

Declaration of contribution

Below is a declaration of my contribution to each paper on which this thesis is based.

Paper I: I designed the study with my PhD mentors; Bryndis Benediktsdottir, Jon Fridrik Sigurdsson and Thorarinn Gislason. I participated in the data collection (database quality assurance). I performed all statistical analysis with the help of Christer Janson, drafted the paper and participated in all revisions of the paper from co-authors.

Paper II: I designed the study with my PhD mentors; Bryndis Benediktsdottir, Jon Fridrik Sigurdsson and Thorarinn Gislason. I participated in the data collection (database quality assurance). I performed all statistical analysis with the help of Christer Janson, drafted the paper and participated in all revisions of the paper from co-authors.

Paper III: I designed the study with my PhD mentors; Bryndis Benediktsdottir, Jon Fridrik Sigurdsson and Thorarinn Gislason. I participated in the data collection (database quality assurance). Together with Brendan Keenan, I performed all statistical analysis. I drafted the paper and participated in all revisions of the paper from co-authors.

Paper IV: I designed the study with my PhD mentors Jon Fridrik Sigurdsson, Bryndis Benediktsdottir and Thorarinn Gislason as well as Sam Kuna, Allan Pack and Erna Sif Arnardottir. I applied for ethical permission, study funding and performed part of the subject recruitment, measurements and data analysis. I performed all statistical analysis, drafted the paper and participated in all revisions of the paper from co-authors.

1 Introduction

1.1 Obstructive sleep apnea

Obstructive sleep apnea (OSA) has been described in the literature as "The Pickwickian syndrome", a disorder named after Joe, the fat and red-faced boy in Charles Dickens first novel *The Pickwick Papers*. The character of Joe has many of the classic symptoms of OSA. He is described as constantly hungry, red-faced and falling asleep in the middle of tasks (Dickens, 1836). The Pickwickian syndrome included obesity, hypoventilation, periodic breathing and low oxygen levels in the blood (Guilleminault et al., 1976). Later, when sleep studies were introduced in the research on sleep-related breathing disorders new mechanisms were discovered including upper airway obstruction (Figure 1), which led to the new term "obstructive sleep apnea" (Guilleminault et al., 1976).

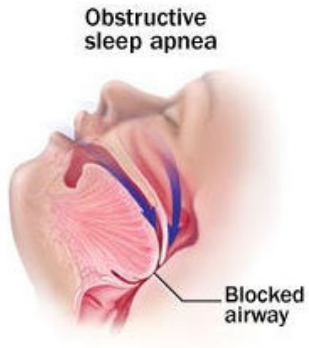

Figure 1. Schematic of a blocked airway. Reproduced from http://www.medprorespiratory.com/obstructive-sleep-apnea-treatment/sleep-apnea-treatment/

OSA is a sleep disorder characterized by repeated cessation of breathing (apneas) or reduction in ventilation (hypopneas) during sleep due to obstruction of the upper airway (Mbata & Chukwuka, 2012). These breathing disturbances result in decrease in oxygen saturation and sleep fragmentation (Punjabi, 2008). This disorder is estimated to affect at least 5% of adults in western countries (Young et al., 2002) and the percentage is rising along with the increased prevalence of obesity, the most important risk factor for OSA (Pack, 2006). OSA is less common among women, especially premenopausal women and postmenopausal women with hormone replacement therapy (HRT) (Bixler et

al., 2001). It is assumed that normal hormonal function in premenopausal women is the reason for a lower prevalence of OSA (Block et al., 1980), indicating that progesterone levels may play a role in protecting women from OSA before menopause (Bixler et al., 2001).

It has been postulated that a great majority of OSA patients are undiagnosed (Young et al., 1997) and according to Peppard et al. (2013) the prevalence of sleep disordered breathing, including OSA, has increased substantially in the last two decades. These results were based on a comparison of data from 1988-1994 with data from 2007-2010 revealing an increase in prevalence from 14% up to 55%, depending on subgroup, among adults from 30 to 70 years of age. More awareness of OSA symptoms among health care providers, as well as the constant increase in obesity, might explain this increase in the prevalence of OSA.

1.1.1 Severity and diagnosis of obstructive sleep apnea

The apnea hypopnea index (AHI), i.e. the number of apneas/hypopneas per hour of sleep, is commonly used to measure the severity of OSA. An AHI of 5-15 indicates mild OSA; 15-30 is moderate OSA and above 30 indicates severe OSA. Several additional measures of disease severity exist, including the degree of nocturnal hypoxia and the extent of sleep fragmentation (Punjabi, 2008) and these factors as well as daytime symptoms are also taken into account when measuring the degree of OSA (Shamasuzzaman et al., 2003). Women tend to have less severe OSA as compared to men (O´Connor et al., 2000; Ware et al., 2000). In a study by Millman et al. (1995) it was found that despite similar BMI and waist circumference, men have proportionally more upper body fat with a larger subscapular skin fold thickness, waist-hip ratio, and neck circumference. This fat distribution may partially explain the greater severity of OSA among men (Maislin et al., 2012).

An overnight polysomnography is the gold standard test for diagnosing OSA. It measures multiple physiological signals during sleep, including the electroencephalogram (EEG), electrooculogram, electromyogram, nasal airflow, and oxygen saturation. (Punjabi, 2008). These recordings allow identification of apneas, hypopnea, oxygen saturation and arousals. There are also simpler methods available that are done at home and measure all the relevant respiratory variables during sleep (Rofail et al., 2010). These are so called type III portable monitors that are widely used in most European countries (Fietze et al., 2011). These devices do not record EEG and therefore the AHI has to be

calculated from total recording time instead of total sleep time. Studies have shown that results obtained by using the type III device are highly correlated to PSG results (Ng et al., 2010; Gjevre et al., 2011).

1.1.2 Symptoms of obstructive sleep apnea and gender differences

The main nighttime symptoms of OSA include loud snoring, witnessed apneas during sleep, excessive sweating, nighttime urination, frequent awakenings and restless sleep. The main daytime symptoms include excessive daytime sleepiness, fatigue, morning headaches, gastroesophageal reflux (GER), lack of concentration and irritability (Young et al., 2002).

Excessive sleepiness is the most common daytime symptom but the relationship between OSA and sleepiness is not simple since those with the most severe OSA do not necessarily suffer from the most daytime sleepiness (Sauter et al., 2000). Other factors such as obesity (Vgontzas et al., 1998) and gender (Jordan & McEvoy, 2003) are also important in relation to daytime sleepiness, whereas obese persons have elevated sleepiness regardless of OSA and sleepiness is more frequent among women with OSA as compared to men.

Even though several studies have indicated that women seem to report the same classical symptoms of OSA as men, that is loud snoring, snorting and/or witnessed apneas (Young et al., 1996; Olson et al., 1995; Redline et al., 1994) there are important differences between the genders. In the study of Redline et al. (1994) there were many fewer women with AHI >15 that reported these typical OSA symptoms compared to men with the same degree of OSA. A study by Shepertycky (2005) revealed several differences in clinical presentation between men and women with OSA while controlling for OSA severity, subjective sleepiness, BMI and age. In his study, a history of depression and hypothyroid disease and the presenting complaint of insomnia were more common in women, whereas men were more likely to have a history of witnessed apneas, more consumption of caffeine and greater alcohol consumption. Furthermore, in a study by Macey et al., (2012) it was found that the women with OSA had more symptoms of depression and anxiety than the men.

1.1.3 Risk factors of obstructive sleep apnea

Apart from obesity, the main risk factors for OSA include; male gender, age, family history of OSA, smoking, nasal obstruction and increased neck circumference (Young et

al., 2004). Even though there is strong evidence for increased risk of OSA with excess weight (Peppard et al., 2000), the conditions also exists in non-obese persons and therefore other factors need to be considered when diagnosing OSA (Young et al., 2004). The structure of the upper airway plays an important role and those who have a small and narrow airway are at an increased risk of OSA (Schwab et al., 1995; Dempsey et al., 2002). Narrow nasal cavities, tonsillar hypertrophy and enlarged tonsils and tongue can also increase the risk of developing OSA (Young et al., 2004).

Age is another important risk factor but the prevalence of OSA increases with age, with older persons (>65 yrs. old) having a 2-3 fold higher risk for developing OSA (Young et al., 2004). Ancoli-Israel et al. (1991) reported that 70% of men and 56% of women between 65 and 99 years of age had OSA defined as AHI ≥ 10. However, there is a decrease in severity of OSA among the elderly (Bixler et al., 1998; Young et al., 2002), which might be at least partially explained by the decrease in BMI among this age group. Some have found that when controlling for BMI, the association between age and OSA diminishes (Bixler et al., 2001).

Several studies have shown an increased risk of OSA in families where OSA already exists. Some of these associations could be explained by shared lifestyles and risk factors such as obesity, but there is, however, support for a genetic predisposition of OSA (Redline & Tishler, 2000; Pack, 2006). It has been reported that first-degree relatives of those with OSA are more likely to be at risk compared with first-degree relatives of those without the disorder and that the familial susceptibility to OSA increases directly with the number of affected relatives (Redline et al., 1995; Gislason et al., 2002).

1.1.4 Consequences of obstructive sleep apnea

Untreated OSA is characterized by apneas, hypopneas, and recurrent arousals, which disturb the normal sleep pattern and lead to hypoventilation, hypoxia and activation of the sympathetic nervous system (Al Lawati et al., 2009). These long term sleep disturbances can lead to reduced neurocognitive function, cardiovascular disease, the development of diabetes and premature death (Al Lawati et al., 2009). The consequences of OSA are therefore diverse and can impact various aspects of daily life.

Originally, OSA was considered to be primarily a breathing disorder but now it is also known to have considerable systemic effects including increased sympathetic activation and systemic inflammation (Pack, 2006; McNicholas & Bonsigore, 2007; Arnardottir et al., 2009). The chronic intermittent hypoxia associated with OSA increases

sympathetic activation and blood pressure (Arnardottir et al., 2009) and a causative link has been shown between chronic intermitted hypoxia and atherosclerosis (Savransky et al., 2007). Several studies also suggest that OSA results in increased cardiovascular disease and mortality (Peker et al., 2000; Young et al., 2002; Marshall et al., 2008; Pack & Gislason, 2009).

Due to excessive sleepiness and impairment in performance, OSA is associated with an increased risk of motor vehicle crashes which in some studies is two to seven fold compared with the general population (George, 2007; Sassani et al., 2004). In addition, OSA is co-morbid with many other chronic diseases and health conditions such as diabetes, hypertension and heart diseases (Huang et al., 2008). Furthermore, OSA is frequently co-morbid with chronic obstructive pulmonary disease (COPD) and patients with both disorders have a worse prognosis and an increased risk of death (Marin et al., 2010). In addition, OSA has been linked to symptoms of several psychiatric disorders such as depression, anxiety, psychosis and mania (Aikens & Mendelson, 1999; Sharafkhaneh et al., 2005). Even though those with the most severe OSA normally experience more negative consequences (Finn et al., 1998), patients with mild OSA also have difficulties in carrying out their daily activities (Young et al., 2002; Baldwin et al., 2001).

It has been suggested that OSA may affect the genders in a different way. In a recent study by Macey et al. (2012) it was indicated that women with OSA experience more damage to their brain cells in regions involved in the regulation of moods and decision-making compared to men with OSA.

1.1.5 Treatment of obstructive sleep apnea

The most common treatment for moderate and severe OSA is Positive airway pressure (PAP) treatment. The PAP device blows compressed air into a mask that covers the nose and/or mouth and provides support to the airway during sleep. This positive airflow keeps the airway open, preventing apneas and allowing normal breathing during sleep. There are three different types of PAP treatment available; continuous positive airway pressure (CPAP) delivers the same level of pressure to the airway during both inhalation and exhalation; with bilevel PAP (BIPAP) the pressure during inhalation is higher than during exhalation and finally AutoPAP automatically varies PAP pressure during the night to the lowest level needed to keep the airway open (Loube et al., 1999).

Evidence suggests that using PAP for 6 hours or more per night decreases sleepiness, improves daily functioning, and restores memory to normal levels (Weaver et al., 2007). However, 4-hour usage per night can significantly decrease daytime sleepiness and is most often used as a cutting point for successful treatment (Kribbs et al., 1993; Rauscher et al., 1993; Hui et al., 2001; Russo-Magno et al., 2001; Sin et al., 2002).

Dental appliances can be prescribed for patients with mild OSA (Lim et al., 2004) and have been shown to be successful in reducing snoring and to improve OSA to some degree (Schmidt-Nowara et al., 1995). Hypopharyngeal surgery has also proven to be successful to some degree among selected subgroups of OSA patients (Kezirian & Goldberg, 2006). Lifestyle interventions aimed at increased exercise and healthier diet can also be helpful for those with mild disease (Tuomilehto et al., 2009). Several factors, including OSA severity, the structure of the airway and patient preference, impact the type of treatment that is used.

Daytime sleepiness often improves with successful treatment and studies have even shown a linear dose-response relationship between increased PAP use and less objective and subjective daytime sleepiness (Weaver et al., 2007). Furthermore, successful treatment of OSA reduces the risk of traffic accidents (Krieger et al., 2002) cardiovascular disease (Yaggi et al., 2005) and mortality (Young et al., 2008).

Compliance with PAP treatment is often poor. Lindberg et al. (2006) reported that up to 70% of patients from a population-based sample discontinue treatment but most studies on cinical cohorts show slightly higher compliance rates (Zozula &Rosen, 2001; for review see Sawyer et al., 2011). PAP compliance seems to be related to OSA severity, whereas patients with mild OSA tend to show a high rate of PAP discontinuation (Rosenthal et al., 2000; Janson et al., 2000). Simple interventions like improved education and support (Hoy et al., 1999) and cognitive behavioral treatment (CBT) can, however, be used to improve treatment compliance (Chervin et al., 1997; Aloia et al., 2001; Jean Wiese et al., 2005; Richards et al., 2007).

1.2 Quality of life among patients with obstructive sleep apnea

Typical daytime symptoms of OSA include sleepiness, decreased energy, lack of concentration, morning headaches and irritability. It is therefore not surprising that many patients are more aware of the daytime consequences of OSA than the nocturnal events. Patients may not notice their snoring and breathing pauses during sleep but on the other

hand be extremely aware of the diverse daytime consequences, often resulting in impaired work performance and reduced participation in everyday activities (Chervin, 2000; Engleman & Douglas, 2004). Accordingly, OSA patients often report a poor quality of life in the social, emotional and physical domains (Lacasse et al., 2002; Akashiba et al., 2002; Baldwin et al., 2001) and studies have shown that patients with severe OSA have reduced quality of life compared to normal controls in components of positive affect, current health perceptions and vitality (Yang et al., 2000). The most commonly used instrument in assessing quality of life among OSA patients is the SF-36. In studies using the SF-36, poor mental and physical quality of life among OSA patients has repeatedly been demonstrated when compared to age- and gender-matched controls (Moyer et al., 2001).

In a recent study, Dutt et al. (2013) found impairments in components of daily activities, emotional functioning and social interaction in OSA patients when compared to controls. However, they did not find a proportional relationship between OSA severity and diminished quality of life, which is similar to findings from others (Yang et al., 2000; Gall et al., 1993; Akashiba et al., 2002). Furthermore, Baldwin et al. (2001) demonstrated that patients with severe OSA (AHI > 30) have lower scores in six of eight domains on the SF-36 when compared to healthy subjects, and that daytime sleepiness was associated with a reduced quality of life. Their results also indicated that those who suffer from co-morbid insomnia have worse quality of life with twice as high odds of scoring poorly on domains of mental health and vitality. Meslier et al. (1998) showed that OSA patients had poor quality of life, especially on domains related to energy.

Since OSA is a complex disorder, with adverse health related co-morbidities, several factors, apart from OSA, can impact quality of life among these patients (Moyer et al., 2001). Daytime sleepiness needs to be considered when looking at the relationship between OSA and poor quality of life. Daytime sleepiness is a common symptom in patients with OSA and an important factor for daily activities and therefore expected to be related to a decrease in quality of life. A number of studies have examined the relationship between daytime sleepiness and quality of life and found a positive correlation (Briones et al., 1996: Bennett et al., 1999; Baldwin et al., 2001). There are also studies, however, that have not confirmed this relationship (Akashiba et al., 2002). A study by Silva et al. (2009) reported that changes in quality of life over a 5 year period were not related to changes in AHI or ODI but rather to the worsening of difficulties

initiating and maintaining sleep as well as daytime sleepiness. Akashiba et al. (2002) indicated that mood and depression may play a more important role in explaining reduced quality of life than daytime sleepiness. Apart from sleepiness, obesity is another important factor that is known to affect quality of life (for review, see Kolotkin et al., 2001) and may partially explain the poor quality of life among the OSA population.

A gender difference has been noted in quality of life among OSA patients with women being more likely to score poorly in all domains (Meslier et al., 1998). Others have reported that women with OSA are more likely to suffer from poor mental health as compared to men (Baldwin et al., 2001), which may partially explain the lower life qualities.

Successful treatment of OSA can affect quality of life among these patients and studies have shown that a few weeks of PAP treatment seem to improve daytime functioning and quality of life among PAP adherent patients (D'Ambrosio et al., 1999; Jenkinson et al., 1999; Ballester et al., 1999; Weaver et al., 2012). In a study by D'Ambrosio et al. (1999), eight weeks of PAP treatment improved aspects of quality of life related to vitality, social functioning, and mental health. In their study, however, the magnitude of improvement was most strongly related to the degree of impairment in quality of life at baseline, indicating a regression to the mean. In a randomized controlled trial by Jenkinson et al. (1999) improvements were seen in vitality scores and social function after one month of PAP treatment and Ballester et al. (1999) found positive effects on social isolation and energy subscales of quality of life after three months of PAP treatment. Furthermore, Weaver et al. (2012) found that 8 weeks of PAP treatment improved functional outcomes among sleepy patients with mild to moderate OSA.

Even though the amount of research on quality of life and OSA has grown in recent years, more studies are needed. Many of the existing reports are cross-sectional and do not assess changes over time. It is important to identify which factors are related to long-term changes in quality of life and how these factors develop over the course of time. In many existing studies the sample sizes are small and the results may therefore not apply in other settings. Most studies assessing changes of quality of life during PAP treatment only include patients that are adherent with PAP and are therefore lacking a control group.

1.3 Insomnia

There are several different diagnostic criteria existing to define and identify insomnia. According to the American Psychiatric Association's *Diagnostic and Statistical Manual*, Fifth Edition (DSM-5), symptoms of insomnia must cause clinically significant distress or impairment in daily functioning and be present at least three nights per week for at least three months. Additionally, the insomnia symptoms may not be better explained by another sleep disorder or occur exclusively during the course of another sleep-wake disorder or by coexisting mental or physical illnesses (American Psychiatric Association, 2013). The International Classification of Sleep Disorders (ICSD-2) subdivides insomnia into descriptive categories such as adjustment insomnia, paradoxical insomnia and insomnia caused by a mental disorder, substance use or medical condition. According to the ICSD-2, insomnia symptoms must have been present for at least one month to be counted as chronic insomnia (American Academy of Sleep Medicine, 2005) for a diagnosis of the disorder. The International Classification of Diseases (ICD-10) uses the broadest approach for diagnosing insomnia. They categorize insomnia based on underlying pathology and give a diagnosis based on frequency of symptoms but no specific time frame is required (World Health Organization, 1992). Most studies on insomnia and its co-morbidities are, however, based on symptoms of insomnia but not the diagnosis of an insomnia disorder (Ohayon, 2002).

Insomnia is characterized by subjective complaints about sleep dissatisfaction and the diagnosis is based on clinical symptoms without objective laboratory findings. Different subtypes of insomnia are characterized by their main symptoms:

a) Difficulties falling asleep (initial insomnia)

b) Difficulties maintaining sleep (middle insomnia)

c) Early morning awakenings (late insomnia)

Some patients present with only one subtype while others have some combination of all three.

Insomnia is the most common sleep disorder with around one quarter of adults reporting dissatisfaction with their sleep and 10-15% complaining of symptoms of insomnia accompanied by daytime consequences. The prevalence is variable according to

which definition of insomnia is used (Figure 2) and the disorder is more prevalent among women and the elderly (Ohayon, 2002; Morin & Benca, 2012).

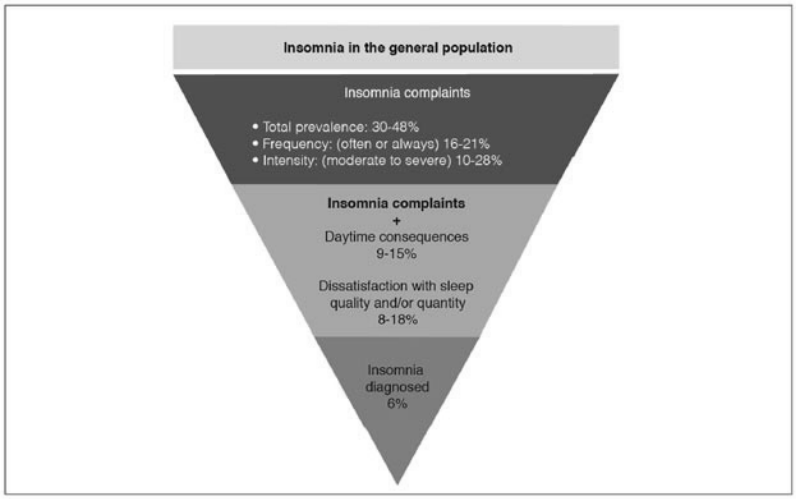

Figure 2. The prevalence of insomnia symptoms and diagnosis. Reproduced from Ohayon (2002).

Insomnia symptoms are highly prevalent, affecting up to 50% of the general population at some point in their lifetime, whereas insomnia diagnosis is much less common (Ohayon, 2002). It can be difficult to predict whether symptoms of insomnia will be transient or chronic. Chronic insomnia applies when symptoms have been persistent for at lest 1 – 3 months, depending on the diagnostic criteria (American Academy of Sleep Medicine, 2005; American Psychiatric Association, 2013). Acute insomnia has received little attention in the literature but Ellis et al. (2011) state in their review that further studies are needed in order to better understand what determines whether those with acute insomnia resume normal sleep as opposed to developing chronic insomnia. In a study by Morin et al. (2009) it was indicated that the severity of insomnia is related to its persistence and when a patient reports insomnia that meets diagnostic threshold, it should not be expected to remit spontaneously. In this study, it was showed that individuals with less severe subsyndromal insomnia at baseline were 3 times more likely to experience remission than worsening of insomnia during the next assessment periods. Although this higher remission rate suggests a more favorable course in individuals with symptoms of insomnia, the most frequent course over the three years of the study was to go from subsyndromal to syndromal insomnia (Morin et al., 2009).

Several studies have shown that symptoms of insomnia are more frequently reported among women (Lindberg et al., 1997; Jaussent et al., 2011; Ohayon & Sagales, 2010; Roth et al., 2011; Uhlig et al., 2014) and that these symptoms also increase with age (Morin et al., 2011; Calem et al., 2012; Wong & Fielding, 2011; Ohayon & Sagales, 2010). The increased prevalence of insomnia with age could be explained, however, by factors such as poor health, less mobility and higher rates of depression and physical disability among the elderly (Ohayon, 2002; Uhlig et al., 2014). Furthermore, a higher prevalence of insomnia has been reported among individuals with lower education (Ancoli-Israel & Roth, 1999; Kim et al., 2000) and lower income (Ohayon et al., 1997; Newman et al., 1997). A familial vulnerability to insomnia has also been suggested (McCarren et al., 1994; Bastien & Morin, 2000; Watson et al., 2006) but shared lifestyle and environment probably constitute a part of the explanation for a familial vulnerability to the disorder. Further studies are needed on the genetics of insomnia (Palagini et al., 2014).

Chronic insomnia is a disorder of 24-hour hyperarousal where patients suffer from a constant conflict between the sleep system and inappropriate activation of the central nervous system (for reviews see: Riemann et al., 2010; Bonnet & Arand, 2010). The hyperaroused state of insomnia is different from the daytime sleepiness that normally results from sleep restriction as these patients have difficulties falling asleep during the day in spite of experiencing extreme fatigue (Roth et al., 2007; Riedel & Lichstein, 2000).

Insomnia has been linked to a number of individual adverse medical and psychological consequences, in addition to having large socioeconomic consequences in terms of lost productivity and risk of accidents (Roth & Roehrs, 2003).

Insomnia is co-morbid with many psychiatric and medical disorders such as depression, anxiety, chronic pain and cardiovascular disease (Morin & Benca, 2012; Ancoli-Israel, 2006). When sleep difficulties are present in medical illnesses, sleep maintenance problems are more common than problems with sleep initiation (Ancoli-Israel, 2006). It is important to keep in mind that the relationship between chronic insomnia and chronic illness can be bidirectional and it is often difficult to identify a causal relationship. Even though insomnia is co-morbid it usually needs separate treatment (Morin & Benca, 2012; Stepanski & Rybarczyk, 2006) and, accordingly, the term “secondary insomnia” is no longer in use (Roth, 2009). Stating that insomnia is secondary would indicate that symptoms of insomnia improve if the underlying medical

condition is treated but that is not necessarily the case. Therefore the term co-morbid insomnia is now used instead of secondary insomnia (Stepanski & Rybarczyk, 2006). Furthermore, the same methods are used to treat insomnia, whether it is co-morbid or not (Morin & Benca, 2012; Stepanski & Rybarczyk, 2006).

Insomnia may often be undiagnosed and it has been estimated that many chronic insomniacs receive no treatment for their condition (Mellinger et al., 1985; Morin et al., 2006). Furthermore, it is estimated that nearly 50% of all primary care patients experience sleep difficulties, but most of these are left undetected by health professionals (Allaert & Urbinelli, 2004; Haponik et al., 1996; Shochat et al., 1999).

Insomnia is most often treated either with sleep hygiene advice, pharmacological interventions such as hypnotics or psychological interventions such as CBT (Hetta, Axelsson & Eckerlund, 2010). The main goals of insomnia treatment include improved sleep, reduction of distress and improvement of daytime function (Schutte-Rodin et al., 2008). Psychological and behavioral interventions and benzodiazepine receptor agonists (BzRAs) have demonstrated short-term efficacy for the treatment of chronic insomnia. CBT has shown both short and long term efficacy and can be used in treating both primary and co-morbid insomnia (Smith & Neubauer, 2003; Morin, 2006.). The use of benzodiazepines in the treatment of insomnia is associated with several adverse effects and should not be used as a long-term solution (Holbrook et al., 2000) and long-term hypnotics use in general should be avoided, especially among older people. Even though these drugs improve sleep the benefits may not justify the increased risk among individuals over 60 years of age (Glass et al., 2005). When hypnotics are used, the most appropriate short-acting agent should be considered (Ancoli-Israel, 2000).

1.3.1 Insomnia among OSA patients

Complaints of insomnia are frequent among patients diagnosed with OSA. The co-morbidity of these conditions was first described by Guilleminault et al. (1973) and since then the prevalence of insomnia has been reported in various studies to be around 40-60% among OSA patients, which is a lot higher than in the general population (Krakow et al., 2001; Smith et al., 2004; Chung, 2005; Krell & Kapur, 2005; Ong & Crawford, 2013). Since fatigue and daytime sleepiness are the core daytime symptoms of OSA it may sound surprising that insomnia is so common among these patients. In this context it is extremely important to distinguish between different types of insomnia since their relations to OSA may be diverse. Electroencephalographic arousals and sleep

fragmentation that are common during and after apneic episodes in OSA (Shamasuzzaman et al., 2003), for example, may lead to nighttime awakenings and hence middle insomnia. On the other hand, it could be speculated that initial insomnia would not be as prevalent among this population due to the excessive sleepiness frequently associated with OSA.

Given the high co-morbidity of these disorders it is important to explore whether insomnia aggravates symptoms of OSA and/or negatively affects PAP therapy. It could be more difficult for patients with initial insomnia to adapt to and tolerate PAP treatment because of the intrusive nature of the therapy and the fact that they already have difficulties falling asleep at night. Existing studies have in fact indicated that different subtypes of insomnia have a different impact on OSA symptoms. A study by Chung (2005) suggested that those OSA patients that report difficulties falling asleep have a significantly lower AHI and arousal index compared to subjects with sleep maintenance difficulties and those with no insomnia symptoms. In the same study it was reported that the relationship between insomnia and daytime sleepiness is dependent on insomnia subtypes. Despite being sleep deprived, subjects with initial insomnia reported lower daytime sleepiness indicating a state of hyperarousal, a typical symptom of chronic insomnia. On the other hand, subjects that suffered from recurrent awakenings reported excessive daytime sleepiness and therefore did not have the distinctive symptoms of chronic insomnia (Riemann et al., 2010).

Existing data regarding whether the coexistence of insomnia aggravates symptoms of OSA and decreases the effectiveness and compliance of PAP treatment are limited and inconsistent (Benetó et al., 2009). According to Krakow et al. (2001) patients suffering from co-morbid insomnia and OSA commonly present with psychiatric disorders such as anxiety and depression. The authors speculated that insomnia could make it more difficult for patients to adapt to PAP treatment and that adding CBT could be beneficial in order to successfully treat the insomnia. In a study by Gupta and Knapp (2014) it was reported that OSA patients with co-morbid insomnia diagnosis were more likely to suffer from hypertension and be provisionally at higher risk for cerebrovascular disease. However, they did not find higher psychiatric morbidity among patients with OSA and insomnia, which is contradictory to many former studies (Krakow et al., 2001; Smith et al., 2004; Krell & Kapur, 2005; Sivertsen et al., 2013). In a recent study by Luyster et al. (2014) it

was suggested that patients with OSA and insomnia are not at an increased risk of cardiovascular disease when compared to OSA patients without insomnia.

Currently, few studies have explored how PAP treatment affects insomnia that is comorbid with OSA (both overall and by subtype), and evaluated how insomnia affects PAP adherence. Results from existing studies are mixed. Nguyen et al. (2010) showed that even though insomnia symptoms were highly prevalent among patients with OSA, they had no effect on PAP adherence. In contrast, Wickwire et al. (2010) showed that symptoms of middle insomnia were related to poor PAP adherence. In addition, a recent study by Pieh et al. (2013) found a negative effect of psychological factors related to insomnia symptoms on PAP adherence.

It is possible that insomnia persists in some patients even though symptoms of OSA improve following PAP therapy. If that is true, it is likely that OSA patients suffering from insomnia require additional treatment distinct from and supplemental to PAP. It is therefore important to examine how different subtypes of insomnia change with PAP treatment and whether they affect treatment compliance.

1.4 Depression among OSA patients

Disrupted sleep affects the stress system of the body and makes people more vulnerable to developing depression (Meerlo et al., 2008). Many patients with untreated OSA experience frequent nighttime awakenings as well as poor sleep quality followed by fatigue and sleepiness during the day. A high prevalence of depression in this population is therefore to be expected. In fact, studies have revealed high rates of depression among OSA patients in both community and clinical populations (Harris et al., 2009; Peppard et al., 2006). In several studies it is also indicated that OSA patients with high levels of depression have the lowest quality of life score and suffer most from daytime sleepiness and fatigue (Kjelsberg et al., 2005; Bardwell et al., 2003; Akashiba et al., 2002; Sforza et al., 2002).

In a study by Mosko et al. (1989) 58% of OSA patients are reported to have met the DSM criteria for depression. In the Wisconsin Sleep Cohort Study, longitudinal data demonstrated a dose-response association between OSA and depression in a community sample of 1408 participants (Peppard et al., 2006). In other studies, however, an association between OSA and other psychological problems has not been found (Cassel, 1993). Cassel (1993) concluded that the supposed psychological consequences of OSA

are mainly due to a misinterpretation of sleepiness by medical staff and the overlap of symptoms like fatigue between OSA and depression (Cassel, 1993). Furthermore, Bardwell et al. (1999) concluded that many of the previously reported links between depression and OSA diminish after controlling for covariates such as age, BMI, and hypertension. In other studies, however, a strong relationship between OSA and depression is reported even after controlling for potential confounders (Ohayon, 2003).

Studies of untreated OSA patients have indicated that depressive symptoms are stronger predictors of fatigue than OSA severity and that, individually, neither respiratory disturbance index (RDI) nor oxygen saturation are significantly predicted by fatigue (Bardwell et al., 2007). Bardwell et al. (2003) used the Centre for Epidemiological Studies Depression Scale (CES-D) to assess depression and found that one third of the people they assessed with OSA had significant levels of depression which predicted their level of fatigue.

The high co-morbidity of insomnia among OSA patients could also partially explain elevated levels of depression among this population. Epidemiological studies have found individuals with insomnia to be at greater risk for developing depression (Szelenberger & Soldatos, 2005; Holbrook et al., 2000). In fact, it has been indicated that insomniacs have nearly a four times higher risk for developing a new depressive disorder in the following 3.5 years after a diagnosis of insomnia (Szelenberger & Soldatos, 2005).

If there were a direct causative link between OSA and the onset of depression, then depression would be expected to improve with successful treatment of OSA. Some studies have reported improvements of psychological functioning after CPAP treatment (Sánchez et al., 2001; Kuna et al., 2011; Diamanti et al., 2013) but others have not (Munoz et al., 2000; Gagnadoux et al., 2014). Several placebo-controlled studies of the improvement of depression have been conducted with mixed results (Engleman et al., 1999; Barnes et al., 2002). Furthermore, in a number of studies a bidirectional relationship between poor sleep and depression is indicated and some have suggested that sleep difficulties may lead to or exacerbate depression and that by improving sleep quality it is possible to improve symptoms of depression as well (Wiebe et al., 2012; Jansson-Fröjmark & Lindblom, 2008). Sateia (2003) concluded in a review paper on neuropsychological impairment and quality of life in OSA that even though the clinical impression suggests that OSA is related to depression and that treatment can improve

depressive symptoms, the literature does not provide unequivocal support for these associations and that further studies are needed.

It is likely that the relationship between OSA and depression is at least partially due to uncontrolled confounding factors. Obesity is the most commonly suggested confounder, but the association between depression and obesity is well known (Roberts et al., 2000; Onyike et al., 2003; Simon et al., 2006, Araghi et al., 2013). It has been suggested that OSA severity and obesity contribute differently to depressive symptoms in OSA (Aloia et al., 2005). Depressive symptoms in patients with OSA have been proposed to be related to oxygen desaturation and nocturnal hypoxemia (Cheshire et al., 1992) or to sleep fragmentation and excessive daytime sleepiness (Yue et al., 2003) but sleep fragmentation is known to produce symptoms of depression (Martin et al., 1996).

It is unclear whether OSA and depression constitute a real co-morbidity or only share similar symptoms (Baran & Richert, 2003). Research on the relationship between OSA and mental health has to date focused on whether or not there is a significant amount of depression in this population. The problem with this approach, however, has been the inappropriate use of depression measures that has potentially confused outcomes. Symptoms such as fatigue, loss of interest, decreased libido and poor concentration are common in both depression and OSA (Sforza et al., 2002), which means that frequently used depression scales may not be valid in assessing depressive symptoms among OSA patients (Harris et al., 2009).

Even though the prevalence of depression among OSA patients has been studied, the results are mixed and there is still need for further studies. First of all, it is important to carefully select the instruments used to measure depression in this population due to the frequent symptom overlap. Using a standardized psychiatric interview conducted by a health professional would be the gold standard to obtain the true co-morbidity of OSA and depression. The CES-D has proven to be useful in assessing depression among OSA patients (Radloff, 1977) and the Hospital Anxiety and Depression Scale (HAD-D) has also proved to be valid for inpatient populations (Le-Fevre et al., 1999; Snaith, 2003). When these instruments are used in conjunction with a clinical evaluation, it is anticipated that judgments about the extent of depression among OSA patients will become clearer. The inconsistency in research results to date might be due to failure to employ this approach. Furthermore, depression has most often been studied in isolation without considering co-morbid features, such as obesity (Andrews & Oei, 2004). Further research

needs to be conducted to test possible interactions that may account for differing levels of mental health issues in this population.

It is also unknown whether successful treatment of OSA improves symptoms of depression or how depression affects adherence to PAP treatment. Since depression often negatively affects compliance with medical treatment (DiMatteo et al., 2000) it is possible that PAP treatment is less effective among depressed OSA patients. In fact, new studies indicate that depressive OSA patients may have poorer adherence with CPAP treatment (Law et al., 2014).

Patients with OSA often sleep poorly, have a high co-morbidity of insomnia and evidence suggests elevated levels of depression among this patient population. All of these conditions affect quality of life and accordingly it can be difficult to identify the most important contributors for poor health and life qualities among these patients. It is important to look at all of these factors in combination and figure out whether some subgroups of OSA patients require additional interventions prior to or simultaneously with PAP to maximize treatment effects. Such an approach would be a step towards more personalized medicine.

2 Primary aims of this study

The overall aim of this study was to investigate insomnia, depression and quality of life among patients with OSA. Firstly, their prevalence among untreated OSA patients and the relationship with OSA severity, secondly, how these factors change with long term PAP tratment and thirdly if they have some impact on treatment outcome and adherence. The specific aims of each paper were as following:

Paper I: The aims of the study were:

(a) To compare the prevalence of initial and middle insomnia in untreated OSA patients versus controls from the general population in Iceland

(b) To examine whether OSA symptoms are risk factors for insomnia symptoms in a general population sample from Iceland

(c) To investigate whether the coexistence of OSA and insomnia has an additional effect on quality of life compared to OSA alone

Paper II: The aims of the study were:

(a) To examine how different subtypes of insomnia (initial, middle and late insomnia) relate to symptoms of untreated OSA

(b) To explore how PAP treatment affects symptoms of different insomnia subtypes

(c) To examine how different subtypes of insomnia affect adherence to PAP treatment

Paper III: The aims of the study were:

(a) To compare health-related quality of life between the general population and a large group of moderate-to-severe OSA patients prior to treatment initiation

(b) To examine differences in the changes of quality of life after two years of PAP treatment between PAP adherent patients and non-users

Paper IV: The aims of the study were:

(a) To use a standardized psychiatric interview, conducted by a trained psychologist to assess the prevalence of depression among untreated OSA patients

(b) To identify if OSA severity or other co morbid disorders (insomnia, hypertension and diabetes) are related to depression among untreated OSA patients

3 Materials and methods

3.1 Study cohorts

The papers described in this thesis are based on results from three different study cohorts. Papers I and III are based on the Icelandic Sleep Apnea Cohort (ISAC) as well as the general population cohort (BOLD). Paper II is based on the ISAC cohort and paper IV is based on the untreated OSA cohort (Table 1).

3.1.1 Icelandic Sleep Apnea Cohort (ISAC)

All patients with moderate to severe OSA (AHI ≥15 events/hr) who were referred to the Department of Respiratory Medicine and Sleep, Landspitali – The National University Hospital of Iceland for treatment with PAP from September 2005 to December 2009 were invited to participate in the ISAC study (Arnardottir et al., 2012; Arnardottir et al., 2013). No other inclusion or exclusion criteria were used. All ISAC subjects were invited to a two-year follow-up study after starting PAP treatment. Paper I is based on the baseline data from the ISAC cohort, but papers II and III use both baseline and follow up data from ISAC. The study design at baseline that relates to this thesis was the following: Untreated OSA patients underwent a type 3 sleep study, body measurements and answered standardized questionnaires regarding their sleep and health. At two-year follow-up, PAP adherence was assessed, and questionnaires and body measurements repeated.

3.1.2 General population cohort

The general population cohort was primarily invited to participate in the Burden of Obstructive Lung Diseases (BOLD) initiative in Iceland; a multi-centre international study aiming to estimate the burden of chronic obstructive pulmonary disorder (COPD) worldwide (Buist et al., 2007; Benediktsdottir et al., 2010)

This cohort was a random sample of Icelanders, ≥40 years living in the capital area of Reykjavik. Of the 73,391 subjects ≥40 years living in the area, 939 subjects were randomly selected to participate and altogether 762 of the 939 eligible subjects (81.2%) responded. Results from the BOLD cohort were used in paper I. The study design that relates to this thesis was answering standardized questionnaires about health and sleep and body measurements. Papers I and III present results from this cohort.

3.1.3 Untreated OSA cohort

This cohort includes 284 patients diagnosed with OSA in Iceland and referred for PAP treatment to the Department of Respiratory Medicine and Sleep at Landspitali – The National University Hospital of Iceland from February 2010 - December 2013. Altogether 104 among the 284 participants were taking part in an ongoing study of the relationship between OSA and cardiovascular diseases and response to PAP treatment in lean and obese patients. Subjects who had been excluded from the above study were invited to take part in the current study with no other inclusion/exclusion criteria than having AHI>15 (n = 180). All 284 subjects in this cohort went through the same protocol for data collection.

All participants had initially been diagnosed with OSA as defined by an apnea-hypopnea index (AHI) ≥15 events/hr and oxygen desaturation index (ODI) of ≥10 events/hr. When sleep studies were rescored, there were however some subjects who had AHI between 10-15 events/hr but they were not excluded from the study. Altogether, over 90% of approached subjects agreed to participate in the study. The study design at baseline that relates to this thesis was the following: Untreated OSA patients underwent a type 3 sleep study, body measurements, a standardized psychiatric interview and answered standardized questionnaires regarding their sleep and health. Paper IV is based on results from this cohort.

Table 1. The cohorts described in this thesis, by research papers.

	ISAC baseline (n = 822)	ISAC 2 year follow-up	General population cohort (n = 762)	Untreated OSA cohort (n = 284)
Paper I	X		X	
Paper II	X	X (n = 705)		
Paper III	X	X (n = 655)	X	
Paper IV				X

3.2 Measurements

Subjects in all three study cohorts were evaluated in a similar manner at the Department of Respiratory Medicine and Sleep, Landspitali – The National University Hospital of Iceland. All subjects answered the same core questionnaire on general health status, including questions about smoking and whether they had hypertension and/or diabetes (medical diagnosis and medication), or cardiovascular disease (CVD) which was defined as a medical diagnosis of coronary artery occlusion (myocardial infarction or heart attack), heart failure and/or stroke. Subjects in all cohorts listed their medication use for hypertension and diabetes, which was subsequently coded according to the Anatomical Therapeutic Chemical (ATC) drug classification system (www.whocc.no/atcddd) and ISAC subjects also gave a detailed list of all other medications they used. Furthermore, ISAC patients were asked whether they were taking medication to help them sleep. Subjects from the untreated OSA cohort were also asked to list if they were taking medication to help them sleep which was subsequently coded according to the ATC system. Those who listed medications with the ATC code N05C were registered as using sleep medications and those who listed medications with the ATC code N06A were listed as using antidepressants. All questionnaires were translated from English into Icelandic and back-translated to assure accuracy.

Height and weight were measured in the same manner for all participants. Subjects were asked to remove their shoes and heavy outer garments for the measurements.

3.2.1 Type 3 sleep studies

Prior to referral for PAP treatment, all OSA patients had a sleep study with an Embletta type 3 portable monitor or an Embla 12 channel system (Natus Medical Inc., Ontario, Canada) or a T3 device (Nox Medical, Reykjavik, Iceland). The same signals were recorded on all studies; nasal airflow by cannula, oxygen saturation, heart rate, respiratory movements by respiratory inductance plethysmography (RIP) belts, body position and activity by accelerometer. Trained sleep technologists scored all sleep studies and the studies had to have ≥4 hours of a scorable O_2 saturation signal. Events were scored according to the following definitions: a classification of hypopnea required a ≥30% decrease in flow with ≥4% oxygen desaturation or a ≥50% decrease in flow for ≥10 sec with a sudden increase in flow at the end of the event. A classification of an obstructive apnea required a ≥80% decrease in flow for ≥10 sec. The AHI was calculated as the number of apneas plus hypopneas/hr. of recording (excluding upright time). ODI was calculated as the number of falls in oxygen of ≥4% per hour of recording (excluding upright time). Hypoxia time was defined as the number of minutes with SaO2 <

90%. The minimum SaO2 was defined as the lowest oxygen saturation reached during the study.

To test for systematic differences in the measurement of OSA severity by Embletta vs. T3 devices, 13 subjects slept with both devices simultaneously during their laboratory diagnostic OSA study. Their AHI ranged from 0 - 58 events/hr. The intraclass correlation coefficient (ICC) for AHI was 0.99 ($p < 0.001$) and for ODI 0.97 ($p < 0.001$), showing no significant differences in measured OSA severity between devices.

Sleep studies were not performed in the general population cohort (papers I and III). Therefore some subjects may have undiagnosed sleep apnea. Subjects in this cohort were defined as high or low risk for OSA based on the Multivariable Apnea Prediction (MAP) index (Maislin et al., 1995). The MAP score is based on self-reported frequency of occurrence of apnea symptoms (snoring or gasping, breathing stops, choking or struggling for breath during the night) as well as BMI, age and gender. The MAP index ranges from 0 - 1 where subjects with a score of 0 are least likely to have OSA. A MAP index cut-off of 0.75 was used to define high risk OSA (paper I).

3.2.2 PAP use

All PAP treatment in Iceland is administered by the Department of Respiratory Medicine and Sleep at Landspitali – The National University Hospital of Iceland, which is the sole provider of ventilator treatment in Iceland. All OSA patients were treated with autoPAP or CPAP (ResMed Corp. San Diego, CA, USA) and treatment was only changed to BiPAP or adaptive servoventilation if treatment efficacy on autoPAP or CPAP was inadequate (defined by AHI $\geq$ 15 using PAP and/or persistent patient complaints).

In the ISAC 2 year follow-up (Paper II and III), PAP adherence was objectively measured by downloading the mask on time stored by the PAP unit in the previous 4 weeks if available (in those patients on ResMed S8 machines). Subjects recruited at the beginning of the study period had older models of PAP devices, which did not provide this type of information. Self-report data from all patients were also collected at the follow-up visit, based on three multiple choice questions about average PAP use: 1) Do you use PAP for your sleep apnea? (Yes, no or don't know), 2) How many nights per week do you use PAP? (Response alternatives: 1, 2, 3, 4, 5, 6 or 7 nights/week), 3) How much of the sleeping time each night do you use PAP? (Response alternatives: all the sleeping time [100%]; almost all the sleeping time [80 - 99%]; most of the sleeping time [60 - 79%]; about half of the sleeping time [40 - 59%]; about one third of the sleeping time [20 - 39%]; almost none of the sleeping time [1 -

19%]; none of the sleeping time [0%]; don´t know). For further details, see Arnardottir et al., 2013.

In addition to assessing PAP adherence, OSA subjects in the ISAC cohort answered the same questionnaires regarding health and sleep and had repeated body measurements at the follow-up visit (Papers II and III).

3.2.3 Sleep symptoms

Subjects in all study cohorts answered the Epworth Sleepiness Scale (ESS) (Johns, 1992) and sleep symptoms were assessed using the Basic Nordic Sleep Questionnaire (BNSQ), which includes questions on sleep quality, insomnia symptoms, snoring, nocturnal sweating, gastroesophageal reflux (GER) and daytime sleepiness (Partinen & Gislason, 1995). Answers were rated on a five point scale: never/almost never (1); less than once a week (2); once or twice a week (3); three to five times a week (4); every day or almost every day of the week. In addition, subjects answered questions on restless legs syndrome (RLS) symptoms based on recommendations from the International Restless Legs Syndrome Study Group (Allen et al., 2003). Those who answered the questionnaire as follows were regarded as having symptoms of RLS: a strong urge to move the legs often or very often; the discomfort in the legs was relieved by moving the legs or walking; the symptoms had to be most prominent in the evening, at bedtime or no different between times of day (Benediktsdottir et al., 2010).

3.2.4 Insomnia

Insomnia was defined as a score of 4 or 5, i.e. reporting insomnia symptoms ≥3x week according to the BNSQ. Three subtypes of insomnia symptoms were defined: difficulty initiating sleep (initial insomnia), difficulty maintaining sleep (middle insomnia) and early morning awakenings (late insomnia). However, the questionnaire for the general population cohort only included questions on two of these subtypes (initial and middle insomnia).

3.2.5 Quality of life

Participants in all cohorts completed the Short Form 12 (SF-12) questionnaire to assess quality of life. Two summary component scores are derived from The SF-12, the physical component score (PCS) and mental component score (MCS). These scores range from 0-100, where a zero score indicates the lowest life quality and 100 indicates the highest life quality (Ware et al., 1996). The SF-12 is derived from the SF-36 and has been widely used and demonstrated to be reliable and valid in assessing quality of life in large group comparisons (Gandek et al., 1998).

3.2.6 Depression

In the untreated OSA cohort, depression was evaluated with the Mini International Neuropsychiatric Interview (MINI), a short diagnostic structured interview that contains 120 questions and screens 17 axis I disorders according to the DSM IV criteria for 24 current and lifetime diagnoses. A trained psychologist, whith experience in working with OSA patients and training in administrating the MINI conducted all the interviews. The average administration time of the MINI is 15-20 minutes (Sheenan et al., 1998). Only depressive disorders (major depression and dysthymia) were investigated in this study. The MINI has two to four screening questions per disorder and only when the screening questions are positively answered, are additional symptom questions within each disorder section asked. Studies have showed that the MINI provides reliable DSM III-R diagnosis within a short time frame (Lecrubier et al., 1997). For the English version of the MINI, excellent inter-rater and test-retest reliability, and moderate validity of MINI versus the World Health Organisation Composite International Diagnostic Interview (CIDI) have been reported (Lecrubier et al., 1997; Sheehan et al., 1998). The Icelandic version of the MINI has not been extensively studied but one preliminary study gives support to its validity (Sigurðsson, 2008).

A diagnosis of dysthymia, according to the DSM-IV includes depressed mood most of the day for two or more years. And in addition at least two of the following symptoms causing distress in your life or interfering with your functional ability: poor appetite or overeating, sleep problems, tiredness or lack of energy, low self-esteem, hopelessness, poor concentration and trouble making decisions. A diagnosis of major depression includes having five or more of the following symptoms over a two-week period, most of the day, nearly every day. At least one of the symptoms must be either a depressed mood or a loss of interest or pleasure. Other symptoms may include: depressed mood, such as feeling sad, empty or tearful, significantly diminished interest or feeling no pleasure in almost all activities, significant weight loss when not dieting, weight gain, or decrease or increase in appetite, insomnia or increased desire to sleep, restlessness or slowed behavior that can be observed by others, fatigue or loss of energy, feelings of worthlessness, or excessive guilt, trouble making decisions, or trouble thinking or concentrating, recurrent thoughts of death or suicide, or a suicide attempt. These symptoms must be severe enough to cause noticeable problems in day-to-day activities, such as work, school, social activities or relationships with others (American Psychiatric Association, 2000).

3.3 Statistical analysis

STATA 11.0 and STATA 12.0 were used for all statistical analyses and a p value of ≤ 0.05 was considered significant for all analyses.

Paper I: Differences between the groups of subjects with and without OSA were first compared using the chi square test and unpaired *t*-test. Logistic regression was used for multivariable analyses and assessment of adjusted odds ratios (OR) with 95% confidence intervals (95% CI).

Paper II: Change in the prevalence of insomnia symptoms with PAP treatment was estimated using population-averaged generalized estimating equations for the binomial outcome. The Wald test was used to examine differences in change of prevalence by level of PAP use. Logistic regression was used to analyze risk factors for non-compliance with PAP treatment and assessment of adjusted odds ratios (OR) with 95% confidence intervals (95% CI).

Paper III: For bivariate analysis, the chi square test and *t*-test were used for nominal and continuous variables respectively. Linear regression was used in adjusted analyses and results are presented as adjusted β estimates and 95% confidence intervals or adjusted least squares mean estimates and standard errors.

Subclassification using propensity score (PS) quintiles, following an established sequential heuristic described in detail by Maislin & Rubin (2010), was used in two separate analyses: 1) to obtain a comparable sample of OSA patients and subjects from the general population with respect to relevant covariates; and 2) to minimize selection bias due to measured covariate imbalance in our non-randomized treatment group comparison between PAP adherent patients and non-users, thereby allowing for causal inference (Keenan et al., 2014).

In order to obtain a comparable sample of OSA patients and subjects from the general population, populations were first restricted to participants aged 40-75 years and with BMIs between 25-40 kg/m^2, based on the obvious distributional differences in age and BMI between the two samples. Within this restricted sample, subclassification by PS quintiles was used to further match samples on relevant covariates.

Within the OSA cohort only, PS sub-classification was used to construct a sample of PAP full and non-users in which to obtain an unbiased assessment of the effect of PAP adherence on changes in quality of life. Full and non-users were balanced within subclass with respect to relevant measured covariates at baseline.

Paper IV: For bivariate analysis, the chi square test and *t*-test were used for nominal and continuous variables respectively. Logistic regression was used for multivariable analyses and assessment of adjusted OR with 95% confidence intervals (95% CI).

The consent of the National Bioethics Committee and the Data Protection Authority of Iceland was granted for all study cohorts and written consent obtained from all participants in the studies. Additionally, the consent of the Institutional Review Board of the University of Pennsylvania was granted for the ISAC study.

4 Results

4.1 The study cohorts

The results in this thesis are presented in the following order:

First the baseline characteristics of subject in all study cohorts are presented; secondly, symptoms of insomnia and quality of life are compared among untreated ISAC subjects and controls from the general population. Thirdly, results regarding depression among subjects from the untreated OSA cohort are presented and finally changes in insomnia and quality of life among ISAC subjects after PAP treatment are reported.

4.1.1 Baseline characteristics

In the ISAC cohort (Papers I – III) over 90% of eligible and approached subjects agreed to participate in the study, a total of 826 subjects. Four subjects withdrew from the study, leaving 822 subjects in the baseline cohort, n = 666 males and 156 females with an age range of 21 - 83 years. The subjects in ISAC were invited to a 2-year follow-up visit, done in the same manner as the initial visit (Paper II and III). This follow-up was completed in 741 (90.1%) subjects from October 2007 to January 2012. No significant differences were found in age, BMI, OSA severity (AHI or ODI) or gender between non-responders (n = 81) and responders (n = 741). At follow-up, three subjects did not complete the questions on insomnia (Paper II) and n = 53 did not answer questions on quality of life (Paper III). Furthermore, 33 subjects were using a mandibular advancement device instead of PAP at the follow-up, and three had missing adherence data on PAP, leaving n = 705 in follow-up analysis in Paper II (Figure 3); 473 PAP users and 232 non-users and n = 655 in paper III; 441 PAP users and 214 non-users (Figure 4).

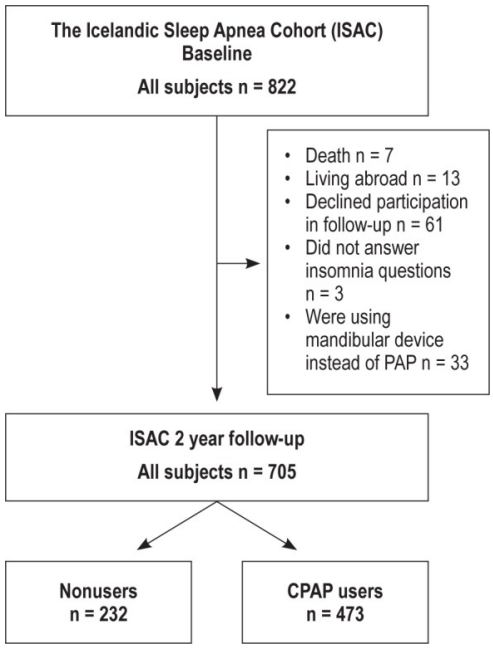

Figure 3. Flow chart of ISAC subjects in insomnia analyses pre and post PAP treatment. Reproduced from Paper II.

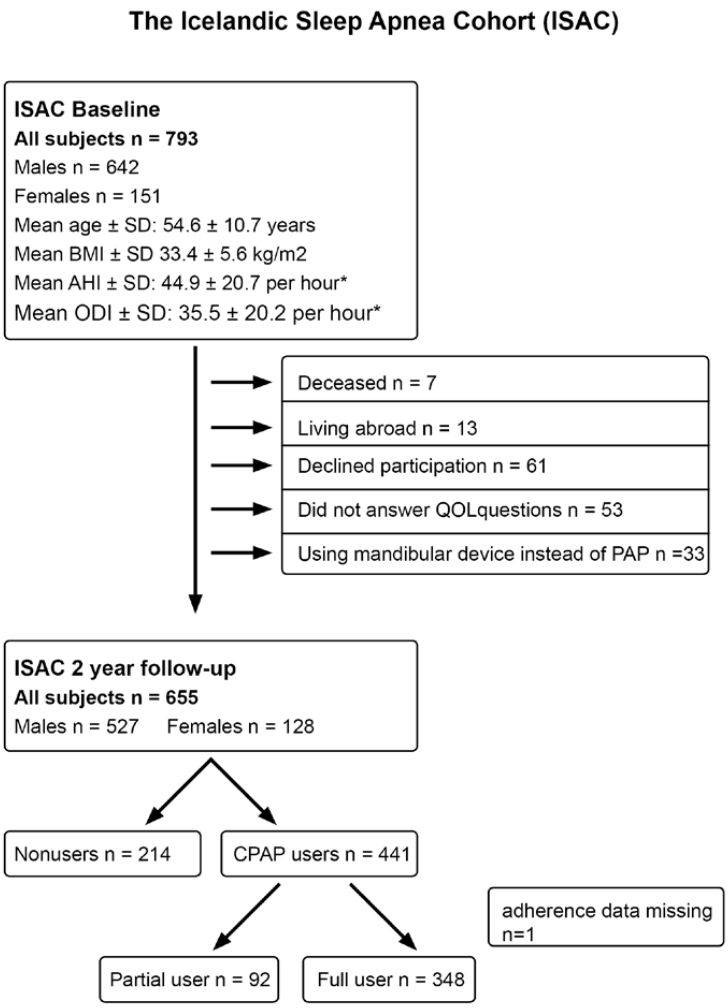

Figure 4. Flow chart of ISAC subjects in quality of life analyses pre and post PAP treatment. Reproduced from Paper III.

The general population cohort (Papers I and III) included a total of 762 randomly selected Icelanders, ≥40 years living in the capital area of Reykjavik. Altogether 762 (404 males and 358 females) of the 939 eligible subjects (81.2%) responded. The mean age in this cohort was 57.0 ±11.8 years and the mean BMI was 27.9 ± 4.9 kg/m^2.

Subjects in the untreated OSA cohort were 284 patients diagnosed with OSA in Iceland and referred for positive airway pressure (PAP) treatment to the Landspitali - University Hospital in Reykjavik from February 2010 - December 2013. Over 90% of eligible and

approached subjects agreed to participate in the study. The majority of the sample were males (78%) and the mean age was 53.9 ± 9.1 years.

The characteristics of the three study cohorts are shown in Table 2. Subjects in the untreated OSA cohort were on average 0.7 years younger than the untreated ISAC subjects and 3.1 years younger than subjects from the general population. The majority of both ISAC (81%) and untreated OSA subjects (79%) were males while the gender distribution among the general population subjects was more even (males 53%). As expected, OSA patients (both untreated ISAC and untreated OSA cohort) had higher BMI scores and a higher prevalence of diabetes and hypertension. Furthermore, OSA subjects reported more daytime sleepiness as measured by the ESS than subjects from the general population. Subjects from the ISAC cohort had a higher sleepiness score and more severe OSA as compared to subjects from the untreated OSA cohort (Table 2).

Table 2. Demographic factors of all three study cohorts. Adapted from Papers I-IV.

	General population cohort (Papers I and III)	ISAC cohort* (Papers I, II and III)	Untreated OSA cohort (Paper IV)
	n = 762	***n = 793***	***n = 284***
Age (years)	57.0 ± 11.8	54.6 ± 10.7	53.9 ± 9.1
Males (%)	53.0	81.0	78.5
BMI	27.9 ± 4.9	33.4 ± 5.6	33.0 ± 6.0
AHI	N/A	44.9 ± 20.7	33.1 ± 18.3
ODI	N/A	35.5 ± 20.2	29.8 ± 18.1
ESS	6.0 ± 3.9	11.7 ± 5.1	10.3 ± 4.4
Hypertension (%)	25.1	45.3	59.4
Diabetes (%)	2.9	8.7	9.2

Values are given as mean ± standard deviation for continuous variables and percentages for nominal variables. BMI, body mass index (kg/m^2), AHI, apnea-hypopnea index (events/hr); ODI, Oxygen desaturation index (events/hr); ESS, Epworth sleepiness score. * Baseline data from ISAC subjects used in Paper III.

4.2 Untreated ISAC subjects compared to the general population subjects:

4.2.1 Symptoms of insomnia

The prevalence of having some symptoms of insomnia among untreated ISAC subjects was 68.3%, but there was considerable overlap between the three different subtypes of insomnia. Symptoms of initial insomnia were reported by 15.5% of patients, 59.3% had symptoms of middle insomnia, and 27.7% exhibited symptoms of late insomnia (Figure 5). Almost half of those who had symptoms of initial insomnia at baseline also had symptoms

of middle and late insomnia. Most of those with symptoms of late insomnia at baseline also had symptoms of middle insomnia. Interestingly, most of those with symptoms of middle insomnia did not present with one or the other subtypes (Figure 5).

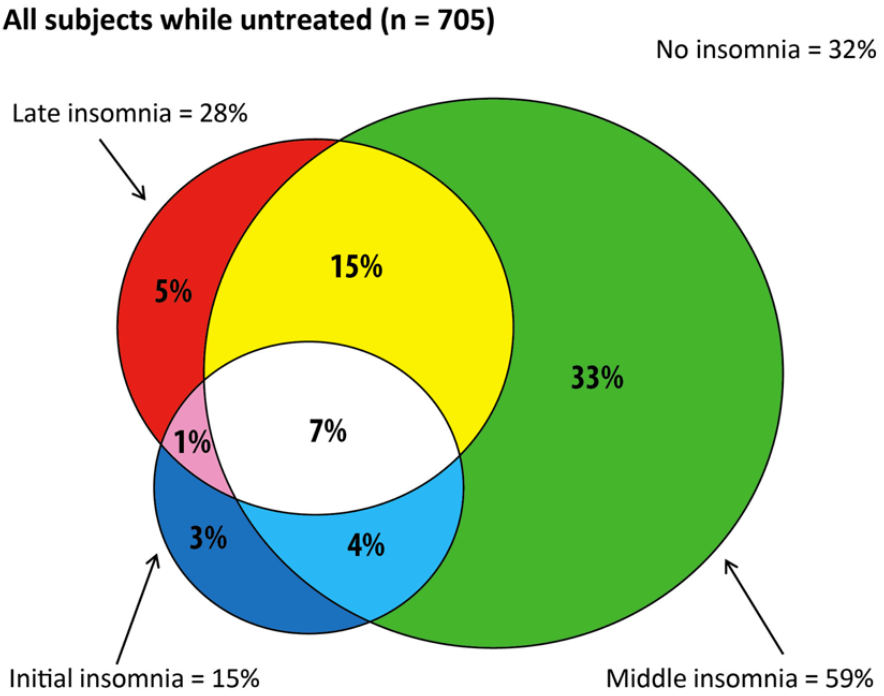

Figure 5. Symptoms of initial, middle and late insomnia among untreated ISAC subjects. Reproduced from Paper II.

Symptoms of middle insomnia were less frequent among the general population subjects compared to the untreated ISAC subjects (32% vs. 59.3%; $p<0.001$). However, there was not a significant difference in the prevalence of initial insomnia between subjects from these two cohorts. Overall, women in both groups had a higher prevalence of insomnia symptoms (Figures 6 and 7). Middle insomnia was similarly common among men and women, while having initial insomnia and a combination of the two subtypes was more common among women ($P < 0.05$).

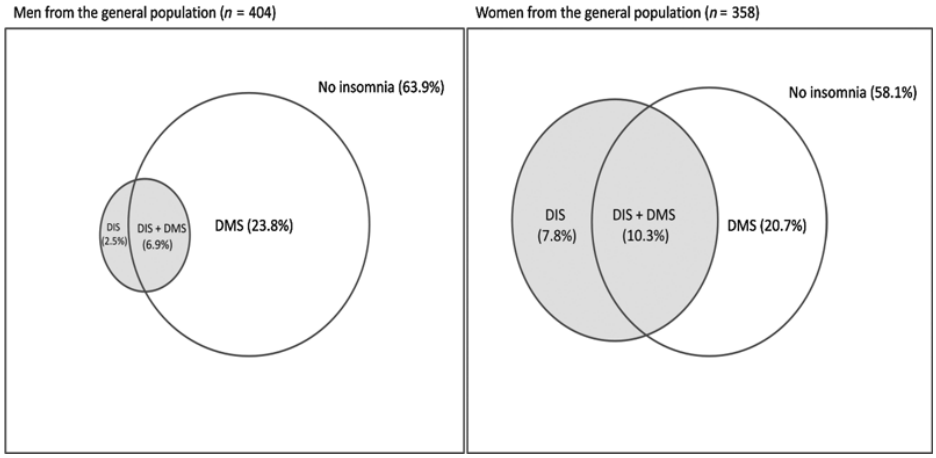

Figure 6. Prevalence of initial insomnia (DIS: initial insomnia), middle insomnia (DMS: middle insomnia) and a combination of the two subtypes (DIS + DMS) among men and women from the general population. Reproduced from Paper I.

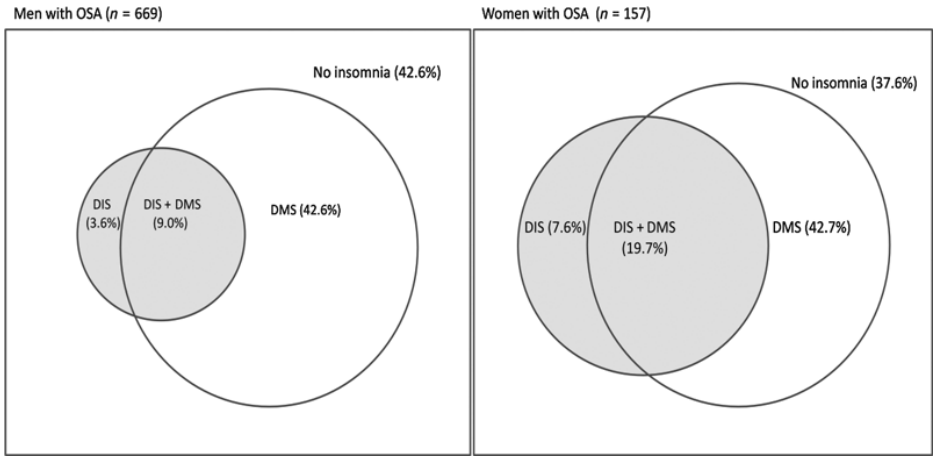

Figure 7. Prevalence of initial insomnia (DIS: initial insomnia), middle insomnia (DMS: middle insomnia) and a combination of the two subtypes (DIS + DMS) among men and women from the ISAC cohort while untreated. Reproduced from Paper I.

4.2.1.1 Factors associated with insomnia in the general population and untreated ISAC subjects

Table 3 shows that among the general population subjects, poor mental and physical quality of life, hypertension and RLS were independent risk factors for both initial and middle insomnia. In addition, a high MAP score was an independent risk factor for middle insomnia.

Table 3. Factors associated with initial and middle insomnia in the general population. The association is expressed as adjusted odds ratio (OR) with a 95% confidence interval [OR (95% CI)]. Adapted from Paper I.

	Initial insomnia *OR (95% CI)**	Middle insomnia *OR (95% CI)**
Smoking history	0.96 (0.69–1.33)	0.98 (0.77–1.24)
RLS	**2.69 (1.60–4.53)**	**2.08 (1.36–3.18)**
MCS	**0.91 (0.87–0.95)**	**0.95 (0.92–0.99)**
PCS	**0.93 (0.90–0.95)**	**0.97 (0.94–0.99)**
Diabetes	0.59 (0.21–1.66)	0.92 (0.44–1.95)
Hypertension	1.21 (0.74–1.96)	**1.64 (1.15–2.34)**
MAP index	1.59(0.59–4.35)	**2.13 (1.02–4.43)**

RLS, restless leg syndrome; MCS, mental component score from the SF-12; PCS, physical component score from the SF-12; MAP, multivariable apnea index. Significance is marked as **bold.** *Adjusted for all the variables in the table.

Among the untreated ISAC subjects, female gender and smoking were independent risk factors for initial insomnia, whereas age and RLS were independent risk factors for middle insomnia. Lower mental and physical qualities of life were associated with both initial and middle insomnia among untreated ISAC subjects (see table 4).

Table 4. Factors associated with initial and middle insomnia among untreated ISAC subjects. The association expressed as the adjusted odds ratio (OR) with a 95% confidence interval [OR (95% CI)]. Adapted from Paper I.

	Initial insomnia *OR (95% CI)**	Middle insomnia *OR (95% CI)**
Age per 10 years	0.89 (0.70–1.10)	**1.27 (1.08–1.48)**
Female gender	**2.43 (1.51–3.91**	0.89 (0.60–1.31)
BMI by 5 units	1.04 (0.86–1.27)	1.14 (0.98–1.32)
Ex-smoker	0.97 (0.56–1.68)	1.12 (0.80–1.63)
Current smoker	**2.40 (1.35–4.25)**	0.96 (0.63–1.47)
Snoring every day	0.64 (0.38–1.07)	1.29 (0.88–1.88)
RLS	1.11 (0.69–1.77)	**1.71 (1.18–2.46)**
MCS	**0.96 (0.94–0.98)**	**0.98 (0.97–1.00)**
PCS	**0.97 (0.95–0.99)**	**0.98 (0.97–1.00)**
Diabetes	1.03 (0.54–2.00)	0.69 (0.42–1.13)
Hypertension	1.12 (0.70–1.78)	1.00 (0.72–1.38)

BMI, body mass index (kg/m^2); RLS, restless legs syndrome; MCS, mental component score from the SF-12; PCS, physical component score from the SF-12; Significance is marked as **bold**. *Adjusted for all the variables in the table.

4.2.1.1.1 OSA high and low risk subjects from the general population

Subjects from the general population were defined as low and high risk for OSA based on the MAP index. The OSA high-risk definition was met by 92 (12.0%) of general population subjects with a mean MAP score of 0.81 ± 0.05. The low-risk subjects were 672 (88.0%) individuals with a mean MAP score of 0.33 ± 0.2.

Middle insomnia was reported among 39.7% of high-risk subjects compared to 31.1% of low-risk subjects (p = 0.135). Symptoms of initial insomnia were reported among 22.9% of high-risk subjects compared to 13.2% of low-risk subjects (p = 0.027). Both initial and middle insomnia were most frequent among subjects with the highest MAP score (0.75–1.0). Symptoms of initial insomnia were particularly common among subjects with a MAP score between 0.75 and 1.0 compared to subjects with a lower MAP score (p < 0.05) (Figure 8).

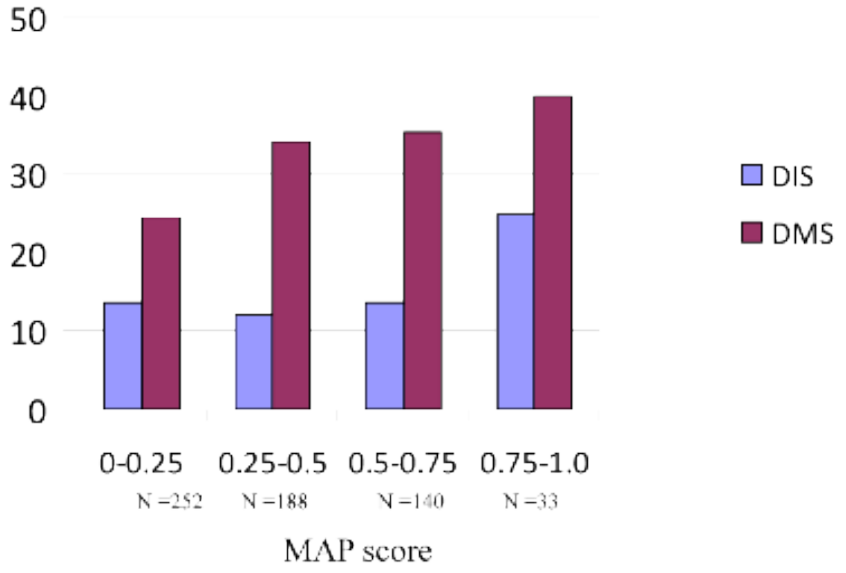

Figure 8. Prevalence (%) of initial and middle insomnia among the general population subjects based on the multivariable apnea index (MAP). Adapted from Paper I.

4.2.2 Quality of life

Untreated ISAC subjects reported worse quality of life when compared to subjects from the general population. Both MCS and PCS remained significantly lower among untreated ISAC subjects after adjusting for age, BMI, gender, smoking and the co-morbidities listed in table 5; on average, OSA patients had PCS scores 9.48 points lower (95% CI: -10.53, -8.44; p<0.0001) and MCS scores 3.35 points lower (95% CI: -4.35, -2.35; p<0.0001) than the general population.

Table 5. Smoking, co-morbidities and quality of life among the untreated ISAC subjects and subjects from the general population cohort. Adapted from Paper III .

	General population (n = 762)	OSA (n = 793)	P value
Smoking history			**<0.001**
Never smoker (%)	39.2	27.3	
Previous smoker (%)	42.6	51.0	
Current smoker (%)	18.2	21.7	
Hypertension (%)	25.1	45.3	**<0.001**
Cardiovascular disease (%)	15.1	18.4	0.078
Diabetes (%)	2.9	8.7	**<0.001**
Epworth Sleepiness Scale	6.0 ± 3.9	11.7 ± 5.1	**<0.001**
Initiall insomnia (%)	14.1	15.3	0.520
Middle insomnia (%)	17.3	34.8	**<0.001**
Late insomnia (%)	—	27.9	—
Mental component score	51.4 ± 4.7	48.3 ± 10.9	**<0.001**
Physical component score	50.9 ± 7.8	40.3 ± 10.9	**<0.001**

Values are given as mean ± standard deviation for continuous variables and percentages for nominal variables. Significance is marked as **bold.**

4.2.2.1 Determinants of physical and mental quality of life

When assessing potential determinants of physical and mental quality of life among untreated ISAC subjects and the general population it was found that PCS was lower for those with a higher BMI, both for ISAC subjects and the general population. Furthermore, higher age, female gender, and cardiovascular disease were significantly associated with a lower PCS in both groups and diabetes was associated with a worse PCS in the general population subjects. A lower MCS was associated with lower age, current smoking and hypertension among the general population subjects, and with lower age, current smoking, female gender, and a lower BMI among the untreated ISAC patients (table 6).

Table 6. Independent association with physical and mental component scores in the general population cohort and untreated ISAC subjects. Adapted from Paper III.

	General population (n = 762)		Untreated ISAC subjects (n = 793)	
	PCS	MCS	PCS	MCS
Age (years)	**-0.12 (-0.17, -0.07)**	**0.09 (0.05, 0.12)**	**-0.16 (-0.23, -0.08)**	**0.16 (0.07, 0.24)**
Female gender	**-2.21 (-3.25, -1.16)**	-0.52 (-1.2, 0.16)	**-5.17 (-6.99, -3.36)**	**-2.48 (-4.45, -0.51)**
BMI	**-0.20 (-0.31, -0.10)**	0.04 (-0.03, 0.11)	**-0.53 (-0.66, -0.40)**	**0.15 (0.01, 0.29)**
Smoking history				
Previous smoker	-1.05 (-2.19, 0.09)	-0.71 (-1.46, 0.03)	-1.4 (-3.07, 0.26)	-0.74 (-2.56, 1.07)
Current smokers	**-2.77 (-4.26, -1.28)**	**-1.01 (-1.98, -0.04)**	**-2.62 (-4.61, -0.63)**	**-4.18 (-6.34, -2.01)**
Hypertension	-0.62 (-1.93, 0.69)	**-1.35 (-2.2, -0.49)**	0.25 (-1.31, 1.8)	-0.9 (-2.59, 0.79)
Cardiovascular disease	**3.54 (-5.20, -1.87)**	0.44 (-0.64, 1.52)	**-5.77 (-7.67, -3.86)**	-1.27 (-3.34, 0.79)
Diabetes	**-6.97 (-10.18, -3.77)**	0.98 (-1.1, 3.06)	0.00 (-2.59, 2.59)	1.1 (-1.71, 3.91)

Values are given as adjusted beta-values (95% CI); estimates are adjusted for all other variables in the table. BMI, body mass index (kg/m^2); MCS, mental component score from the SF-12; PCS, physical component score from the SF-12. Significance is marked as **bold.**

Table 7 shows that symptoms of initial and middle insomnia were both associated with lower MCS and PCS among the general population subjects. Among the ISAC subjects, there was no significant relationship between severity of OSA, based on AHI and ODI, and either PCS or MCS. Initial insomnia was associated with a lower PCS and MCS, and late insomnia was associated with a lower MCS among the untreated ISAC subjects. Furthermore, more daytime sleepiness was associated with a decreased quality of life among the ISAC subjects but no such relationship was found among the general population subjects. Sleep medication and antidepressant use was associated with poorer PCS and MCS in the ISAC subjects. These data were not available in the general population sample (Table 7).

Table 7. Independent associations of sleep symptoms with physical and mental component scores in the general population subjects and untreated ISAC subjects. Adapted from Paper III.

	General population (n = 762)		OSA patients (n = 793)	
	PCS	MCS	PCS	MCS
Epworth sleepiness score	0.06 (-0.08, 0.20)	-0.08 (-0.16, 0.01)	**-0.36 (-0.50, -0.22)**	**-0.27 (-0.42, -0.13)**
Initial insomnia	**-2.90 (-4.49, -1.32)**	**-1.94 (-2.94, -0.95)**	**-2.62 (-4.72, -0.51)**	**-2.98 (-5.19, -0.77)**
Middle insomnia	**-1.49 (-2.94, -0.03)**	**-1.04 (-1.96, -0.13)**	-1.03 (-2.49, 0.43)	0.32 (-1.21, 1.85)
Late insomnia	n/a	n/a	-0.26 (-1.89, 1.36)	**-2.24 (-3.94, -0.54)**
Sleep medication use	n/a	n/a	**-2.75 (-5.14, -0.36)**	**-4.37 (-6.87, -1.87)**
Antidepressant use	n/a	n/a	**-3.88 (-5.79, -1.98)**	**-5.88 (-7.88, -3.88)**

Values are given as adjusted beta-values (95% CI). The beta estimates are adjusted for all variables in the table and for gender, age and body mass index. MCS, mental component score from the SF-12; PCS, physical component score from the SF-12 Significance is marked as **bold.**

The covariate balance achieved by applying PS methodology to the untreated ISAC subjects and the general population subjects is shown in Figure 9, a modified version of a Love plot (Ahmed et al., 2006). Prior to implementing the PS heuristic, there were significant differences between the untreated ISAC subjects and the general population subjects for BMI, gender, past smoking status, never smoker status, hypertension, diabetes and cardiovascular disease (all $p<0.05$). However, after sub-classification and controlling for the PS quintile, there were no differences between the ISAC cases and the general population subjects (all $p>0.686$).

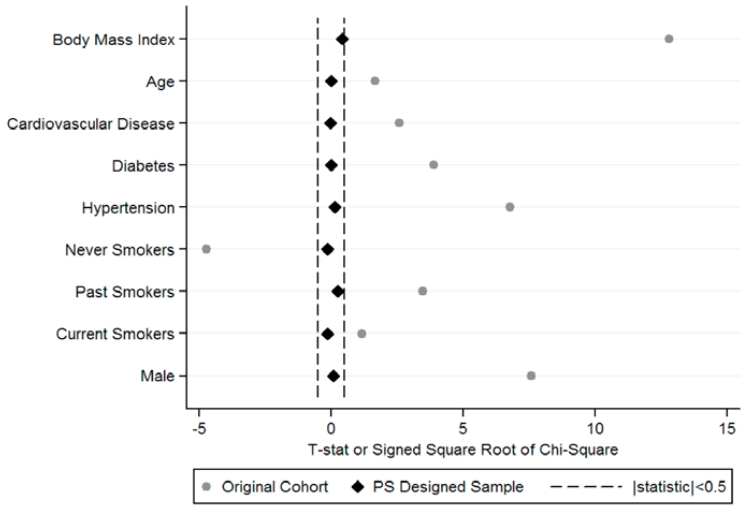

Figure 9. Modified Love plot comparing the untreated ISAC subjects (n = 494) and the general population subjects (n = 418) before and after PS matching. Reproduced from Paper III.

Comparison of PCS and MCS within the PS designed sample of the ISAC cases and the general population subjects (Table 8), the untreated ISAC subjects had a significantly lower quality of life in both measures; with a PCS score 9.5 points lower than controls ($p<0.001$) and an MCS score 3.0 points lower ($p<0.001$).

Table 8. Comparison of baseline quality of life measures in the ISAC - general population propensity score sample. Adapted from Paper III.

	LS Mean ± SE			
	ISAC	General population	Difference (95% CI)	p*
Physical component score	41.4 ± 0.45	50.9 ± 0.48	-9.48 (-10.81, -8.14)	<0.001
Mental component score	48.3 ± 0.40	51.3 ± 0.43	-2.95 (-4.15, -1.75)	<0.001

*p-value adjusted for propensity score subclass

4.3 Depression among OSA patients: Results from the untreated OSA cohort

Among subjects in the untreated OSA cohort, the women were on average 2.7 years older than the men. The women were also more obese but with less severe OSA, as measured by AHI and ODI. Furthermore, women were more likely to report symptoms of initial and middle insomnia and to use sleep medications (ATC code N05C) and antidepressants (ATC code N06A) (Table 9).

Table 9. Gender differences in baseline characteristics of subjects from the untreated OSA cohort. Adapted from Paper IV.

	Men (n = 223)	Women (n = 61)	P value for gender difference
Age	53.3 ± 9.2	56.0 ± 8.2	**0.041**
BMI	32.5 ± 5.7	34.8 ± 6.4	**0.006**
AHI	34.3 ± 18.9	28.6 ± 15.3	**0.036**
ODI	30.9 ± 18.7	25.6 ± 15.0	**0.049**
ESS	10.4 ± 4.3	9.8 ± 4.7	0.401
Hypertension (%)	57.2	67.2	0.159
Diabetes (%)	9.1	9.8	0.851
Initial insomnia (%)	13.6	36.1	**<0.001**
Middle insomnia (%)	50.0	75.4	**<0.001**
Late insomnia (%)	26.7	32.8	0.348
Sleep medication (%)	10.3	32.8	**<0.001**
Antidepressant use (%)	15.7	27.9	**0.029**

Values are given as mean ± standard deviation for continuous variables and percentages for nominal variables. BMI, body mass index (kg/m^2); AHI, apnea-hypopnea index (events/hr); ODI, oxygen desaturation index (events/hr); ESS, Epworth sleepiness score. Significance is marked as **bold.**

4.3.1 Prevalence of depression

Overall, 15.5% of subjects in the untreated OSA cohort met the diagnosis for dysthymia, but women had a significantly higher prevalence than men (29.5% vs. 11.7%, p<0.001). The prevalence of major depression was 6% in the overall sample and there was no difference between genders (5.8% among men vs. 6.6 % among women). The prevalence of depression

overall (dysthymia or major depression) was 20.8% with women showing a significantly higher prevalence, 36.1% vs. 16.6% among men, ($p<0.001$) but this difference was driven by the dysthymia results (Figure 10). Furthermore, 82% of the women were postmenopausal, and depression was more common among them as compared to premenopausal women (31.8% vs. 10.3%; $p = 0.04$).

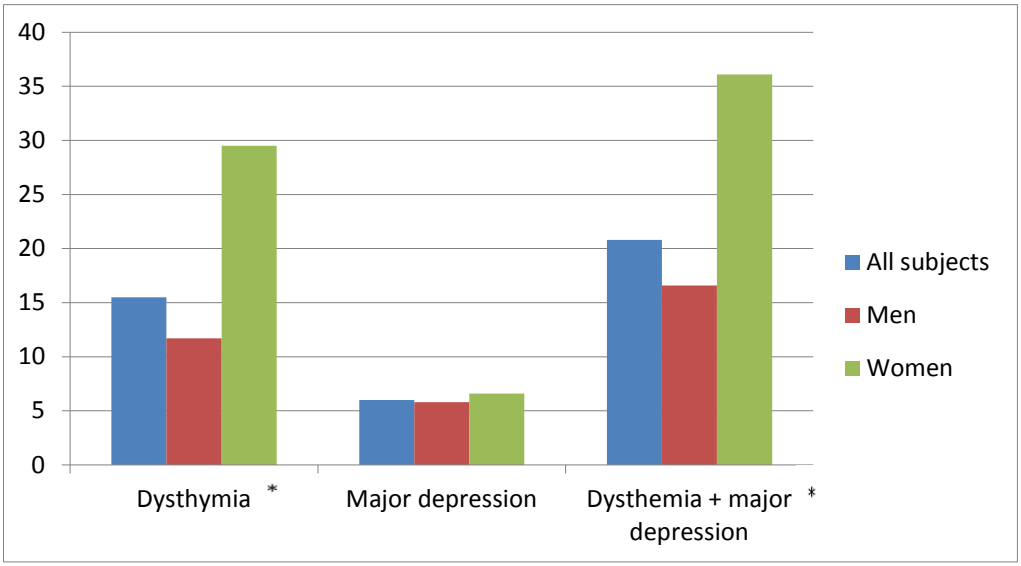

Figure 10. The prevalence (%) of depression in the overall untreated OSA cohort and by genders separately. * gender difference in dysthymia and dysthymia + major depression ($p<0.001$). Reproduced from Paper IV.

4.3.2 Characteristics of subjects with and without depression

Subjects who met the diagnosis for depression (dysthymia or major depression) were more obese, more sleepy and with a lower OSA severity. In addition, they had a lower mental and physical quality of life, were more likely to suffer from initial and late insomnia and to use sleep medications and antidepressants (Table 10).

Table 10. Characteristics of OSA patients with and without depression (dysthymia or major depression)**.** Adapted from Paper IV.

	Subjects without depression (n = 225)	Subjects with depression (n = 59)	P value
Women (%)	17.3	37.3	
Age (yrs.)	54.2±9.0	52.7±9.4	0.281
BMI	32.6±5.8	34.5±6.3	**0.023**
ESS	9.9±4.5	11.5±3.5	**0.017**
AHI	33.5±18.7	31.7±16.9	0.527
ODI	29.8±18.2	29.7±18.0	0.956
PCS	41.9±9.4	36.5±10.0	**<0.001**
MCS	45.4±11.0	36.7±8.5	**<0.001**
Hypertension (%)	58.0	64.4	0.375
Diabetes (%)	9.0	10.2	0.777
Exercise (%)	66.1	50	**0.047**
Initial insomnia (%)	13.5	37.3	**<0.001**
Middle insomnia (%)	53.6	62.7	0.211
Late insomnia (%)	24.2	42.4	**0.006**
Sleep medication (%)	8.9	39.0	**<0.001**
Antidepressant use (%)	12.4	40.7	**<0.001**

Values are given as mean ± standard deviation for continuous variables and percentages for nominal variables. BMI, body mass index (kg/m^2); AHI, apnea-hypopnea index (events/hr); ODI, oxygen desaturation index (events/hr); ESS, Epworth sleepiness score; MCS, mental component score from the SF-12; PCS, physical component score from the SF-12. Significance is marked as **bold.**

4.3.3 Determinants of depression

Table 11 shows the results of logistic regression where several variables were tested for their independent associations with depression. Apart from the variables listed in table 11, diabetes, hypertension, exercise and the other subtypes of insomnia were tested but the results were not significant. The results are presented in stepwise order. Sleep medication use was most strongly related to depression but sleepiness as measured by the ESS total score and symptoms of initial insomnia (yes/no) were also independently related to depression (dysthymia or major depression). Other subtypes of insomnia (yes/no) were not independently related to depression. OSA severity and body mass index were also not independently associated with depression in the overall sample (Table 11). This was also examined separately for the genders and the results did not change for men, but for women, depression was only independently related to initial insomnia (daytime sleepiness as measured by the ESS was no longer significant).

Table 11. Factors associated with depression among the untreated OSA patients. The association is expressed as the adjusted odds ratio with a 95% confidence interval (OR (95% CI). Adapted from Paper IV.

	Depression (dysthymia + major depression) OR (95% CI)*
STEP 1	
Gender	**3.07 (1.61-5.86)**
Age	0.97 (0.94-1.01)
	R2 = 0.04
STEP 2	
Gender	**2.99 (1.53-5.82)**
Age	0.98 (0.95-1.02)
Body mass index	1.03 (0.98-1.08)
ESS	1.09 (1.01-1.17)
	R2 = 0.07
STEP 3	
Gender	1.94 (0.89-4.20)
Age	0.98 (0.94-1.01)
BMI	1.00 (0.95-1.06)
ESS	**1.12 (1.04-1.22)**
Initial insomnia	**3.02 (1.37-6.67)**
Sleep medications	**4.89 (2.25-10.64)**
	R2 = 0.17

BMI, Body mass index; ESS, Epworth sleepiness score. Significance is marked as **bold.**

* adjusted for all the variables in the table.

4.4 Changes of insomnia and quality of life from baseline to follow-up among PAP users and non-users from the ISAC cohort

4.4.1 PAP follow-up

Objective data on PAP use were available for 77.6% of PAP users (367 of 473) in the ISAC cohort, and based on these data the average (± SD) use per night was 6.2 (± 2.0) h for the previous 4 weeks. Only 46 of these individuals used the device less than 4 h per night on average. All patients were initially prescribed automatic positive airway pressure (autoPAP) and treatment was changed to continuous positive airway pressure (CPAP) if the pressure requirements over the night were stable. Of the PAP users, 53% were on autoPAP and 43% were on fixed CPAP, 3% on bilevel pressure (BiPAP), and 1% on adaptive servoventilation. Treatment was only changed to BiPAP or adaptive servoventilation if treatment efficacy was inadequate. The average (± SD) PAP pressure was 10.9 (± 1.5) cm H_2O and the pressure

below which participants on autoPAP spent 95% of the time over the previous 7 days was 11.1 (± 1.9) cm H_2O.

Patients using PAP for ≥ 5 days/w and ≥ 4 h/night on average for the previous 4 weeks were considered full users (n = 287 of 367 with objective data). On average, full users were using their device for 26.7 ± 2.0 nights for the previous 4 weeks and 6.8 ± 1.2 h per night based on objective data.

Among the 367 with both objective (memory cards) and self-reported data on frequency of PAP use, we compared those reporting PAP usage ≥ 5 nights/w and ≥ 60% of the night with those fulfilling criteria for full PAP use based on memory cards (≥ 5 days/w and ≥ 4 h/night). Self-reported data had 98.6% sensitivity and 45.1% specificity in distinguishing full versus partial users. Consequently, objective data were used when available, but for the remaining patients, the self-reported data were used to define patients as full, partial, and non-PAP users. Therefore, a total of n = 372 were classified as full users and n = 101 as partial users (367 and 106 were classified based on objective and subjective data, respectively).

On average, partial users were using their device for 14.3 ± 7.2 nights for the previous 4 weeks and 3.5 ± 2.2 h per night (for all 28 nights) based on objective data.

Among the 232 non-users, n = 60 (26.0%) returned their devices within 3 months from starting PAP. Most of the non-users (n = 133) had a repeat sleep study at the 2-year follow-up. On average, AHI in these individuals increased from baseline to follow-up (mean increase ± SD = 10.7 ± 22.2 events per hour). There were 98% of the 133 patients who still had an AHI > 15 at the 2-y follow-up. A few of the non-users (n = 11) had lost more than 10 kg from baseline to follow-up but they were not different in insomnia status or OSA severity at follow-up compared to baseline. Of these 11 patients, seven had a repeat sleep study at follow-up and they were all still affected with OSA (AHI ≥ 15) despite their weight loss. In total, the non-users (n = 133) lost on average 0.2 ± 8.2 kg from baseline to follow-up.

The primary analyses of Paper II were conducted by comparing all PAP users (full and partial) with non-users. Additional sensitivity analysis was performed by assessing the three use designations for group differences (full users, partial users, and non-users). Using three groups of PAP users did not affect the significance of the results. Partial users were not significantly different from full users and therefore only two groups were used in the analysis, all PAP users and non-users. Furthermore, all analyses were repeated using only PAP users with objective data (n = 367), which did not affect the significance of any of the results.

In Paper III partial users were excluded from the propensity score sample estimating the effect of PAP treatment on changes in quality of life to allow propensity score matching between the two primary groups of interest — full users and non-users.

4.4.2 Changes in insomnia symptoms from baseline to follow-up among ISAC PAP users and non-users

The prevalence of the three different insomnia subtypes (initial, middle and late) was assessed among the ISAC subjects prior to and two years after starting PAP treatment.

4.4.2.1 Symptoms of Initial Insomnia

The baseline prevalence of symptoms of initial insomnia was 12.9% among ISAC subjects who were using PAP at follow-up, compared with 20.8% among non-users (p = 0.007). At follow-up, 9.3% of PAP users had symptoms of initial insomnia compared with 17.7% of non-users (p = 0.001). The improvement in these symptoms from baseline to follow-up was of the same magnitude for PAP users and non-users (Table 12 and Figure 11).

Table 12. The difference in changes of insomnia subtypes from baseline to follow-up between PAP users and non-users. Reproduced from Paper II.

	Baseline (%)	Follow-up (%)	p_{change}	P for difference in change between PAP users and non-users
Initial insomnia				
Non-users	20.8	17.7	0.25	
PAP users	12.9	9.3	0.03	0.75
Middle insomnia				
Non-users	59.1	43.5	<0.001	
PAP users	59.4	30.7	<0.001	**0.001**
Late insomnia				
Non-users	36.6	26.0	0.001	
PAP users	23.3	21.2	0.34	**0.05**

Significance is marked as **bold.**

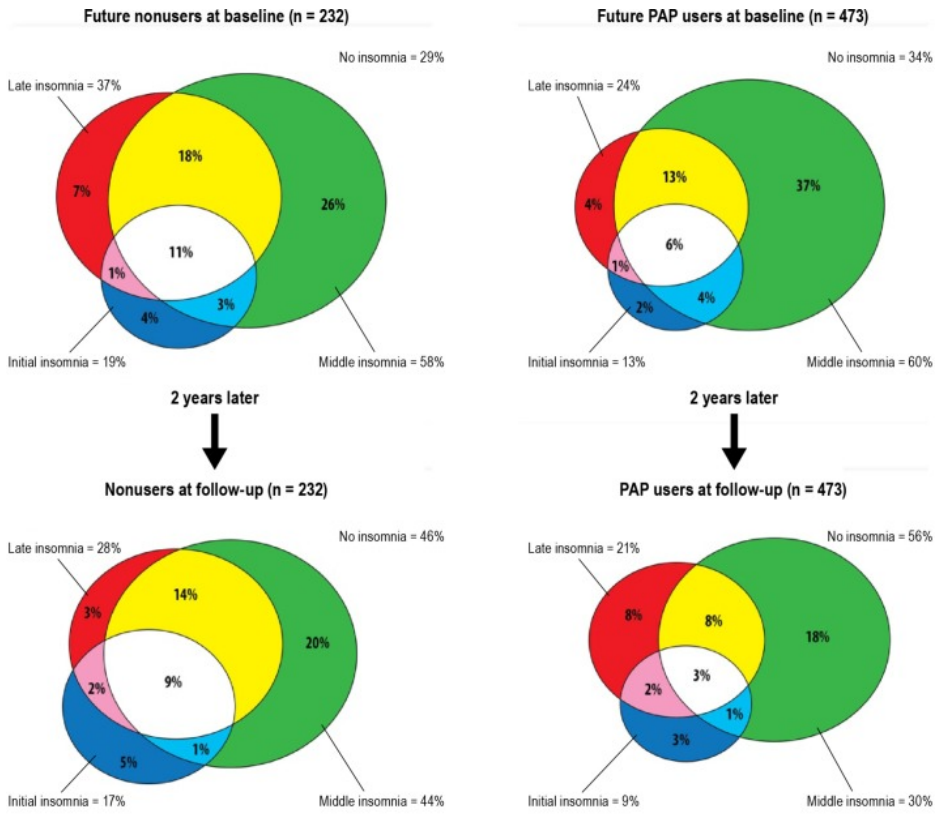

Figure 11. The changes and overlap of insomnia subtypes for both PAP users and non-user in the ISAC cohort. Reproduced from Paper II.

In total, 45.9% of those who had symptoms of initial insomnia at baseline also had these symptoms at follow-up. However, there was no baseline difference in regard to age, BMI, or OSA severity between those whose initial insomnia improved and those with persistent symptoms of initial insomnia. There was, however, more improvement in daytime sleepiness among those without symptoms of initial insomnia at follow-up (Table 13).

Table 13. Change in daytime sleepiness and quality of life among those whose insomnia improved and persisted. Reproduced from Paper II.

	Initial insomnia persisted (n = 50)	Initial insomnia improved (n = 59)	P - value	Middle insomnia persisted (n = 199)	Middle insomnia improved (n = 219)	P - value	Late insomnia persisted (n = 91)	Late insomnia improved (n = 103)	P - value
ESS change	-1.0±4.3	-3.5±4.8	**0.006**	-2.6±4.5	-4.6±5.0	**<0.001**	-1.8±4.8	-3.9±4.5	**0.002**
MCS change	-0.5±10.2	1.5±9.9	0.34	1.3±10.0	3.5±9.4	**0.02**	1.4±10.6	2.9±10.0	0.29
PCS change	3.0±14.3	2.2±13.9	0.78	2.5±11.8	3.3±11.8	0.48	0.3±12.3	4.2±11.7	**0.03**

ESS, Epworth Sleepiness Scale; MCS, mental component score from the SF-12; PCS, physical component score from the SF-12. Significance is marked as **bold.**

Patients who reported symptoms of initial insomnia at baseline were more likely to be PAP non-users at follow-up and this effect remained significant after adjusting for age, sex, BMI, smoking, and OSA severity (Table 14).

Table 14. Unadjusted and adjusted effects of insomnia subtypes on PAP non-use. Reproduced from Paper II.

	PAP use Unadjusted odds Ratio (95% CI)	P value	PAP use Adjusted odds Ratio (95% CI)*	P value*
Initial insomnia (n = 109)	0.56 (0.37-0.86)	**0.007**	0.59 (0.38-0.91)	**0.01**
Middle insomnia (n = 418)	1.01 (0.73-1.40)	0.93	0.98 (0.70-1.37)	0.89
Late insomnia (n = 194)	0.53 (0.37-0.74)	**<0.001**	0.55 (0.39-0.79)	**<0.001**
Isolated middle insomnia (n = 244)	1.61 (1.14-2.27)	**0.007**	1.48 (1.04-2.12)	**0.03**

*adjusted for gender, age, BMI and OSA severity (AHI and ODI). Significance is marked as **bold.**

4.4.2.2 Symptoms of middle insomnia

Overall, 33% of untreated ISAC sample had symptoms of isolated middle insomnia at baseline and these patients were more obese, had more severe OSA and better mental quality of life compared with patients with other symptoms of insomnia (initial, late, or mixed insomnia) (Table 15).

Table 15. Baseline differences between those with isolated middle insomnia and those with other types of insomnia (initial, late or mixed). Adapted from Paper II.

	Isolated middle insomnia (n = 244)	Other type of insomnia (n = 258)	P value
Age	55.2±10.7	55.5±9.6	0.77
BMI	34.2±6.1	33.1±5.5	**0.04**
AHI	48.4±21.1	41.6±20.0	**<0.001**
ODI	39.1±21.2	32.5±18.2	**<0.001**
ESS	12.5±5.0	11.8±5.0	0.11
PCS	39.3±11.1	39.0±11.0	0.77
MCS	49.1±10.0	45.7±11.2	**<0.001**

Values are given as mean ± standard deviation. BMI, body mass index (kg/m^2); AHI, apnea-hypopnea index (events/hr); ODI, oxygen desaturation index (events/hr); ESS, Epworth sleepiness score; MCS, mental component score from the SF-12; PCS, physical component score from the SF-12; Significance is marked as **bold.**

The baseline prevalence of middle insomnia was 59.1% among those who were PAP users at follow-up compared with 59.4% among non-users (p = 0.93). Compared with baseline, there was a significant improvement in the symptoms of middle insomnia for both PAP users and non-users at follow-up (follow-up prevalence was 30.7% among PAP users compared with 43.5% among non-users; $p \leq 0.001$). However, improvement in these symptoms was much more likely to occur among patients who were adherent with PAP treatment (p = 0.001 for the difference in change between PAP users and non-users) (Table 12 and Figure 11).

Patients whose middle insomnia improved (as compared with those with persistent symptoms of middle insomnia) were younger, more obese, and had more severe OSA at baseline. There was also greater improvement in physical quality of life and daytime sleepiness among these patients (Table 16).

Table 16. Baseline characteristics among those whose middle insomnia improved and persisted. Reproduced from Paper II.

	Middle insomnia persisted (n = 199)	Middle insomnia improved (n = 219)	P value
Male (%)	81.0	76.3	0.23
Age	57.3±9.4	54.8±10.2	**0.01**
BMI	32.8±5.1	35.1±6.4	**<0.001**
AHI	43.4±20.1	47.3±20.9	**0.05**
ODI	33.3±18.5	39.9±20.5	**<0.001**

Values are given as mean ± standard deviation for continuous variables and percentages for nominal variables. BMI, body mass index (kg/m^2); AHI, apnea-hypopnea index (events/hr); ODI, oxygen desaturation index (events/hr.). Significance is marked as **bold.**

Having symptoms of middle insomnia overall did not affect PAP adherence, but individuals with symptoms of isolated middle insomnia were more likely to be PAP users at follow-up and the effect remained significant after adjusting for age, sex, BMI, smoking, and OSA severity (Table 14).

4.4.2.3 Symptoms of late insomnia

The baseline prevalence of having symptoms of late insomnia was 23.3% among those who were PAP users at follow-up compared with 36.6% among non-users ($p < 0.001$). Non-users were more likely to experience improvement in late insomnia compared with PAP users ($p = 0.05$), improving to levels comparable to those of PAP users (PAP users: 21.2%, non-users: 26%) (Table 12 and Figure 11).

In total, 46.7% of those who had symptoms of late insomnia at baseline also had these symptoms at follow-up, but there was no baseline difference in regard to age, BMI, or OSA severity between those whose late insomnia improved compared with those with persistent symptoms of late insomnia. However, patients whose late insomnia improved did show a greater improvement in mental quality of life and daytime sleepiness (Table 13).

Patients who reported symptoms of late insomnia at baseline were more likely to be PAP non-users at follow-up and this effect remained significant after adjusting for age, sex, BMI, smoking, and OSA severity (Table 14).

When looking at how long the mask was worn based on objective PAP data, PAP users with symptoms of late insomnia at follow-up had on average 36 min. shorter mask-on time than those without late insomnia ($p = 0.02$). This difference in mask-on time was not seen for patients with other types of insomnia.

4.4.2.4 No insomnia symptoms

Having no symptoms of insomnia at baseline was equally prevalent among PAP users and non-users at follow-up (PAP users: 33.3%, non-users: 28.5%, $p = 0.20$). At follow-up, 55.7% of PAP users had no insomnia compared with 47.4% of non-users ($p = 0.04$). Most patients who reported no symptoms of insomnia at baseline were also without insomnia symptoms at follow-up. However, 22.4% of them reported some insomnia symptoms at follow-up. Developing symptoms of middle and late insomnia was much more prevalent than developing symptoms of initial insomnia (12.6%, 13.1%, and 2.7%, respectively). Among those who reported symptoms of insomnia at follow-up, PAP users were most likely to report symptoms of late insomnia whereas non-users were more likely to report symptoms of middle insomnia ($p < 0.05$) (Figure 12).

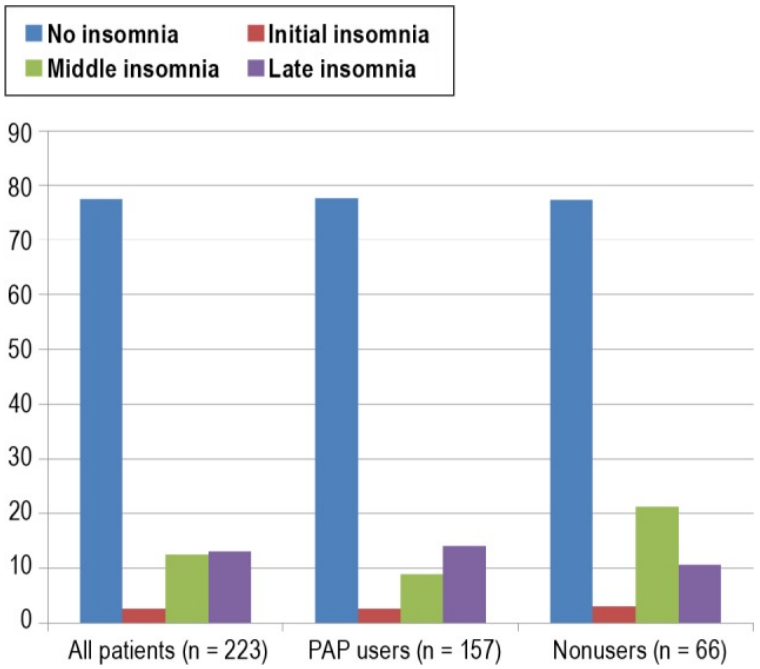

Figure 12. Insomnia status at follow-up (%) among ISAC subjects who had no symptoms of insomnia at baseline. Reproduced from Paper II.

4.4.3 Changes in quality of life from baseline to follow-up among ISAC PAP users and non-users

Quality of life was assessed among ISAC subjects prior to and two years after starting PAP treatment.

4.4.3.1 Change in quality of life among ISAC subjects two years after initiating PAP treatment

When looking at changes in quality of life among ISAC subjects from baseline to follow up, both PCS (mean ± SE change: 2.6 ± 0.4; $p<0.0001$) and MCS (1.9 ± 0.5; $p<0.001$) increased significantly two years after treatment initiation. Despite these significant increases, PCS values in ISAC subjects at the two-year follow-up remained significantly lower than the values seen in the general population at baseline (mean ± SE after two years: 43.9 ± 0.5 vs. 50.9 ± 0.5, $p<0.0001$). MCS values were marginally significantly lower in the ISAC group after two years of therapy than the general population at baseline (50.3 ± 0.40 vs. 51.3 ± 0.42, $p = 0.072$). In the current PS sample, full PAP users had an average increase in BMI of 0.9 kg/m^2, compared to a non-significant increase of 0.09 kg/m^2 in non-users ($p<0.001$ comparing full vs. non-users). Within the overall observational sample, we observed a significant negative correlation ($\rho=-0.18$, $p<0.0001$)

between BMI change and PCS change, controlling for baseline BMI and PCS; thus, patients with more weight loss had more positive PCS changes.

4.4.3.2 PAP full vs. non-users: Results in the PAP treatment PS sample

The covariate balance achieved by applying our PS methodology to PAP full and non-users is shown in Figure 13. Prior to implementing the PS heuristic there were significant differences between full and non-users in terms of BMI, gender, hypertension, initial and late insomnia, sleep medication use and all OSA severity measures (all $p<0.05$). After sub-classification and controlling for the PS quintile, there were no differences between full and non-users (all $p>0.677$).

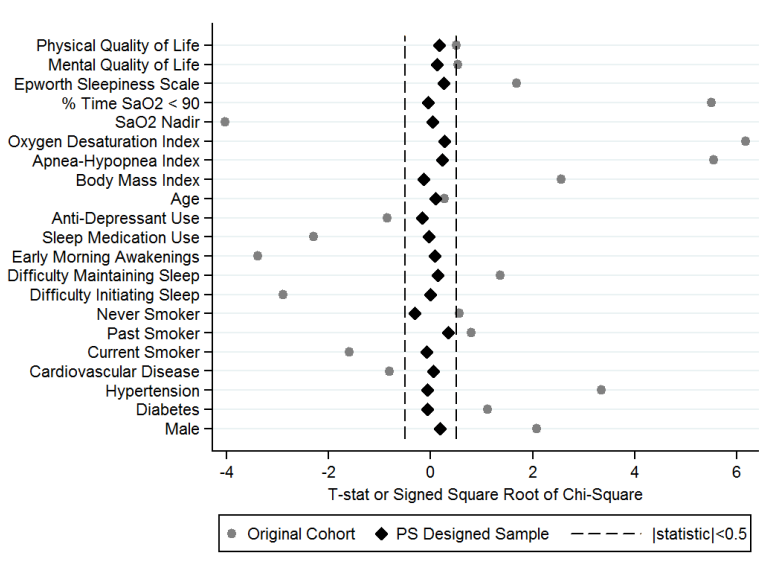

Figure 13. Modified love clot Comparing PAP full (n = 308) and non-users (n = 200). Reproduced from Paper III.

Significant two-year increases ($p<0.05$) in both quality of life measures were observed for full and non-users, separately. When comparing the changes in physical and mental quality of life between PAP groups, only a marginal difference between full and non-users for change in PCS ($p = 0.06$) was found and no differences in the change in MCS ($p = 0.80$). While significant evidence for a PAP by BMI group interaction was not found, a significant difference for PCS was reported when restricting analysis to BMI>35 ($p = 0.02$) such that subjects adherent to PAP had a significantly greater improvement in

PCS than non-users. No differences in PAP full and non-users related to BMI groups were found for MCS (Table 17).

Table 17. Comparison of change in quality of life in PAP treatment propensity score sample. Adapted from Paper III.

	BMI Group[*,†]	**LS Mean±SE Change**		p[‡]
		Full users	Non-Users	
Physical Quality of Life	*Overall*	3.42 ± 0.53[§]	1.79 ± 0.66[§]	0.063
	<30	2.91 ± 0.97[§]	1.73 ± 1.15	0.451
	30-35	2.50 ± 0.89[§]	2.49 ± 1.08[§]	0.996
	≥35	**4.64 ± 0.88**[§]	**1.05 ± 1.22**	**0.022**
Mental Quality of Life	*Overall*	2.13 ± 0.54[§]	2.35 ± 0.68[§]	0.799
	<30	2.60 ± 0.97[§]	4.06 ± 1.15[§]	0.353
	30-35	0.98 ± 0.96	1.32 ± 1.17	0.831
	≥35	2.80 ± 0.88[§]	1.96 ± 1.22	0.589

[‡]p-value from ANCOVA model, adjusted for PS subclass and baseline PCS or MCS; [§] within group estimate of quality of life change significantly ($p<0.05$) different from zero; **p-value for PAP x BMI group interaction: 0.5266 for PCS and 0.4579 for MCS. Significance is marked as **bold.**

Table 18 shows results on the effect of PAP treatment within strata defined by baseline subjective sleepiness or insomnia (Table 18). There was no significant interaction between PAP group and any of the measures. There was no significant difference in quality of life changes between PAP groups when comparing patients based on the ESS score at baseline. When looking within patients with and without insomnia at baseline, a significant difference in PCS change between full users and PAP non-users for those who did not have initial ($p = 0.02$), middle ($p = 0.01$) or late ($p = 0.02$) insomnia at baseline was found; full users had greater increases in PCS.

Table 18. Comparison of change in quality of life between full and non-users in propensity score matched sample stratified by sleepiness and insomnia symptoms at baseline among ISAC subjects. Adapted from Paper III.

Quality of Life Measure	Subgroup	LS Mean±SE Change		p‡
		Adherent	Non-Users	
Epworth Sleepiness Scale[1]				
PCS	≤10	2.25 ± 0.91§	0.85 ± 1.06	0.345
	>10	4.18 ± 0.64§	2.54 ± 0.85§	0.131
MCS	≤10	1.49 ± 0.85	0.37 ± 0.99	0.419
	>10	2.72 ± 0.69§	3.70 ± 0.92§	0.404
Initial insomnia[2]				
PCS	No	**3.95 ± 0.54§**	**1.80 ± 0.70§**	**0.019**
	Yes	-0.08 ± 1.71	1.51 ± 1.82	0.548
MCS	No	2.11 ± 0.55§	2.17 ± 0.71§	0.945
	Yes	2.38 ± 1.83	3.05 ± 1.94	0.813
Middle insomnia[3]				
PCS	No	**4.19 ± 0.63§**	**1.45 ± 0.77**	**0.009**
	Yes	2.10 ± 0.93§	2.39 ± 1.24	0.858
MCS	No	1.95 ± 0.65§	2.45 ± 0.79§	0.641
	Yes	2.25 ± 0.94§	2.47 ± 1.26	0.892
Late insomnia[4]				
PCS	No	**3.68 ± 0.56§**	**1.52 ± 0.75§**	**0.025**
	Yes	2.81 ± 1.27§	2.12 ± 1.39	0.731
MCS	No	2.15 ± 0.59§	2.21 ± 0.79§	0.946
	Yes	2.09 ± 1.22	2.61 ± 1.33	0.790

‡p-value from ANCOVA model, adjusted for PS subclass and baseline PCS or MCS; § within group estimate of change significantly ($p<0.05$) different from zero; [1]p-value for PAP x ESS status interaction: 0.7552 for PCS and 0.7315 for MCS; [2]p-value for PAP x initial insomnia interaction: 0.1690 for PCS and 0.3844 for MCS; [3]p-value for PAP x middle insomnia interaction: 0.1063 for PCS and 0.9421 for MCS; [4]p-value for PAP x late insomnia interaction: 0.1722 for PCS and 0.7638 for MCS. MCS, mental component score from the SF-12; PCS, physical component score from the SF-12; Significance is marked as **bold.**

While we observed statistically significant results within these strata, we note that we did not observe significant interactions between PAP group and any of these cut points; thus, results should be considered suggestive and replicated within independent populations.

Given the established relationship between quality of life and depression, we also examined the effect of PAP in patients stratified by antidepressant use at baseline. We did not observe a significant interaction between PAP adherence and antidepressant medication use for either PCS ($p = 0.498$) or MCS ($p = 0.327$) and there were no significant differences between PAP groups in PCS or MCS change within strata (Table 19).

Table 19. Association between PAP adherence and PCS and MCS change, stratified by antidepressant medication use. Reproduced from paper IV.

Quality of Life Measure	Subgroup	LS Mean±SE Change		$p^{\ddagger}$
		Adherent	Non-Users	
Antidepressant Medication Use[1]				
PCS	No	3.54 ± 0.57[§]	2.00 ± 0.72[§]	0.1059
	Yes	2.93 ± 1.34[§]	0.74 ± 1.68	0.3457
MCS	No	2.47 ± 0.56[§]	2.15 ± 0.71[§]	0.7334
	Yes	0.29 ± 1.44	3.60 ± 1.81[§]	0.1845

[‡]p-value from ANCOVA model, adjusted for PS subclass and baseline PCS or MCS; [§] Within group estimate of change significantly ($p<0.05$) different from zero; [1]p-value for PAP x Antidepressant use interaction: 0.4978 for PCS and 0.3269 for MCS. MCS, mental component score from the SF-12; PCS, physical component score from the SF-12; Significance is marked as **bold.**

5 Discussion

Obstructive sleep apnea is a multifaceted disorder that has a profound impact on health and well-being. Results from the current study showed that when compared to the general population, subjects with untreated OSA have impaired physical and mental quality of life. Furthermore, patients with untreated OSA have a high prevalence of insomnia and depression which further diminish their life qualities. The majority of patients with untreated OSA wake up frequently during the night and these symptoms significantly improve with successful PAP treatment. Other subtypes of insomnia (initial and late) tend to persist regardless of PAP treatment and have a negative impact on treatment adherence. Even though quality of life is significantly improved from baseline to follow-up for all OSA patients (both PAP users and non-users) in our study, these patients still have much poorer physical health than subjects from the general population even after two years of therapy.

5.1 Insomnia and OSA

The majority of patients with untreated OSA in our study have symptoms of middle insomnia compared to one-third of general population subjects. These results are in accordance with other studies that have reported elevated levels of insomnia among OSA patients (Krakow et al., 2001; Luyster et al., 2010; Krell & Kapur, 2005; Subramanian et al., 2010). One explanation for the high prevalence of middle insomnia in OSA is that repeated breathing disturbances in untreated OSA results in sleep fragmentation and hence difficulties maintaining sleep.

The prevalence of initial insomnia was similar among OSA patients and the general population in our study. This is somewhat surprising since excessive daytime sleepiness is a common symptom of untreated OSA (Yong et al., 2002) and therefore one might think that these patients would be protected against initial insomnia. It is possible that when falling asleep some OSA patients may be disrupted repeatedly from light sleep by an apnea event, causing them not to perceive sleeping in between the disruptions. These events could recur many times before sleep is established, and as a result the patient might experience long sleep latency. The same pattern could happen when

patients wake up during the night and are having difficulties falling back to sleep. Furthermore, it is possible that some OSA patients doze off during the day and are therefore not as sleepy at bedtime.

Symptoms of insomnia were in general not related to OSA severity in our study and others have reported similar results (Hagen, Patel & McCall, 2009; Kapur et al., 2005). However, ISAC subjects with symptoms of isolated middle insomnia were more obese and had more severe OSA when compared to other subjects. In another study examining the relationship between insomnia subtypes and daytime sleepiness among OSA patients it was also reported that those with symptoms of middle insomnia had more severe OSA as well as increased daytime sleepiness compared with patients with initial insomnia (Chung, 2005). Furthermore, when looking at OSA high and low risk subjects in the general population, we found that having a high MAP index (≥0.75) was a significant predictor for middle insomnia. These results strongly imply that it is necessary to explore different subtypes of insomnia separately.

Symptoms of middle insomnia generally improved among adherent PAP patients in our study, suggesting that these symptoms are more related to disturbed breathing than insomnia per se. OSA patients with middle insomnia suffered from more daytime sleepiness as compared to other OSA patients while patients with initial insomnia were not sleepier than other OSA patients, which is consistent with the idea of insomnia as a state of hyperarousal. This supports the idea that frequent awakenings are a symptom of untreated OSA rather than a "true" insomnia condition.

Symptoms of initial and late insomnia tend to persist regardless of successful PAP treatment and those presenting with these subtypes of insomnia are less likely to adhere to PAP treatment. One explanation for why initial insomnia is associated with poor PAP adherence may be that these patients are awake longer in the evenings trying to fall asleep and thus more likely to experience the adverse aspects of PAP treatment (e.g. claustrophobia or mask or airflow discomfort (Weaver & Grunstein, 2008). Middle insomnia is, on the other hand, not related to poor PAP adherence and those who had symptoms of isolated middle insomnia were even more likely to adhere to PAP. Those patients who, while untreated, wake up frequently because of apneic events, may experience more refreshing sleep and relief both from OSA and insomnia symptoms while being treated with PAP and therefore adjust favorably to the treatment. These

results suggest that initial and late insomnia in patients with OSA are co-morbid but unrelated disorders which might require additional interventions.

Symptoms of late insomnia were more likely to improve among non-users in comparison with PAP users in our study. A possible explanation could be that when sleep gets lighter in the morning, patients become more aware of their device and for some patients this could possibly disrupt their sleep and cause persistence of late insomnia symptoms. This could also explain why PAP users who had no insomnia at baseline were most likely to develop symptoms of late insomnia during the study period.

5.2 Quality of life and OSA

Our study showed that untreated OSA patients have impaired quality of life compared to subjects from the general population. This effect remains significant after using propensity scores to select a sample of OSA patients and a general population sample, balanced with regard to age, BMI, gender, smoking status, diabetes, hypertension and cardiovascular disease.

Sleep parameters such as symptoms of insomnia, daytime sleepiness and sleep medication and antidepressant use were more related to quality of life than OSA severity in our study. Others have found similar results. For example, a population-based study by Baldwin et al. (2001) suggested that mild OSA was related to reduced vitality, while more severe OSA was more broadly associated with diminished quality of life. That study also indicated that subjective sleep symptoms (sleepiness and disturbed sleep) are widely associated with poor quality of life (Baldwin et al., 2001). A study by Silvia et al. (2009) found that changes in quality of life over a 5 year period were not related to changes in OSA severity, but rather to worsening of difficulties initiating and maintaining sleep, as well as daytime sleepiness.

We did not find a statistically significant difference in the improvement in quality of life between full and non-users of PAP, with both groups showing significant improvements from baseline to follow up. However, we did observe a significantly larger improvement in PCS for adherent patients compared to non-users within the most obese patients (BMI>35); this stronger effect of PAP in the most obese has been seen previously for other outcomes (Pak et al., 2014). We also observed a significant effect of PAP on PCS in patients with no insomnia symptoms at baseline, although this result needs to be replicated within independent samples. Taken together, results suggest that PAP may

have a significant impact on physical quality of life within specific subsets of OSA patients. No differences were found in mental quality of life in these subgroups. Even though some subgroups of OSA patients improve their life qualities while using PAP these patients still have lower life qualities, particularly physical quality of life, when compared to subjects from the general population. These results are in line with others who have reported similar associations of OSA and poor life quality (Lacasse et al., 2000; Akashiba et al., 2002; Baldwin et al., 2001).

Previous studies have not assessed the difference in improvement in quality of life between full and non-users of PAP. Others have, however, reported improvement in quality of life among OSA patients who adhere to PAP treatment (Diamanti et al., 2013; Avlonitou et al., 2012). A study by Jenkinson el al. (1997) showed positive effects of 5-7 weeks of CPAP treatment on quality of life and concluded that CPAP treatment returns OSA patients to a quality of life similar to the normal population, which we did not find in our study. However, the study by Jenkinson et al. (1997) did not assess differences in improvement between patients with different adherence to CPAP. Furthermore, Sanner et al. (2000) concluded that long term CPAP treatment had a positive effect on quality of life. They did not, however, find a significant correlation between CPAP use and change in the quality of life measures. These studies may therefore have methodological issues that impacted their results. If we had assessed changes in quality of life among full users in our study, we would have observed similar associations as reported in previous studies (D'Ambrosio et al., 1999; Diamanti et al., 2013, Avlonitou et al., 2012; Jenkinson et al., 1997; Sanner et al., 2000).

In a meta-analysis conducted by Jing et al. (2008), it was concluded that PAP treatment does not improve general quality of life scores but does improve physical domains and vitality. It is possible that some subgroups of patients improve their quality of life on PAP, as we saw for obese subjects and those without insomnia.

5.3 Depression and OSA

In the untreated OSA cohort, 20.8% of subjects met the diagnosis for depression and dysthymia according to a structured diagnostic interview carried out by a trained psychologist. This is considerably higher than reported in the general population in Iceland (Lindal & Stefansson) but lower than frequently reported among OSA patients (Mosko et al., 1989; Reynolds et al., 1984; Millmann et al., 1989; Akashiba et al., 2000).

Altogether, 18.3% of subjects in the untreated OSA cohort used antidepressants. This was more common among those who met the diagnosis for depression according to the MINI but over 40% of those patients were using antidepressants and had therefore previously been diagnosed with depression by their doctor. Similar to previous findings, depression was more common among women (Asghari et al., 2012; Harris et al., 2009) but 82% of the women in this cohort were postmenopausal and the prevalence of both depression (Frey, Lord, & Soares, 2008) and sleep disturbances is known to increase in postmenopausal women (Ohayon, 2006). Sleep medication use, symptoms of initial insomnia and daytime sleepiness were highly related to depression while OSA severity was not. Others have reported similar results regarding the lack of association between OSA severity and depression, suggesting that depression is more related to disrupted sleep and sleepiness than OSA severity per se (Asghari et al., 2012; Jackson et al, 2011).

Many previous studies have found a much higher prevalence of depression among OSA patients than found in the current study. For example, in a study by Mosko et al. (1989) 58% of OSA patients are reported to have met the DSM criteria for depression. A study by Reynolds et al. (1984) showed that 40% of male OSA patients met the diagnostic criteria for an affective disorder, with a higher risk of depression in those patients who were sleepier during the day and in a study by Millmann et al. (1989) 45% of OSA patients had depressive symptoms. Akashiba et al. (2000), reported a 48% prevalence of depression in a sample of sixty male OSA patients compared to gender and age-matched controls (n = 34). In their study, OSA patients had a much higher prevalence of depression than controls and depression was associated with poorer quality of life (Akashiba et al., 2000) as was found in our study. Furthermore, Aikens et al. (1999) showed that 32% of their OSA patients had elevated depression scores on the Minnesota Multiphasic Personality Inventory (MMPI) and there were twice as many OSA patients with elevated depression scores than age and sex matched primary snorers (Aikens et al., 1999). These differences in prevalence of depression among OSA patients are probably partially due to different definitions and instruments used to assess depression.

Most previous studies have used self-reported questionnaires to assess depression and as a result, overrepresentation of the prevalence is likely to occur due to the frequent symptom overlap between depression and OSA. An Australian study by Douglas et al. (2013) showed that among patients with suspected OSA, the overall rate of depression based on doctor diagnosis, the Hospital Anxiety and Depression Scale (HADS) or two

screening questions from the MINI was 53%. In that study, the prevalence of depression assessed with the MINI questions was 45% and a significant correlation was reported (0.736; $p<0.001$) between HADS and the MINI depression questions (Douglas et al., 2013). This is a much higher prevalence of depression than reported in our study but Douglas et al. (2013) only used two screening questions from the MINI which has to be considered a limitation and could partially explain the difference in the results. Another recent study indicated that HADS would be an accurate screening tool for assessing major depression among patients in sleep disorder clinics (Law et al., 2013) but further studies comparing the use of self-report questionnaires and structured clinical interviews in large cohorts of OSA patients are needed. The MINI includes questions regarding symptoms that are highly related to untreated OSA and therefore misdiagnosis of depression is possible. However, structured diagnostic interviews like the MINI have become an essential part of psychiatric medicine. Apart from being the diagnostic gold standard in mental health research it is also increasingly being used to help ensure diagnostic precision in clinical practice (Nordgaard et al., 2012). Even though information collected from open clinical interviews may vary depending on how a particular question is asked or framed, structured diagnostic interviews include questions that are precise and carefully linked to diagnostic criteria, thereby minimizing the risk of imprecise diagnosis. Nevertheless, it is possible to miss important symptoms of other disorders while asking questions using a standardized interview. Furthermore, it is time consuming to assess all patients with standardized interviews and therefore it could be more realistic to initially screen patients with self-report questionnaires and subsequently further assess those who screen positively for depression and have difficulties in adapting to PAP treatment.

A number of studies have indicated a bidirectional relationship between poor sleep and depression and some have suggested that sleep difficulties may lead to or exacerbate depression and that by improving sleep quality it is possible to improve symptoms of depression as well (Wiebe et al., 2012; Jansson-Frojmark et al., 2008). However, special care needs to be taken when OSA patients are receiving medical treatment for depression and/or insomnia. Sedative antidepressants may exacerbate symptoms of untreated OSA by further decreasing the muscle tone in the already impaired upper airway and as a result increase the number and duration of apneas (Guilleminault, 1990; Sloan & Shapiro, 1993; Berry et al., 1995; George, 2000).

5.4 Strengths and limitations of the study

The main limitations of this study are that the definition of insomnia was based on three questions answered in a self-report manner, whereas having a more accurate insomnia evaluation based on insomnia diagnosis would have been beneficial.

Subjects from the general population sample were all 40 years or older and therefore results cannot be generalized to younger people in the general population. Furthermore, OSA was not assessed objectively in the general population subjects and therefore we do not know how many subjects in this cohort had treated or untreated OSA. However, we assessed their OSA risk by calculating their MAP index.

Although the extensive two-year follow-up of ISAC subjects is a strength of the study, it can also be considered a limitation. We did not have short term follow-up to evaluate acute effects of PAP treatment on insomnia and quality of life. There are many factors, besides PAP treatment, that may have changed in the two-year study period among the ISAC subjects that could have affeced both insomnia and quality of life. Although a majority of ISAC patients (75%) using PAP had objective adherence information, a subset of patients were classified as PAP users or nonusers based on subjective data only. However, our subjective criteria has high sensitivity (98.6%) and moderate specificity (45.1%) for classifying full vs. partial users. This combination of high sensitivity and low specificity means that full users are likely to be correctly classified, but also that a proportion of patients meeting our subjective criteria of full usage are actually partial users. While not ideal, the misclassification of partial users as full users in this minority of patients is expected to bias us towards the null, i.e., against observing a strong PAP effect. Moreover, there were no significant changes in our estimates or results when restricting to only the subset of PAP users that had objective data. Finally, this was an observational study, not a randomized controlled trial (RCT), which may be considered a limitation. However, a RCT study with such long-term follow-up of severely affected OSA patients would be difficult to perform for ethical reasons. Also, the importance of observational studies was highlighted in a recent NIH workshop report on comparative effectiveness research (Lieu et al., 2011).

The strengths of this study include the large number of OSA subjects and the comparison with a general population cohort, as well as the extensive two-year follow-up of the ISAC cohort with a high response rate (>90%). This study included detailed questionnaire assessments using standardized and validated instruments, a standardized

psychiatric interview to assess depression, as well as sleep studies in all the OSA subjects. In addition, this study included a clinical sample of OSA patients with various co-morbidities, representing the entire spectrum of patients with OSA. Our study is also by far the largest study that has looked prospectively at symptoms of insomnia subtypes among patients with OSA before and following PAP treatment. Furthermore, the comparison with a general population cohort using propensity matching and the comparison between OSA patients with different degree of PAP use is a major strength,

5.5 Conclusion

OSA patients have various co-morbidities, such as obesity, disturbed sleep and depression and these symptoms are often still apparent even though the OSA is well treated. These co-morbid factors have a profound impact on quality of life and need to be taken into consideration and addressed with additional treatment interventions. In our observational sample, full users showed a higher increase in BMI from baseline to follow-up as compared to non-users. This increase in BMI while on PAP is likely to limit the benefit that would have occurred had patients who were adherent to PAP not gained weight. There is a need for more personalized medicine, including broader therapeutic interventions that target co-morbidities such as insomnia and obesity. We see in the current study, that many patients with insomnia and/or depression are already receiving medical treatment but are still affected by these disorders. To be able to successfully treat these patients, it is important to consider different aspects that may contribute to their poor health. Factors such as, lifestyle, social support, physical and mental health as well as other chronic disorders need to be examined and addressed with multifactorial interventions.

This study showed that symptoms of initial insomnia were associated with poor PAP adherence and depression has also been associated with lack of compliance with medical treatment (DiMatteo, Lepper and Croghan, 2000). If OSA is left untreated it is associated with several adverse health consequences (Punjabi, 2008) and therefore both insomnia and depression among these patients can have important implications for the prognosis of OSA.

This study focused on one of the goals of personalized medicine, i.e. to identify individuals with a particular disease with distinct co-morbidities that might further aggravate the disease and require additional interventions. The goal would be more

precisely targeted therapies with the aim of maximizing the outcome for the patient and adherence to PAP treatment. By identifying distinct clinical profiles of OSA it is possible to offer more personalized therapies in the future (Ye et al., 2014).

5.6 Implications for clinical practice

Our results have important clinical implications and show that standard PAP treatment is not sufficient for all OSA patients in order to improve their quality of life. First of all, health care providers should routinely screen for the presence of insomnia in OSA patients, given that it is associated with greater impairment in quality of life than OSA alone and may predict poor adherence to PAP treatment. Assessment of insomnia among OSA patients needs to take into account the insomnia subtypes since different subtypes have different rates, consequences and risk factors. In those patients with co-morbid initial or late insomnia, additional interventions targeting insomnia symptoms should be considered before initiating PAP treatment. This may lead to both direct improvement in symptoms by reducing the severity of insomnia, and indirectly, by positively influencing adherence to PAP treatment and therefore maximizing clinical outcomes.

When it comes to depression, it is important for health professionals, working with depressed patients, to be aware of the high co-morbidity of sleep disorders among these patients, since treating sleep difficulties may improve symptoms of depression (Wiebe et al, 2012; Jansson-Frojmark et al 2008). Sleep problems and particularly OSA are rarely assessed on a regular basis in patients with a depressive disorder (Scröder and O´Hara, 2005), but due to the complex relationship between depression and OSA it could be beneficial to include standardized questions on sleep in psychiatric clinical interviews. Furthermore, given the high symptom overlap between untreated OSA and depression it is important to carefully select the screening tools used to assess depression in sleep clinics. Finally, special care needs to be taken when untreated OSA patients are receiving medical treatment for depression and/or insomnia (Scröder and O´Hara, 2005). A routine screening of OSA could therefore be beneficial when considering medical treatment of depression and/or insomnia.

5.6 Future directions

The results of this study highlight the need for further studies on the effectiveness of additional treatment interventions for subgroups of OSA patients that are either still severely impaired after PAP treatment or do not adhere to PAP.

Future studies should focus on exploring the benefits of additional interventions prior to or during PAP for patients with OSA co-morbid with insomnia. It may be useful to undertake a trial of CBT for insomnia (CBT-I) prior to or during treatment with PAP and assess whether this intervention not only improves the insomnia in the context of OSA, but whether such treatment increases adherence with PAP, especially in cases of initial and late insomnia.

Further studies are also needed on depression in OSA patients. There is a need for more prospective studies on the impact of depression on adherence to PAP treatment and whether successful PAP treatment improves symptoms of depression. It is important to carefully select the screening tools used for assessing depression in these studies, and further studies comparing the use of self-report questionnaires and structured clinical interviews in large cohorts of OSA patients are also needed.

References

Ahmed, A., Husain, A., Love, T. E., Gambassi, G., Dell'Italia, L. J., Francis, G. S., Francis, G. S., Gheorghiade, M., Allman, R. M., Meleth, S., Bourge, R. C. (2006). Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *European Heart Journal*, 27(12), 1431-1439.

Aikens, J. E., & Mendelson, W. B. (1999). A matched comparison of MMPI responses in patients with primary snoring or obstructive sleep apnea. *Sleep*, *22*(3), 355-359.

Akashiba, T., Kawahara, S., Akahoshi, T., Omori, C., Saito, O., Majima, T., & Horie, T. (2002). Relationship between quality of life and mood or depression in patients with severe obstructive sleep apnea syndrome. *CHEST*, *122*(3), 861-865.

Allaert, F.-A., & Urbinelli, R. (2004). Sociodemographic profile of insomniac patients across national surveys. *CNS drugs*, *18 Suppl 1*, 3-7; discussion 41, 43-45.

Allen, R. P., Picchietti, D., Hening, W. A., Trenkwalder, C., Walters, A. S., & Montplaisi, J. (2003). Restless legs syndrome: Diagnostic criteria, special considerations, and epidemiology - A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Medicine*, 4(2), 101-119.

Al Lawati, N. M., Patel, S. R., & Ayas, N. T. (2009). Epidemiology, risk factors, and consequences of obstructive sleep apnea and short sleep duration. *Progress in Cardiovascular Diseases*, *51*(4), 285-293.

Aloia, M. S., Di Dio, L., Ilniczky, N., Perlis, M. L., Greenblatt, D. W., & Giles, D. E. (2001). Improving compliance with nasal CPAP and vigilance in older adults with OSAHS. *Sleep and Breathing*, *5*(1), 13-21.

Aloia, M. S., Arnedt, J. T., Smith, L., Skrekas, J., Stanchina, M., & Millman, R. P. (2005). Examining the construct of depression in obstructive sleep apnea syndrome. *Sleep Medicine*, *6*(2), 115-121.

American Academy of Sleep Medicine. (2005). *The International classification of sleep disorders, second edition (ICSD-2): diagnostic and coding manual*. (2nd ed). Westchester, IL: American Academy of Sleep Medicine.

American Psychiatric Association. (1987). *Diagnostic and Statistical Manual of Mental Disorders* (3rd ed. DSM-III-R). Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual Of Mental Disorders* DSM-IV-TR Fourth Edition. Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2013). Sleep-Wake Disorders. *In Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington, VA: American Psychiatric Association.

Ancoli-Israel, S., Kripke, D. F., Klauber, M. R., Mason, W. J., Fell, R., & Kaplan, O. (1991). Sleep-disordered breathing in community-dwelling elderly. *Sleep, 14*(6), 486-495.

Ancoli–Israel, S., & Roth, T. (1999). Characteristics of insomnia in the United States: Results of the 1991 National Sleep Foundation Survey. I. *Sleep, 22*(2), 347-353.

Ancoli-Israel, S. (2000). Insomnia in the elderly: a review for the primary care practitioner. *Sleep, 23 Suppl 1*, S23-30.

Ancoli-Israel, S. (2006). The impact and prevalence of chronic insomnia and other sleep disturbances associated with chronic illness. *The American Journal of Managed Care*, *12*(8 Suppl), 221-229.

Andrews, J. G., & Oei, T. P. S. (2004). The roles of depression and anxiety in the understanding and treatment of obstructive sleep apnea syndrome. *Clinical Psychology Review, 24*(8), 1031-1049.

Araghi, M. H., Jagielski, A., Neira, I., Brown, A., Higgs, S., Thomas, G. N., & Taheri, S. (2013). The complex associations among sleep quality, anxiety-depression, and quality of life in patients with extreme obesity. *Sleep, 36*(12), 1859-1865.

Arnardottir, E. S., Mackiewicz, M., Gislason, T., Teff, K. L., & Pack, A. I. (2009). Molecular signatures of obstructive sleep apnea in adults: A review and perspective. *Sleep, 32*(4), 447-470.

Arnardottir, E. S., Maislin, G., Schwab, R. J., Staley, B., Benediktsdottir, B., Olafsson, I., Juliusson, S., Romer, M., Gislason, T., Pack, A. I. (2012). The interaction of obstructive sleep apnea and obesity on the inflammatory markers C-reactive protein and interleukin-6: The Icelandic Sleep Apnea Cohort. *Sleep, 35*(7), 921-932.

Arnardottir, E. S., Janson, C., Bjornsdottir, E., Benediktsdottir, B., Juliusson, S., Kuna, S. T., Pack, A. I., Gislason, T. (2013). Nocturnal sweating—a common symptom of obstructive sleep apnoea: The Icelandic sleep apnoea cohort. *BMJ Open, 3*(5).

Asghari, A., Mohammadi, F., Kamrava, S. K., Tavakoli, S., & Farhadi, M. (2012). Severity of depression and anxiety in obstructive sleep apnea syndrome. *European Archives of Oto-Rhino-Laryngology, 269*(12), 2549-2553.

Avlonitou, E., Kapsimalis, F., Varouchakis, G., Vardavas, C. I., & Behrakis, P. (2012). Adherence to CPAP therapy improves quality of life and reduces symptoms among obstructive sleep apnea syndrome patients. *Sleep and Breathing*, *16*(2), 563-569.

Baldwin, C. M., Griffith, K. A., Nieto, F. J., O'Connor, G. T., Walsleben, J. A., & Redline, S. (2001). The association of sleep-disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. *Sleep, 24*(1), 96-105.

Ballester, E., Badia, J. R., Hernández, L., Carrasco, E., De Pablo, J., Fornas, C., Rodriguez-Roisin, R., & Montserrat, J. M. (1999). Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. *American Journal of Respiratory and Critical Care Medicine, 159*(2), 495-501.

Baran, A. S., & Richert, A. C. (2003). Obstructive sleep apnea and depression. *CNS Spectrums*, *8*(2), 128-134.

Bardwell, W. A., Berry, C. C., Ancoli-Israel, S., & Dimsdale, J. E. (1999). Psychological correlates of sleep apnea. *Journal of Psychosomatic Research, 47*(6), 583-596.

Bardwell, W. A., Moore, P., Ancoli-Israel, S., & Dimsdale, J. E. (2003). Fatigue in obstructive sleep apnea: driven by depressive symptoms instead of apnea severity? *The American Journal of Psychiatry*, *160*(2), 350-355.

Bardwell, W. A., Ancoli-Israel, S., & Dimsdale, J. E. (2007). Comparison of the effects of depressive symptoms and apnea severity on fatigue in patients with obstructive sleep apnea: a replication study. *Journal of Affective Disorders, 97*(1-3), 181-186.

Barnes, M., Houston, D., Worsnop, C. J., Neill, A. M., Mykytyn, I. J., Kay, A., Trinder, J., Saunders, N. A., McEvoy, R. D., & Pierce, R. J. (2002). A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine, 165*(6), 773-780.

Bastien, C. H., & Morin, C. M. (2000). Familial incidence of insomnia. *Journal of Sleep Research*, *9*(1), 49-54.

Benediktsdottir, B., Janson, C., Lindberg, E., Arnardóttir, E. S., Olafsson, I., Cook, E., Thorarinsdottir, E. H., Gislason, T. (2010). Prevalence of restless legs syndrome among adults in Iceland and Sweden: Lung function, comorbidity, ferritin, biomarkers and quality of life. *Sleep medicine, 11*(10), 1043-1048.

Benetó, A., Gomez-Siurana, E., & Rubio-Sanchez, P. (2009). Comorbidity between sleep apnea and insomnia. *Sleep Medicine Reviews*, *13*(4), 287-293.

Bennett, L. S., Barbour, C., Langford, B., Stradling, J. R., & Davies, R. J. (1999). Health status in obstructive sleep apnea: Relationship with sleep fragmentation and daytime sleepiness, and effects of continuous positive airway pressure treatment. *American Journal of Respiratory and Critical Care Medicine, 159*(6), 1884-1890.

Berry, R. B., Kouchi, K., Bower, J., Prosise, G., & Light, R. W. (1995). Triazolam in patients with obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine, 151*(2), 450-454.

Bixler, E. O., Vgontzas, A. N., Ten Have, T., Tyson, K., & Kales, A. (1998). Effects of age on sleep apnea in men: I. Prevalence and severity. *American Journal of Respiratory and Critical Care Medicine, 157*(1), 144-148.

Bixler, E. O., Vgontzas, A. N., Lin, H. M., Ten Have, T., Rein, J., Vela-Bueno, A., & Kales, A. (2001). Prevalence of sleep-disordered breathing in women: Effects of gender. *American Journal of Respiratory and Critical Care Medicine, 163*(3), 608-613.

Block, A. J., Wynne, J. W., & Boysen, P. G. (1980). Sleep-disordered breathing and nocturnal oxygen desaturation in postmenopausal women. *The American Journal of Medicine, 69*(1), 75-79.

Bonnet, M. H., & Arand, D. L. (2010). Hyperarousal and insomnia: State of the science. *Sleep Medicine Reviews*, 14(1), 9-15.

Briones, B., Adams, N., Strauss, M., Rosenberg, C., Whalen, C., Carskadon, M., Roebuck, T., Winters, M., & Redline, S. (1996). Relationship between sleepiness and general health status. *Sleep*, 19(7), 583-588.

Buist, A. S., McBurnie, M. A., Vollmer, W. M., Gillespie, S., Burney, P., Mannino, D. M., Menezes, A. M., Sullivan, S. D., Lee, T. A., Weiss, K. B., Jensen, R. L., Marks, G. B., Gulsvik, A. & Nizankowska-Mogilnicka, E. (2007). International variation in the prevalence of COPD (the BOLD Study): A population-based prevalence study. *The Lancet*, 370(9589), 741-750.

Calem, M., Bisla, J., Begum, A., Dewey, M., Bebbington, P. E., Brugha, T., Cooper, C., Jenkins, R., Lindesay, J., McManus, S., Meltzer, H., Spiers, N., Weich, S., & Stewart, R. (2012). Increased prevalence of insomnia and changes in hypnotics use in England over 15 years: Analysis of the 1993, 2000, and 2007 National Psychiatric Morbidity Surveys. *Sleep*, 35(3), 377-384.

Cassel, W. (1993). Sleep apnea and personality. Sleep. *Journal of Sleep Research & Sleep Medicine*, 16(8), S56-S58.

Chervin, R. D., Theut, S., Bassetti, C., & Aldrich, M. S. (1997). Compliance with nasal CPAP can be improved by simple interventions. *Sleep*, 20(4), 284-289.

Chervin, R.D. (2000). Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. *CHEST*, 118(2), 372-379.

Chesire, K., Engleman, H., Deary, I., Shapiro, C., & Douglas, N. J. (1992). Factors impairing daytime performance in patients with sleep apnea/hypopnea syndrome. *Archives of Internal Medicine*, 152(3), 538-541.

Chung, K. F. (2005). Insomnia subtypes and their relationships to daytime sleepiness in patients with obstructive sleep apnea. *Respiration; International Review of Thoracic Diseases*, 72(5), 460-465.

D'Ambrosio, C., Bowman, T., & Mohsenin, V. (1999). Quality of life in patients with obstructive sleep apnea: Effect of nasal continuous positive airway pressure – a prospective study. *CHEST*, 115(1), 123-129.

Dempsey, J. A., Skatrud, J. B., Jacques, A. J., Ewanowski, S. J., Woodson, B. T., Hanson, P. R., & Goodman, B. (2002). Anatomic determinants of sleep-disordered breathing across the spectrum of clinical and nonclinical male subjects. *CHEST*, 122(3), 840-851.

Diamanti, C., Manali, E., Ginieri-Coccossis, M., Vougas, K., Cholidou, K., Markozannes, E., Bakakos, P., Liappas, I., & Alchanatis, M. (2013). Depression, physical activity, energy consumption, and quality of life in OSA patients before and after CPAP treatment. *Sleep & Breathing, 17*(4), 1159-1168.

Dickens, C. (1836). *The Pickwick Papers.* Oxford: Oxford University Press.

DiMatteo, M. R., Lepper, H. S., & Croghan, T. W. (2000). Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine, 160*(14), 2101-2107.

Douglas, N., Young, A., Roebuck, T., Ho, S., Miller, B. R., Kee, K., Dabscheck, E. J. & Naughton, M. T. (2013). Prevalence of depression in patients referred with snoring and obstructive sleep apnoea. *Internal Medicine Journal*, *43*(6), 630-634.

Dutt, N., Janmeja, A. K., Mohapatra, P. R., & Singh, A. K. (2013). Quality of life impairment in patients of obstructive sleep apnea and its relation with the severity of disease. *Lung India: Official Organ of Indian Chest Society*, *30*(4), 289-294.

Ellis, J. G., Gehrman, P., Espie, C. A., Riemann, D., & Perlis, M. L. (2012). Acute insomnia: Current conceptualizations and future directions. *Sleep Medicine Reviews*, *16*(1), 5-14.

Engleman, H. M., Kingshott, R. N., Wraith, P. K., Mackay, T. W., Deary, I. J., & Douglas, N. J. (1999). Randomized placebo-controlled crossover trial of continuous positive airway pressure for mild sleep apnea/hypopnea syndrome. *American Journal of Respiratory and Critical Care Medicine, 159*(2), 461-467.

Engleman, H. M., & Douglas, N. J. (2004). Sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome. *Thorax, 59*(7), 618-622.

Fietze, I., Penzel, T., Alonderis, A., Barbe, F., Bonsignore, M. R., Calverly, P., Backer, W., Diefenbacj, K., Donic, V., Eijsvogel, M. M., Franklin, K. A., Gislason, T., Grote, L., Hedner, J., Jennum, P., Lavie, L., Lavie, P., Levy, P., Lombardi, C., Mallin, W., Marrone, O., Montserrat, J. M., Papathanasiou, E. S., Parati, G., Plywaczewski, R., Pretl, M., Riha, R. L., Rodenstein, D., Saaresranta, T., Schulz, R., Sliwinski, P., Steiropoulos, P., Svaza, J., Tomori, Z., Tonnesen, P., Varoneckas, G., Verbraecken, J., Vesely, J., Vitols, A., Zielinski, J. & McNicholas, W. T. (2011). Management of obstructive sleep apnea in Europe. *Sleep medicine*, *12*(2), 190-197.

Finn, L., Young, T., Palta, M., & Fryback, D. G. (1998). Sleep-disordered breathing and self-reported general health status in the Wisconsin Sleep Cohort Study. *Sleep*, *21*(7), 701-706.

Frey, B. N., Lord, C., & Soares, C. N. (2008). Depression during menopausal transition: a review of treatment strategies and pathophysiological correlates. *Menopause International*, *14*(3), 123-128.

Gall, R., Isaac, L., & Kryger, M. (1993). Quality of life in mild obstructive sleep apnea. *Sleep*, *16*(8 Suppl), S59-61.

Gagnadoux, F., Le Vaillant, M., Pigeanne, T., Chollet, S., Masson, P., Bizieux-Thaminy, A., Humeau, M. P. & Meslier, N. (2014). Depressive symptoms before and after long-term CPAP therapy in patients with sleep apnea. *CHEST*, *145*(5), 1025-1031.

Gandek, B., Ware, J. E., Aaronson, N. K., Apolone, G., Bjorner, J. B., Brazier, J. E., Bullinger, M., Kaasa, S., Leplege, A., Luis, P., Sullivan, M. (1998). Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. *Journal of Clinical Epidemiology*, *51*(11), 1171-1178.

George, C. F. (2000). Perspectives on the management of insomnia in patients with chronic respiratory disorders. *Sleep*, *23*, S31-5.

George, C. F. (2007). Sleep apnea, alertness, and motor vehicle crashes. *American Journal of Respiratory and Critical Care Medicine*, *176*(10), 954-956.

Gislason, T., Johannsson, J. H., Haraldsson, A., Olafsdottir, B. R., Jonsdottir, H., Kong, A., Frigge, M. L., Jonsdottir, G., Hakonarson, H., Gulcher, J. & Stefansson, K. (2002). Familial predisposition and cosegregation analysis of adult obstructive sleep apnea and the sudden infant death syndrome. *American Journal of Respiratory and Critical Care Medicine*, *166*(6), 833-838.

Gjevre, J. A., Taylor-Gjevre, R. M., Skomro, R., Reid, J., Fenton, M., & Cotton, D. (2011). Comparison of polysomnographic and portable home monitoring assessments of obstructive sleep apnea in Saskatchewan women. *Canadian Respiratory journal: Journal of the Canadian Thoracic Society*, *18*(5), 271.

Glass, J., Lanctôt, K. L., Herrmann, N., Sproule, B. A., & Busto, U. E. (2005). Sedative hypnotics in older people with insomnia: Meta-analysis of risks and benefits. *BMJ (Clinical research ed.). 331*(7526), 1169.

Guilleminault, C., Eldrige, F. L., & Dement, W. C. (1973). Insomnia with sleep apnea: a new syndrome. *Science, 181*(4102), 856-858.

Guilleminault, C., Tilkian, A., & Dement, W. C. (1976). The sleep apnea syndromes. *Annual Review of Medicine, 27*, 465-484.

Guilleminault, C. (1990). Benzodiazepines, breathing, and sleep. *The American Journal of Medicine*, *88*(3), 25-S28.

Gupta, M. A., & Knapp, K. (2014). Cardiovascular and Psychiatric Morbidity in Obstructive Sleep Apnea (OSA) with Insomnia (Sleep Apnea Plus) versus Obstructive Sleep Apnea without Insomnia: A Case-Control Study from a Nationally Representative US Sample. *PLoS ONE*, *9*(3), e90021.

Hagen, C., Patel, A., & McCall, W. V. (2009). Prevalence of insomnia symptoms in sleep laboratory patients with and without sleep apnea. *Psychiatry Research*, *170*(2), 276-277.

Haponik, E. F., Frye, A. W., Richards, B., Wymer, A., Hinds, A., Pearce, K., McCall, V., & Konen, J. (1996). Sleep history is neglected diagnostic information. Challenges for primary care physicians. *Journal of General Internal Medicine, 11*(12), 759-761.

Harris, M., Glozier, N., Ratnavadivel, R., & Grunstein, R. R. (2009). Obstructive sleep apnea and depression. *Sleep Medicine Reviews*, *13*(6), 437–444.

Hetta, J., Axelsson, S., & Eckerlund, I. (2010). Klinisk översikt: Behandling av sömnbesvär hos vuxna. Sammanfattning av en systematisk litteraturöversikt från SBU. *Lakartidningen*, *107*(44), 2712. (In Swedish)

Holbrook, A. M., Crowther, R., Lotter, A., Cheng, C., & King, D. (2000). Meta-analysis of benzodiazepine use in the treatment of insomnia. *CMAJ: Canadian Medical Association Journal*, *162*(2), 225-233.

Hoy, C. J., Vennelle, M., Kingshott, R. N., Engleman, H. M., & Douglas, N. J. (1999). Can intensive support improve continuous positive airway pressure use in patients with the sleep apnea/hypopnea syndrome? *American Journal of Respiratory and Critical Care Medicine*, *159*(4), 1096-1100.

Huang, Q. R., Qin, Z., Zhang, S., & Chow, C. M. (2008). Clinical patterns of obstructive sleep apnea and its comorbid conditions: a data mining approach. *Journal of Clinical Sleep Medicine: JCSM, official publication of the American Academy of Sleep Medicine*, *4*(6), 543-550.

Hui, D. S., Choy, D. K., Li, T. S., Ko, F. W., Wong, K. K., Chan, J. K., & Lai, C. K. (2001). Determinants of continuous positive airway pressure compliance in a group of Chinese patients with obstructive sleep apnea. *CHEST, 120*(1), 170-176.

Jackson, M. L., Stough, C., Howard, M. E., Spong, J., Downey, L. A., & Thompson, B. (2011). The contribution of fatigue and sleepiness to depression in patients attending the sleep laboratory for evaluation of obstructive sleep apnea. *Sleep and Breathing, 15*(3), 439-445.

Janson, C., Nöges, E., Svedberg-Randt, S., & Lindberg, E. (2000). What characterizes patients who are unable to tolerate continuous positive airway pressure (CPAP) treatment? *Respiratory Medicine, 94*(2), 145-149.

Jansson-Fröjmark, M., & Lindblom, K. (2008). A bidirectional relationship between anxiety and depression, and insomnia? A prospective study in the general population. *Journal of Psychosomatic Research, 64*(4), 443-449.

Jaussent, I., Dauvilliers, Y., Ancelin, M.-L., Dartigues, J.-F., Tavernier, B., Touchon, J., Ritchie, K., & Besset, A. (2011). Insomnia symptoms in older adults: associated factors and gender differences. *The American Journal of Geriatric Psychiatry: Official Journal of the American Association for Geriatric Psychiatry, 19*(1), 88-97.

Jean Wiese, H., Boethel, C., Phillips, B., Wilson, J. F., Peters, J., & Viggiano, T. (2005). CPAP compliance: Video education may help! *Sleep Medicine, 6*(2), 171-174.

Jenkinson, C., Stradling, J., & Petersen, S. (1997). Comparison of three measures of quality of life outcome in the evaluation of continuous positive airways pressure therapy for sleep apnoea. *Journal of Sleep Research, 6*(3), 199-204.

Jenkinson, C., Davies, R. J., Mullins, R., & Stradling, J. R. (1999). Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. *Lancet, 353*(9170), 2100-2105.

Jing, J., Huang, T., Cui, W., & Shen, H. (2008). Effect on quality of life of continuous positive airway pressure in patients with obstructive sleep apnea syndrome: A meta-analysis. *Lung, 186*(3), 131-144.

Johns, M. W. (1992). Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep, 15*(4), 376-381.

Jordan, A. S., & Doug McEvoy, R. D. (2003). Gender differences in sleep apnea: Epidemiology, clinical presentation and pathogenic mechanisms. *Sleep Medicine Reviews, 7*(5), 377-389.

Kapur, V. K., Baldwin, C. M., Resnick, H. E., Gottlieb, D. J., & Nieto, F. J. (2005). Sleepiness in patients with moderate to severe sleep-disordered breathing. *Sleep, 28*(4), 472-477.

Keenan, B. T., Maislin, G., Sunwoo, B. Y., Arnardottir, E. S., Jackson, N., Olafsson, I., Juliusson, S., Schwab, R. J., Gislason, T., Benediktsdottir, B., Pack, A. I. (2014). Obstructive sleep apnoea treatment and fasting lipids: A comparative effectiveness study. *European Respiratory Journal*, erj00436-2014.

Kezirian, E. J., & Goldberg, A. N. (2006). Hypopharyngeal surgery in obstructive sleep apnea: An evidence-based medicine review. *Archives of Otolaryngology–Head & Neck Surgery*, 132(2), 206-213.

Kim, K., Uchiyama, M., Okawa, M., Liu, X., & Ogihara, R. (2000). An epidemiological study of insomnia among the Japanese general population. *Sleep, 23*(1), 41-47.

Kjelsberg, F. N., Ruud, E. A., & Stavem, K. (2005). Predictors of symptoms of anxiety and depression in obstructive sleep apnea. *Sleep Medicine, 6(4), 341-346.*Kolotkin, R. L., Meter, K., & Williams, G. R. (2001). Quality of life and obesity. *Obesity Reviews: An Official Journal of the International Association for the Study of Obesity*, *2*(4), 219-229.

Krakow, B., Melendrez, D., Ferreira, E., Clark, J., Warner, T. D., Sisley, B., & Sklar, D. (2001). Prevalence of insomnia symptoms in patients with sleep-disordered breathing. *CHEST*, *120*(6), 1923-1929.

Krell, S. B., & Kapur, V. K. (2005). Insomnia complaints in patients evaluated for obstructive sleep apnea. *Sleep & Breathing*, *9*(3), 104-110.

Kribbs, N. B., Pack, A. I., Kline, L. R., Smith, P. L., Schwartz, A. R., Schubert, N. M., Redline, S., Henry, J. N., Getsy, J. E., & Dinges, D. F. (1993). Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. *American Review of Respiratory Disease, 147*(4), 887-895.

Krieger, J., McNicholas, W. T., Levy, P., De Backer, W., Douglas, N., Marrone, O., Montserrat, J., Peter, J. H., Rodenstein, D. (2002). Public health and mediocolegal implications of sleep apnoea. *The European Respiratory Journal, 20*(6), 1594-1609.

Kuna, S. T., Gurubhagavatula, I., Maislin, G., Hin, S., Hartwig, K. C., McCloskey, S. Hachadoorian, R., Hurley, S., Gupta, R., Staley, B. & Atwood, C. W. (2011). Noninferiority of functional outcome in ambulatory management of obstructive sleep apnea. *American journal of respiratory and critical care medicine, 183*(9), 1238-1244.

Lacasse, Y., Godbout, C., & Sériés, F. (2002). Health-related quality of life in obstructive sleep apnoea. *The European Respiratory Journal, 19*(3), 499-503.

Lecrubier, Y., Sheehan, D. V., Weiller, E., Amorim, P., Bonora, I., Harnett Sheehan, K., Janavs, J., Dunbar, G. C. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. *European psychiatry*, *12*(5), 224-231.

Law, M., Naughton, M. T., Dhar, A., Barton, D., & Dabscheck, E. (2013). Validation of two depression screening instruments in a sleep disorders clinic. *Journal of Clinical Sleep Medicine: JCS -: official publication of the American Academy of Sleep Medicine,* 10(6), 683-688.

Law, M., Naughton, M., Ho, S., Roebuck, T., & Dabscheck, E. (2014). Depression may reduce adherence during CPAP titration trial. *Journal of Clinical Sleep Medicine: JCSM - official publication of the American Academy of Sleep Medicine, 10*(2), 163-169.

Le Fevre, P., Devereux, J., Smith, S., Lawrie, S. M., & Cornbleet, M. (1999). Screening for psychiatric illness in the palliative care inpatient setting: A comparison between the Hospital Anxiety and Depression Scale and the General Health Questionnaire-12. *Palliative Medicine, 13*(5), 399-407.

Lieu, T. A., Au, D., Krishnan, J. A., Moss, M., Selker, H., Harabin, A., & Connors, A. (2011). Comparative effectiveness research in lung diseases and sleep disorders: Recommendations from the National Heart, Lung, and Blood Institute workshop. *American Journal of Respiratory and Critical Care Medicine, 184*(7), 848-856.

Lim, J., Lasserson, T. J., Fleetham, J., & Wright, J. (2004). Oral appliances for obstructive sleep apnoea. *The Cochrane Database of Systematic Reviews,* (4), CD004435.

Lindberg, E., Janson, C., Gislason, T., Björnsson, E., Hetta, J., & Boman, G. (1997). Sleep disturbances in a young adult population: Can gender differences be explained by differences in psychological status? *Sleep 20*(6), 381-387.

Lindberg, E., Berne, C., Elmasry, A., Hedner, J., & Janson, C. (2006). CPAP treatment of a population-based sample: What are the benefits and the treatment compliance? *Sleep Medicine, 7*(7), 553-560.

Loube, D. I., Gay, P. C., Strohl, K. P., Pack, A. I., White, D. P., & Collop, N. A. (1999). Indications for positive airway pressure treatment of adult obstructive sleep apnea patients: A consensus statement. *CHEST, 115*(3), 863-866.

Luyster, F. S., Buysse, D. J., & Strollo Jr, P. J. (2010). Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. *Journal of Clinical Sleep Medicine: JCSM- official publication of the American Academy of Sleep Medicine, 6*(2), 196.

Luyster, F. S., Kip, K. E., Buysse, D. J., Aiyer, A. N., Reis, S. E., & Strollo, P. J. (2014). Traditional and nontraditional cardiovascular risk factors in comorbid insomnia and sleep apnea. *Sleep, 37*(3), 593-600.

Macey, P. M., Kumar, R., Yan-Go, F.L., Woo, M. A., & Harper, R. M. (2012). Sex differences in white matter alterations accompanying obstructive sleep apnea. *Sleep, 35*(12), 1603-1613.

Maislin, G., Pack, A. I., Kribbs, N. B., Smith, P. L., Schwartz, A. R., Kline, L. R., Schwab, R. J., & Dinges, D. F. (1995). A survey screen for prediction of apnea. *Sleep 18*(3), 158-166.

Maislin, G. & Rubin, D.B. (2010). Design of non-randomized medical device trials based on sub-classification using propensity score quintiles. *In JSM Proceedings, Biopharmaceutical Section. Alexandria, VA: American Statistical Association*. 2182-2196.

Maislin, G., Ahmed, M. M., Gooneratne, N., Thorne-Fitzgerald, M., Kim, C., Teff, K., Arnardottir, E. S., Benediktsdottir, B., Einarsdottir, H., Juliusson, S. Pack, A. I., Gislason, T. & Schwab, R. J. (2012). Single slice vs. volumetric MR assessment of visceral adipose tissue: reliability and validity among the overweight and obese. *Obesity*, *20*(10), 2124-2132.

Marin, J. M., Soriano, J. B., Carrizo, S. J., Boldova, A., & Celli, B. R. (2010). Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: The overlap syndrome. *American Journal of Respiratory and Critical Care Medicine*, *182*(3), 325-331.

Marshall, N. S., Wong, K. K. H., Liu, P. Y., Cullen, S. R. J., Knuiman, M. W., & Grunstein, R. R. (2008). Sleep Apnea as an independent risk factor for all-cause mortality: The Busselton Health Study. *Sleep, 31*(8), 1079-1085.

Martin, S. E., Engleman, H. M., Deary, I. J., & Douglas, N. J. (1996). The effect of sleep fragmentation on daytime function. *American Journal of Respiratory and Critical Care Medicine, 153*(4), 1328-1332.

Mbata, G., & Chukwuka, J. (2012). Obstructive sleep apnea hyponea syndrome. *Annals of Medical and Health Sciences Research, 2*(1), 74-77.

McCarren, M., Goldberg, J., Ramakrishnan, V., & Fabsitz, R. (1994). Insomnia in Vietnam era veteran twins: influence of genes and combat experience. *Sleep*, *17*(5), 456-461.

McNicholas, W. T. & Bonsigore, M. R. (2007). Sleep apnea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *The European Respiratory Journal*, *29*(1), 156-178.

Meerlo, P., Sgoifo, A., & Suchecki, D. (2008). Restricted and disrupted sleep: Effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Medicine Reviews*, *12*(3), 197-210.

Mellinger, G. D., Balter, M. B., & Uhlenhuth, E. H. (1985). Insomnia and its treatment: Prevalence and correlates. *Archives of General Psychiatry*, *42*(3), 225-232.

Meslier, N., Lebrun, T., Grillier-Lanoir, V., Rolland, N., Henderick, C., Sailly, J. C., & Racineux, J. L. (1998). A French survey of 3,225 patients treated with CPAP for obstructive sleep apnoea: benefits, tolerance, compliance and quality of life. *European Respiratory Journal, 12*(1), 185-192.

Millman, R. P., Fogel, B. S., McNamara, M. E., & Carlisle, C. C. (1989). Depression as a manifestation of obstructive sleep apnea: reversal with nasal continuous positive airway pressure. *Journal of Clinical Psychiatry*.

Millman, R. P., Carlisle, C. C., McGarvey, S. T., Eveloff, S. E., & Levinson, P. D. (1995). Body fat distribution and sleep apnea severity in women. *CHEST, 107*(2), 362-366.

Morin, C. M. (2006). Combined therapeutics for insomnia: should our first approach be behavioral or pharmacological? *Sleep Medicine, 7 Suppl 1*, S15-19.

Morin, C. M., LeBlanc, M., Daley, M., Gregoire, J. P., & Mérette, C. (2006). Epidemiology of insomnia: prevalence, self-help treatments, consultations, and determinants of help-seeking behaviors. *Sleep Medicine, 7*(2), 123-130.

Morin, C. M., Bélanger, L., LeBlanc, M., Ivers, H., Savard, J., Espie, C. A., Mérette, C., Baillargeon, L. & Grégoire, J. P. (2009). The natural history of insomnia: A population-based 3-year longitudinal study. *Archives of Internal Medicine, 169*(5), 447-453.

Morin, C. M., LeBlanc, M., Bélanger, L., Ivers, H., Mérette, C., & Savard, J. (2011). Prevalence of insomnia and its treatment in Canada. *Canadian Journal of Psychiatry: Revue canadienne de psychiatrie, 56*(9), 540-548.

Morin, C. M., & Benca, R. (2012). Chronic insomnia. *Lancet, 379*, 1129-1141.

Mosko, S., Zetin, M., Glen, S., Garber, D., Deantonio, M., Sassin, J., McAnich, J., Warren, S. (1989). Self-reported depressive symptomatology, mood ratings, and treatment outcome in sleep disorders patients. *Journal of Clinical Psychology, 45*(1), 51-60.

Moyer, C. A., Sonnad, S. S., Garetz, S. L., Helman, J. I., & Chervin, R. D. (2001). Quality of life in obstructive sleep apnea: a systematic review of the literature. *Sleep Medicine, 2*(6), 477-491.

Munoz, A., Mayoralas, L. R., Barbe, F., Pericas, J., & Agusti, A. N. (2000). Long-term effects of CPAP on daytime functioning in patients with sleep apnoea syndrome. *European Respiratory Journal, 15*(4), 676-681.

Newman, A. B., Enright, P. L., Manolio, T. A., Haponik, E. F., & Wahl, P. W. (1997). Sleep disturbance, psychosocial correlates, and cardiovascular disease in 5201 older adults: The Cardiovascular Health Study. *Journal of the American Geriatrics Society*, *45*(1), 1-7.

Ng, S. S., Chan, T. O., To, K. W., Ngai, J., Tung, A., Ko, F. W., & Hui, D. S. (2010). Validation of Embletta portable diagnostic system for identifying patients with suspected obstructive sleep apnoea syndrome (OSAS). *Respirology*, *15*(2), 336-342.

Nguyên, X. L., Chaskalovic, J., Rakotonanahary, D., & Fleury, B. (2010). Insomnia symptoms and CPAP compliance in OSAS patients: A descriptive study using Data Mining methods. *Sleep medicine*, *11*(8), 777-784.

Nordgaard, J., Revsbech, R., Sæbye, & Parnas, J. (2012). Assessing the diagnostic validity of a structured psychiatric interview in a first-admission hospital sample. *World Psychiatry*, *11*(3), 181-185.

O'Connor, C., Thornley, K. S., & Hanly, P. J. (2000). Gender differences in the polysomnographic features of obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine*, *161*(5), 1465-1472.

Ohayon, M. M., Caulet, M., & Guilleminault, C. (1997). How a general population perceives its sleep and how this relates to the complaint of insomnia. *Sleep*, *20*(9), 715-723.

Ohayon, M. M. (2002). Epidemiology of insomnia: What we know and what we still need to learn. *Sleep Medicine Reviews*, *6*(2), 97-111.

Ohayon, M. M. (2003). The effects of breathing-related sleep disorders on mood disturbances in the general population. *The Journal of Clinical Psychiatry*, *64*(10), 1195-1200.

Ohayon, M. M. (2006). Severe hot flashes are associated with chronic insomnia. *Archives of Internal Medicine*, *166*(12), 1262-1268.

Ohayon, M. M., & Sagales, T. (2010). Prevalence of insomnia and sleep characteristics in the general population of Spain. *Sleep Medicine*, *11*(10), 1010-1018.

Olson, L. G., King, M. T., Hensley, M. J., & Saunders, N. A. (1995). A community study of snoring and sleep-disordered breathing symptoms. *American Journal of Respiratory and Critical Care Medicine*, *152*(2), 707-710.

Ong, J. C., & Crawford, M. R. (2013). Insomnia and obstructive sleep apnea. *Sleep Medicine Clinics*, *8*(3), 389-398.

Onyike, C. U., Crum, R. M., Lee, H. B., Lyketsos, C. G., & Eaton, W. W. (2003). Is obesity associated with major depression? Results from the Third National Health and Nutrition Examination Survey. *American Journal of Epidemiology*, *158*(12), 1139-1147.

Pack, A. I. (2006). Advances in sleep-disordered breathing. *American Journal of Respiratory and Critical Care Medicine*, *173*(1), 7–15.

Pak, V. M., Keenan, B. T., Jackson, N. et al. (2014). Adhesion molecule increases in sleep apnea: beneficial effect of positive airway pressure and moderation by obesity. *International Journal of Obesity*. [Epub ahead of print].

Palagini, L., Biber, K., & Riemann, D. (2014). The genetics of insomnia-evidence for epigenetic mechanisms? *Sleep Medicine Reviews, 18*(3), 225-235.

Partinen, M., & Gislason, T. (1995). Basic Nordic Sleep Questionnaire (BNSQ): A quantitated measure of subjective sleep complaints. *Journal of Sleep Research, 4*(s1), 150-155.

Peker, Y., Hedner, J., Kraiczi, H., & Löth, S. (2000). Respiratory disturbance index: An independent predictor of mortality in coronary artery disease. *American Journal of Respiratory and Critical Care Medicine, 162*(1), 81-86.

Peppard, P. E., Young, T., Palta, M., Dempsey, J., & Skatrud, J. (2000). Longitudinal study of moderate weight change and sleep-disordered brathing. *JAMA, 284*(23), 3015–3021.

Peppard, P. E., Szklo-Coxe, M., Hla, K. M., & Young, T. (2006). Longitudinal association of sleep-related breathing disorder and depression. *Archives of Internal Medicine, 166*(16), 1709-1715.

Peppard, P. E., Young, T., Barnet, J. H., Palta, M., Hagen, E. W., & Hla, K. M. (2013). Increased prevalence of sleep-disordered breathing in adults. *American Journal of Epidemiology, 177*(9), 1006–1014.

Pieh, C., Bach, M., Popp, R., Jara, C., Crönlein, T., Hajak, G., & Geisler, P. (2013). Insomnia symptoms influence CPAP compliance. *Sleep and Breathing, 17*(1), 99-104.

Punjabi, N. M. (2008). The epidemiology of adult obstructive sleep apnea. *Proceedings of the American Thoracic Society, 5*(2), 136-143.

Radloff, L. S. (1977). The CES-D scale: A self-report depression scale for research in the general population. *Applied Psychological Measurement, 1*(3), 385–401.

Rauscher, H., Formanek, D., Popp, W., & Zwick, H. (1993). Self-reported vs. measured compliance with nasal CPAP for obstructive sleep apnea. *CHEST, 103*(6), 1675-1680.

Redline, S., Kump, K., Tishler, P. V., Browner, I., & Ferrette, V. (1994). Gender differences in sleep disordered breathing in a community-based sample. *American Journal of Respiratory and Critical Care Medicine, 149*(3), 722-726.

Redline, S., Tishler, P. V., Tosteson, T. D., Williamson, J., Kump, K., Browner, I., Ferrette, V., & Krejci, P. (1995). The familial aggregation of obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine, 151*(3 Pt 1), 682-687.

Redline, S., & Tishler, P. V. (2000). The genetics of sleep apnea. *Sleep Medicine Reviews, 4*(6), 583-602.

Reynolds, C. F., Kupfer, D. J., McEachran, A. B., Taska, L. S., Sewitch, D. E., & Coble, P. A. (1984). Depressive psychopathology in male sleep apneics. *Journal of Clinical Psychiatry*.

Richards, D., Bartlett, D. J., Wong, K., Malouff, J., & Grunstein, R. R. (2007). Increased adherence to CPAP with a group cognitive behavioral treatment intervention: a randomized trial. *Sleep, 30*(5), 635-640.

Riedel, B. W., & Lichstein, K. L. (2000). Insomnia and daytime functioning. *Sleep Medicine Reviews, 4*(3), 277-298.

Riemann, D., Spiegelhalder, K., Feige, B., Voderholzer, U., Berger, M., Perlis, M., & Nissen, C. (2010). The hyperarousal model of insomnia: a review of the concept and its evidence. *Sleep Medicine Reviews, 14*(1), 19-31.

Roberts, R. E., Kaplan, G. A., Shema, S. J., & Strawbridge, W. J. (2000). Are the obese at greater risk for depression? *American Journal of Epidemiology, 152*(2), 163-170.

Rofail, L. M., Wong, K. K H., Unger, G., Marks, G. B., & Grunstein, R. R. (2010). The utility of single-channel nasal airflow pressure transducer in the diagnosis of OSA at home. *Sleep, 33*(8), 1097-1105.

Rosenthal, L., Gerhardstein, R., Lumley, A., Guido, P., Day, R., Syron, M. L., & Roth, T. (2000). CPAP therapy in patients with mild OSA: Implementation and treatment outcome. *Sleep Medicine, 1*(3), 215-220.

Roth, T., & Roehrs, T. (2003). Insomnia: Epidemiology, characteristics, and consequences. *Clinical cornerstone, 5*(3), 5-15.

Roth, T., Roehrs, T., & Pies, R. (2007). Insomnia: Pathophysiology and implications for treatment. *Sleep Medicine Reviews, 11*(1), 71-79.

Roth, T. (2009). Comorbid insomnia: Current directions and future challenges. *The American Journal of Managed Care, 15 Suppl*, S6-13.

Roth, T., Coulouvrat, C., Hajak, G., Lakoma, M. D., Sampson, N. A., Shahly, V., Shillington, A. C., Stephenson, J. J., Walsh, J. K., & Kessler, R. C. (2011). Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Research Diagnostic Criteria/International Classifiaction of Sleep Disorders, Second Edition Criteria: Results from the America Insomnia Survey. *Biological Psychiatry, 69*(6), 592-600.

Russo-Magno, P., O'Brien, A., Panciera, T., & Rounds, S. (2001). Compliance with CPAP therapy in older men with obstructive sleep apnea. *Journal of the American Geriatrics Society, 49*(9), 1205-1211.

Sanner, B. M., Klewer, J., Trumm, A., Randerath, W., Kreuzer, I., & Zidek, W. (2000). Long-term treatment with continuous positive airway pressure improves quality of life in obstructive sleep apnoea syndrome. *European Respiratory Journal, 16*(1), 118-122.

Sassani, A., Findley, L. J., Kryger, M., Goldlust, E., George, C., & Davidson, T. M. (2004). Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. *Sleep, 27*(3), 453-458.

Sateia, M. J. (2003). Neuropsychological impairment and quality of life in obstructive sleep apnea. *Clinics in Chest Medicine, 24*(2), 249-259.

Sauter, C., Asenbaum, S., Popovic, R., Bauer, H., Lamm, C., Klösch, G., & Zeitlhofer, J. (2000). Excessive daytime sleepiness in patients suffering from different levels of obstructive sleep apnoea syndrome. *Journal of Sleep Research, 9*(3), 293-301.

Savransky, V., Nanayakkara, A., Li, J., Bevans, S., Smith, P. L., Rodriguez, A., & Polotsky, V. Y. (2007). Chronic intermittent hypoxia induces atherosclerosis. *American Journal of Respiratory and Critical Care Medicine, 175*(12), 1290-1297.

Sawyer, A. M., Gooneratne, N. S., Marcus, C. L., Ofer, D., Richards, K. C., & Weaver, T. E. (2011). A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Medicine Reviews, 15*(6), 343-356.

Sánchez, A. I., Buela-Casal, G., Bermúdez, M. P., & Casas-Maldonado, F. (2001). The effects of continuous positive air pressure treatment on anxiety and depression levels in apnea patients. *Psychiatry and Clinical Neurosciences, 55*(6), 641-646.

Schmidt-Nowara, W., Lowe, A., Wiegand, L., Cartwright, R., Perez-Guerra, F., & Menn, S. (1995). Oral appliances for the treatment of snoring and obstructive sleep apnea: a review. *Sleep, 18*(6), 501-510.

Schröder, C. M., & O'Hara, R. (2005). Depression and obstructive sleep apnea (OSA). *Annals of General Psychiatry*, 4(1), 13.

Schutte-Rodin, S., Broch, L., Buysse, D., Dorsey, C., & Sateia, M. (2008). Clinical guideline for the evaluation and management of chronic insomnia in adults. *Journal of Clinical Sleep Medicine: JCSM - official publication of the American Academy of Sleep Medicine, 4*(5), 487-504.

Schwab, R. J., Gupta, K. B., Gefter, W. B., Metzger, L. J., Hoffman, E. A., & Pack, A. I. (1995). Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing: Significance of the lateral pharyngeal walls. *American Journal of Respiratory and Critical Care Medicine, 152*(5), 1673-1689.

Sforza, E., De Saint Hilaire, Z., Pelissolo, A., Rochat, T., & Ibanez, V. (2002). Personality, anxiety and mood traits in patients with sleep-related breathing disorders: effect of reduced daytime alertness. *Sleep Medicine, 3*(2), 139-145.

Shamasuzzaman, A. S. M., Gersh, B. J., & Somers, V. K. (2003). Obstructive sleep apnea: Implications for cardiac and vascular disease. *JAMA, 290*(14), 1906-1914.

Sharafkhaneh, A., Giray, N., Richardson, P., Young, T., & Hirshkowitz, M. (2005). Association of psychiatric disorders and sleep apnea in a large cohort. *Sleep, 28*(11), 1405-1411.

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G. C. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry 59*(20), 22–33.

Shepertycky, M. R., Banno, K., & Kryger, M. H. (2005). Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. *Sleep, 28*(3), 309-314.

Shochat, T., Umphress, J., Israel, A. G., & Ancoli-Israel, S. (1999). Insomnia in primary care patients. *Sleep, 22, Suppl 2,* S359-365.

Sigurðsson, B. H. (2008). *Comparison Between Two Standardized Psychiatric Interviews and Two Self-report Measures: MINI, CIDI, PHQ and DASS* (Cand Psych). University of Iceland.

Silva, G. E., An, M.-W., Goodwin, J. L., Shahar, E., Redline, S., Resnick, H., Baldwin, C. M., & Quan, S. F. (2009). Longitudinal evaluation of sleep-disordered breathing and sleep symptoms with change in quality of life: The Sleep Heart Health Study (SHHS). *Sleep, 32*(8), 1049-1057.

Simon, G. E., Von Korff, M., Saunders, K., Miglioretti, D. L., Crane, P. K., van Belle, G., & Kessler, R. C. (2006). Association between obesity and psychiatric disorders in the US adult population. *Archives of general psychiatry, 63*(7), 824-830.

Sin, D. D., Mayers, I., Man, G. C. W., & Pawluk, L. (2002). Long-term compliance rates to continuous positive airway pressure in obstructive sleep apnea: A population based study. *CHEST, 121*(2), 430-435.

Sivertsen, B., Björnsdóttir, E., Øverland, S., Bjorvatn, B. & Salo, P. (2013), The joint contribution of insomnia and obstructive sleep apnoea on sickness absence. *Journal of Sleep Research, 22*(2), 223-230.

Sloan, E. P., & Shapiro, C. M. (1993). Hypnotics should never be used in patients with sleep apnea. *Journal of Psychosomatic Research, 37*, 59-65.

Smith, M. T., & Neubauer, D. N. (2003). Cognitive behavior therapy for chronic insomnia. *Clinical Cornerstone, 5*(3), 28-40.

Smith, S., Sullivan, K., Hopkins, W., & Douglas, J. (2004). Frequency of insomnia report in patients with obstructive sleep apnoea hypopnea syndrome (OSAHS). *Sleep Medicine, 5*(5), 449-456.

Snaith, R. P. (2003). The Hospital Anxiety and Depression Scale. *Health and Quality of Life Outcomes, 1*, 29-33.

Stefánsson, J.G. & Líndal, E. (2009). Algengi geðraskana á Stór-Reykjavíkursvæðinu. Læknablaðið 9, 559-564. (In Icelandic)

Stepanski, E. J., & Rybarczyk, B. (2006). Emerging research on the treatment and etiology of secondary or comorbid insomnia. *Sleep Medicine Reviews, 10*(1), 7-18.

Subramanian, S., Guntupalli, B., Murugan, T., Bopparaju, S., Chanamolu, S., Casturi, L., & Surani, S. (2011). Gender and ethnic differences in prevalence of self-reported insomnia among patients with obstructive sleep apnea. *Sleep and Breathing, 15*(4), 711-715.

Szelenberger, W., & Soldatos, C. (2005). Sleep disorders in psychiatric practice. *World Psychiatry, 4*(3), 186-190.

Tuomilehto, H. P. I., Seppä, J. M., Partinen, M. M., Peltonen, M., Gylling, H., Tuomilehto, J. O. I., Vanninen, E. J., Kokkarinen, J., Sahlman, J. K., Martikainen, T., Soini, E. J. O., Randell, J., Tukiainen, H., & Uusitupa, M. (2009). Lifestyle intervention with weight reduction: first-line treatment in mild obstructive sleep apnea. *American Journal of Respiratory and Critical Care Medicine, 179*(4), 320-327.

Uhlig, B. L., Sand, T., Ødegård, S. S., & Hagen, K. (2014). Prevalence and associated factors of DSM-V insomnia in Norway: the Nord-Trøndelag Health Study (HUNT 3). *Sleep Medicine, 15*(6), 708-713.

Vgontzas, A. N., Bixler, E. O., Tan, T. L., Kantner, D., Martin, L. F., & Kales, A. (1998). Obesity without sleep apnea is associated with daytime sleepiness. *Archives of Internal Medicine, 158*(12), 1333-1337.

Ware Jr, J. E., Kosinski, M., & Keller, S. D. (1996). A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Medical care*, *34*(3), 220-233.

Ware, J. C., McBrayer, R. H., & Scott, J. A. (2000). Influence of sex and age on duration and frequency of sleep apnea events. *Sleep*, *23*(2), 165-170.

Watson, N. F., Goldberg, J., Arguelles, L., & Buchwald, D. (2006). Genetic and environmental influences on insomnia, daytime sleepiness, and obesity in twins. *Sleep*, *29*(5), 645-649.

Weaver, T. E., Maislin, G., Dinges, D. F., Bloxham, T., George, C. F. P., Greenberg, H., Kader, G., Mahowald, M., Younger, J., & Pack, A. I. (2007). Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. *Sleep*, *30*(6), 711-719.

Weaver, T. E., & Grunstein, R. R. (2008). Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. *Proceedings of the American Thoracic Society*, *5*(2), 173-178.

Weaver, T. E., Mancini, C., Maislin, G., Cater, J., Staley, B., Landis, J. R., Ferguson, K. A., George, C. F., Schulman, D. A., Greenberg, H., Rapoport, D. M., Walsleben, J. A., Lee-Chiong, T., Gurubhagavatula, I., & Kuna, S. T. (2012). Continuous positive airway pressure treatment of sleepy patients with milder obstructive sleep apnea: results of the CPAP Apnea Trial North American Program (CATNAP) randomized clinical trial. *American Journal of Respiratory and Critical Care Medicine*, *186*(7), 677-683.

Wiebe, S. T., Cassoff, J., & Gruber, R. (2012). Sleep patterns and the risk for unipolar depression: a review. *Nature and Science of Sleep*, *4*, 63–71.

Wickwire, E. M., Smith, M. T., Birnbaum, S., & Collop, N. A. (2010). Sleep maintenance insomnia complaints predict poor CPAP adherence: A clinical case series. *Sleep medicine*, *11*(8), 772-776.

Wong, W. S., & Fielding, R. (2011). Prevalence of insomnia among Chinese adults in Hong Kong: A population-based study. *Journal of Sleep Research*, *20*(1 pt 1), 117-126.

World Health Organization. (1992). *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization.

Yaggi, H. K., Concato, J., Kernan, W. N., Lichtman, J. H., Brass, L. M., & Mohsenin, V. (2005). Obstructive sleep apnea as a risk factor for stroke and death. *New England Journal of Medicine*, *353*(19), 2034-2041.

Yang, E.H., Hla, K. M., McHorney, C. A., Havighurst, T., Badr, M. S. & Weber, S. (2000). Sleep apnea and quality of life. *Sleep 23*(4), 535-541.

Ye, L., Pien, G. W., Ratcliffe, S. J., Björnsdottir, E., Arnardottir, E. S., Pack, A. I., Benediktsdottir, B. & Gislason, T. (2014). The different clinical faces of obstructive sleep apnoea: a cluster analysis. *European Respiratory Journal*, erj00323-2014.

Young, T., Hutton, R., Finn, L., Badr, S., & Palta, M. (1996). The gender bias in sleep apnea diagnosis: Are women missed because they have different symptoms? *Archives of Internal Medicine*, *156*(21), 2445-2451.

Young, T., Evans, L., Finn, L., & Palta, M. (1997). Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep*, *20*(9), 705–706.

Young, T., Peppard, P. E., & Gottlieb, D. J. (2002). Epidemiology of obstructive sleep apnea: A population health perspective. *American Journal of Respiratory and Critical Care Medicine*, *165*(9), 1217–1239.

Young, T., Shahar, E., Nieto, F. J., Redline, S., Newman, A. B., Gottlieb, D. J., Walsleben, J. A., Finn, L., Enright, P., & Samet, J. M. (2002). Predictors of sleep-disordered breathing in community-dwelling adults: The Sleep Heart Health Study. *Archives of Internal Medicine*, *162*(8), 893-900.

Young, T., Skatrud, J., & Peppard, P. E. (2004). Risk factors for obstructive sleep apnea in adults. *JAMA*, *291*(16), 2013-2016.

Young, T., Finn, L., Peppard, P. E., Szklo-Coxe, M., Austin, D., Nieto, F. J., ... & Hla, K. M. (2008). Sleep disordered breathing and mortality: Eighteen-year follow-up of the Wisconsin sleep cohort. *Sleep*, *31*(8), 1071.

Yue, W., Hao, W., Liu, P., Liu, T., Ni, M., & Guo, Q. (2003). A case-control study on psychological symptoms in sleep apnea-hypopnea syndrome. *Canadian Journal of Psychiatry*, *48*(5), 318-323.

Zozula, R., & Rosen, R. (2001). Compliance with continuous positive airway pressure therapy: Assessing and improving treatment outcomes. *Current Opinion in Pulmonary Medicine*, *7*(6), 391-398.

Original publications

Paper I

Insomnia in untreated sleep apnea patients compared to controls

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SUMMARY

Insomnia and obstructive sleep apnea (OSA) often coexist, but the nature of their relationship is unclear. The aims of this study were to compare the prevalence of initial and middle insomnia between OSA patients and controls from the general population as well as to study the influence of insomnia on sleepiness and quality of life in OSA patients. Two groups were compared, untreated OSA patients ($n = 824$) and controls ≥ 40 years from the general population in Iceland ($n = 762$). All subjects answered the same questionnaires on health and sleep and OSA patients underwent a sleep study. Altogether, 53% of controls were males compared to 81% of OSA patients. Difficulties maintaining sleep (DMS) were more common among men and women with OSA compared to the general population (52 versus 31% and 62 versus 31%, respectively, $P < 0.0001$). Difficulties initiating sleep (DIS) and DIS + DMS were more common among women with OSA compared to women without OSA. OSA patients with DMS were sleepier than patients without DMS (Epworth Sleepiness Scale: 12.2 versus 10.9, $P < 0.001$), while both DMS and DIS were related to lower quality of life in OSA patients as measured by the Short Form 12 (physical score 39 versus 42 and mental score 36 versus 41, $P < 0.001$). DIS and DMS were not related to OSA severity. Insomnia is common among OSA patients and has a negative influence on quality of life and sleepiness in this patient group. It is relevant to screen for insomnia among OSA patients and treat both conditions when they co-occur.

INTRODUCTION

Insomnia is a common and often persistent complaint, and includes symptoms such as difficulties initiating sleep (DIS) and difficulties maintaining sleep (DMS). Studies of population-based samples have found the prevalence of insomnia to range between 10 and 48%, depending on the definition of insomnia that is used and the population studied (LeBlanc *et al.*, 2009; Morphy *et al.*, 2007; Roth *et al.*, 2007). Insomnia can be an independent disorder (primary insomnia) or comorbid with another medical or psychiatric condition. Primary insomnia is estimated to affect about 25% of all patients suffering from chronic insomnia (Buysse *et al.*, 1997). Female gender, age, poor self-rated health and snoring have been associated with increased rates of insomnia symptoms (Hartz *et al.*, 2007; Klink *et al.*, 1992).

Like insomnia, obstructive sleep apnea (OSA) is a prevalent disorder, often with serious adverse consequences. OSA is characterized by loud snoring and frequent breathing pauses during the night due to increased airway resistance which leads to partial (hypopnea) or complete (apnea) upper airway collapse (Pack and Gislason, 2009). These events lead to repeated drops in oxygen saturation

and, over time, OSA can contribute to impaired daytime function including excessive daytime sleepiness (EDS) and increased behavioral, metabolic and cardiovascular morbidity and mortality. Although the most common symptoms of OSA are loud snoring and daytime sleepiness, the condition is often undiagnosed (Young *et al*., 2002).

Complaints of insomnia are frequent among OSA patients (Benetó *et al*., 2009) and in recent years there has been a growing interest in the coexistence of these disorders. When insomnia and OSA co-occur, it is likely that the interaction promotes overall greater illness severity (both in terms of OSA and insomnia) and increases cumulative medical and psychiatric morbidity (Krakow *et al*., 2001; Luyster *et al*., 2010; Smith *et al*., 2004).

Studies on the relationship between OSA and insomnia have estimated that between 40 and 60% of untreated OSA patients are suffering simultaneously from chronic insomnia, a rate which far exceeds the prevalence in the general population (Chung, 2005; Krell and Kapur, 2005; Subramanian *et al*., 2010; Wickwire and Collop, 2010). However, there has been a lack of studies directly comparing the prevalence of insomnia and its subtypes between untreated OSA patients and controls from the general population. Because insomnia is prevalent among OSA patients, it is also of interest whether people from the general population with symptoms of OSA are at increased risk for insomnia.

The aims of the study were (i) to compare the prevalence of difficulties initiating sleep (DIS) and difficulties maintaining sleep (DMS) in untreated OSA patients versus controls; (ii) to examine whether OSA symptoms are risk factors for insomnia symptoms in a general population sample from Iceland; and (iii) to examine whether the coexistence of OSA and insomnia has an additional negative effect on quality of life compared to OSA alone.

SUBJECTS AND METHODS

Participants

Patients diagnosed with OSA in Iceland and referred for treatment with continuous positive airway pressure (CPAP) to the Landspitali, The National University Hospital of Iceland from September 2005 to December 2009 were invited to participate in the study. They are part of the Icelandic Sleep Apnea Cohort (ISAC). More than 90% of the eligible subjects who were approached agreed to participate. Altogether, 824 patients with OSA took part in this study. Among OSA patients, 81% were males and 19% were females, and the mean age was 54.4 ± 10.7 years.

The controls were 762 individuals aged 40+ sampled randomly from the general population in Iceland, with a response rate of 81% (Benediktsdottir *et al*., 2010). Among controls, 53% were males and 47% were females. The controls were, on average, 2 years older (56.4 versus 54.4) than OSA patients ($P < 0.001$).

Questionnaire and procedure

All participants (both OSA patients and controls) were invited to the outpatient clinic at the Landspitali, The National University Hospital of Iceland. After written informed consent was obtained, they answered standardized questionnaires about sleep, daytime sleepiness, health, lifestyle and quality of life. The protocol was approved by the National Bioethics Committee of Iceland.

Insomnia

Insomnia was defined using answers to two questions from the Basic Nordic Sleep Questionnaire: 'I have difficulties falling asleep at night' (DIS) and 'I wake up often during the night' (DMS) based on the past month (Partinen and Gislason, 1995). The answers were rated on a five-point scale: never/almost never (i); less than once a week (ii); once or twice a week (iii); three to five times a week (iv); and every day or almost every day of the week (v). Those who scored ≥ 4 were defined as having insomnia. The prevalence of having both DIS and DMS at the same time (DIS + DMS) was also explored.

Daytime sleepiness, body mass index and snoring

Daytime sleepiness was evaluated with the Epworth Sleepiness Scale (ESS) (Johns, 1992) and excessive daytime sleepiness (EDS) was defined as ESS score ≥ 10. Standardized methods were used to measure height and weight. Body mass index (BMI) was calculated as kg m^{-2}. Habitual snoring was defined as snoring ≥ 3 nights per week.

Quality of life

Assessment of quality of life was based on the SF-12 questionnaire, a short form of the SF-36, the most widely used health survey. Two summary component scores can be derived from the SF-12, both physical (PS) and mental (MS) health summary scores (Ware *et al*., 1996). These scores range from 0 to 100, where a zero score indicates the lowest life quality and 100 indicates the highest life quality.

Restless legs syndrome (RLS)

Diagnostic criteria for RLS were based on answers from the International Restless Legs Syndrome Study Group Questionnaire (IRLS) (Allen *et al*., 2003; Benediktsdottir *et al*., 2010). Those who answered the questionnaire as follows were regarded as having RLS: they had a strong urge to move their legs often or very often. The discomfort in the legs was relieved by moving the legs or walking. The symptoms had to be most prominent in the evening, at bedtime or no difference in symptoms by the time of day.

Diabetes and hypertension

Participants were defined as having diabetes if they indicated that they had been diagnosed by a doctor and were using medication for diabetes. Similarly, they were considered to have hypertension if they had been diagnosed by a doctor and were on antihypertensive medication.

Smoking history

Participants were asked about their smoking history; subjects who smoked more than 20 packs of cigarettes in a lifetime or more than one cigarette each day for a year but were not current smokers were defined as being ex-smokers. Those who had never smoked or smoked fewer than 20 packs of cigarettes in their lifetime were defined as being never smokers, while subjects reporting to be still smoking were classified as current smokers.

Sleep apnea

All OSA subjects had a sleep study while untreated with an Embletta type 3 portable monitor or an Embla 12 channel system (Embla™; Flaga Inc., Reykjavik, Iceland) recording the same channels. The sleep recordings were scored in a uniform manner at the Sleep Study Reading Unit of the University of Pennsylvania. These data were used to calculate an apnea/hypopnea index (AHI). Events were scored according to the following definitions: a classification of hypopnea required a ≥ 30% or greater drop in flow with ≥ 4% oxygen desaturation or a ≥ 50% drop in flow for ≥ 10 s, with a sudden increase in flow at the end of the event. A classification of an obstructive apnea required a ≥ 80% drop in flow for ≥ 10 s. The oxygen desaturation index (ODI) was calculated as the number of falls in oxygen of > 4% per hour of sleep. The minimum SaO_2 was defined as the lowest oxygen saturation reached during the study. Controls did not have a sleep study.

OSA high- and low-risk controls

Controls were defined as OSA high risk or low risk based on the multivariable apnea index (MAP) (Maislin *et al*., 1995). The MAP score is based on self-reported presence of apnea symptoms (snoring or gasping, breathing stops, choking or struggling for breath during night) as well as BMI and gender. The MAP score ranges between 0 and 1 where subjects who score 0 are the least likely to have sleep apnea. A cut-off of 0.5 has been shown to have sensitivity of 0.88, specificity of 0.55 and positive predictive value of 0.75 in predicting OSA (Maislin *et al*., 1995). This cut-off has, however, been used mainly on patient groups, and therefore a cut-off of 0.75 in the MAP index was used in this study to divide controls into OSA high- and low-risk groups.

Statistical analyses

All statistics were calculated with STATA version 11.0 for Windows (Stata Corporation, College Station, TX, USA). Differences between the groups of subjects with and without OSA were first compared using the chi-square test and unpaired *t*-test. Multiple logistic regression was then used to identify which risk factors had an independent association with the outcome variables. A *P*-value < 0.05 was regarded as statistically significant.

RESULTS

Study population characteristics

Table 1 shows that there were more males among the OSA patients and that they had a higher BMI, were sleepier and less

Table 1 Characteristics of the study population

	Men			*Women*		
	Controls (n = *404)*	*OSA* (n = *669)*	P-*value*	*Controls* (n = *358)*	*OSA* (n = *157)*	P-*value*
Age (years)	56.4 ± 11.5	53.5 ± 10.8	**< 0.0001**	57.7 ± 12.2	58.4 ± 9.1	0.903
BMI (kg m^{-2})	28.3 ± 4.4	33.4 ± 5.6	**< 0.0001**	27.5 ± 5.5	34.1 ± 6.3	**< 0.0001**
Smoking history			**< 0.0001**			0.160
Never smoker (%)	38.7	27.1	**< 0.0001**	39.7	30.6	0.068
Ex-smoker (%)	45.8	51.4	0.074	38.9	50.3	**0.018**
Smokers (%)	15.5	21.5	**0.008**	21.4	19.1	0.914
Hypertension (%)	30.2	54.8	**< 0.0001**	36.1	66.2	**< 0.0001**
Diabetes (%)	4.6	10.7	**0.002**	5.3	11.5	**0.026**
RLS (%)	12.9	22.3	**< 0.0001**	24.4	33.8	0.052
EDS (ESS ≥ 10)	22.8	65.4	**< 0.0001**	23.2	63.1	**< 0.0001**
DIS (%)	9.4	12.6	0.221	18.1	27.3	**0.026**
DMS (%)	30.7	51.6	**< 0.0001**	31.0	62.4	**< 0.0001**
DIS + DMS (%)	6.9	9.0	0.412	10.3	19.7	**0.003**

BMI, body mass index; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; RLS, restless legs syndrome; DIS, difficulties initiating sleep; DMS, difficulties maintaining sleep; OSA, obstructive sleep apnea. Significance is shown in bold type.

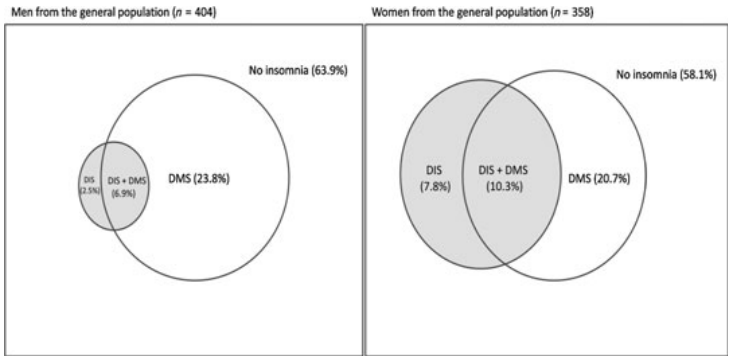

Figure 1. Prevalence of difficulties initiating sleep (DIS), difficulties maintaining sleep (DMS) and DIS + DMS among men and women from the general population.

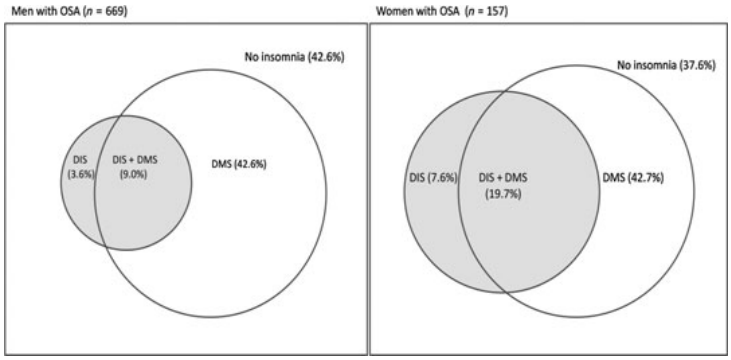

Figure 2. Prevalence of difficulties initiating sleep (DIS), difficulties maintaining sleep (DMS) and DIS + DMS among OSA patients.

likely to be never smokers than controls. In addition, they had a higher prevalence of hypertension, diabetes and RLS compared to the control population. DMS was more common among men and women with OSA compared to the general population. DIS and DIS + DMS were more common among women with OSA compared to women without OSA (Table 1).

The prevalence of insomnia

The majority of the OSA patients (57.6%) reported difficulties maintaining sleep compared to 32% of the controls ($P < 0.001$). The difference in the prevalence of difficulties initiating sleep (DIS) and DIS + DMS were, however, not significant between the two groups. DMS was similarly common among men and women, while having DIS and DIS+DMS was more common among women ($P < 0.05$). Overall, symptoms of insomnia were more frequently reported by women in both groups (Table 1 and Figs 1 and 2).

Associations with insomnia in controls and OSA patients

Table 2 shows that among the controls, poor mental and physical quality of life, hypertension and RLS were independent risk factors for both DIS and DMS. In addition, a high MAP score was an independent risk factor for DMS.

Among the OSA patients, female gender and smoking were independent risk factors for DIS while age and RLS were independent risk factors for DMS. Lower mental and physical qualities of life were associated with both DIS and DMS among controls and OSA patients (Table 3).

DMS was associated significantly with OSA in men when this was tested by combining the patient population and the general population and adjusting for possible confounders (Table 4). No significant association between OSA and DMS was found in women and no significant independent association between OSA and DIS was found in either gender.

Characteristics of OSA patients and controls with and without insomnia

Among the controls, subjects with DIS and DMS were older, had higher BMI, higher prevalence of hypertension and RLS and reported poorer mental and physical life qualities compared to controls without DIS and DMS. In addition, controls with DIS were less sleepy than controls without DIS (Table 5).

Table 6 shows that there was no difference in age, BMI or daytime sleepiness between the OSA patients with and without DIS. However, the OSA patients with DIS reported poorer mental and physical quality of life and a higher prevalence of RLS compared to OSA patients without DIS.

Table 2 Factors associated with DIS and DMS in the general population. The association expressed as adjusted odds ratio (OR) with a 95% confidence interval [OR (95% CI)]

	DIS *OR (95% CI)**	*DMS* *OR (95% CI)**
Smoking history	0.96 (0.69–1.33)	0.98 (0.77–1.24)
RLS	**2.69 (1.60–4.53)**	**2.08 (1.36–3.18)**
SF-12 MS	**0.91 (0.87–0.95)**	**0.95 (0.92–0.99)**
SF-12 PS	**0.93 (0.90–0.95)**	**0.97 (0.94–0.99)**
Diabetes	0.59 (0.21–1.66)	0.92 (0.44–1.95)
Hypertension	1.21 (0.74–1.96)	**1.64 (1.15–2.34)**
Map index	1.59(0.59–4.35)	**2.13 (1.02–4.43)**

RLS, restless legs syndrome; SF-12 MS, Short Form-12 mental score; SF-12 PS, Short Form-12 physical score; MAP, multivariable apnea index; DIS, difficulties initiating sleep; DMS, difficulties maintaining sleep. Significance is shown in bold type. *Adjusted for all the variables in the table.

Table 3 Factors associated with DIS and DMS among OSA patients. The association expressed as adjusted odds ratio (OR) with a 95% confidence interval [OR (95% CI)]

	DIS *OR (95% CI)**	*DMS* *OR (95% CI)**
Age per 10 years	0.89 (0.70–1.10)	**1.27 (1.08–1.48)**
Female gender	**2.43 (1.51–3.91)**	0.89 (0.60–1.31)
BMI by 5 units	1.04 (0.86–1.27)	1.14 (0.98–1.32)
Ex smoker	0.97 (0.56–1.68)	1.12 (0.80–1.63)
Current smoker	**2.40 (1.35–4.25)**	0.96 (0.63–1.47)
Snoring every day	0.64 (0.38–1.07)	1.29 (0.88–1.88)
RLS	1.11 (0.69–1.77)	**1.71 (1.18–2.46)**
SF12 MS	**0.96 (0.94–0.98)**	**0.98 (0.97–1.00)**
SF 12 PS	**0.97 (0.95–0.99)**	**0.98 (0.97–1.00)**
Diabetes	1.03 (0.54–2.00)	0.69 (0.42–1.13)
Hypertension	1.12 (0.70–1.78)	1.00 (0.72–1.38)

BMI, body mass index; RLS, restless legs syndrome; SF-12 MS, Short Form-12 mental score; SF-12 PS, Short Form-12 physical score; DIS, difficulties initiating sleep; DMS, difficulties maintaining sleep. Significance is shown in bold type. *Adjusted for all the variables in the table.

The OSA patients with DMS were older, with more daytime sleepiness, higher prevalence of RLS and poorer quality of life than the OSA patients without DMS (Table 6). When considering the genders separately, the only difference was that men with DMS were older than men without DMS (54.8 years versus 51.9 years; $P < 0.001$), but no significant age difference was found among women. In addition, women with DIS did not report poorer physical health while that difference remained significant among men ($P < 0.001$).

The prevalence of DIS and DMS was not related to OSA severity expressed as AHI, minimum SaO_2 or ODI.

OSA high- and low-risk controls

The OSA high-risk definition was met by 92 (12.0%) controls with a mean MAP score of 0.81 ± 0.05. The low-risk controls were 672 (88.0%) individuals with a mean MAP score of 0.33 ± 0.2.

Table 4 The association between OSA with DIS and DMS in men and women. The association expressed as adjusted odds ratio (OR) with a 95% confidence interval [OR (95% CI)]

	DIS *OR (95% CI)**	*DMS* *OR (95% CI)**
Men	0.55 (0.32–1.97)	**2.11 (1.52–2.93)**
Women	0.60 (0.26–1.23)	1.50 (0.83–2.69)

DIS, difficulties initiating sleep; DMS, difficulties maintaining sleep; OSA: obstructive sleep apnea. Significance is shown in bold type. *Adjusted for population (patient versus controls), age, body mass index (BMI), smoking history, restless legs syndrome (RLS), mental and physical life qualities, hypertension and diabetes.

DMS was reported among 39.7% of high-risk controls compared to 31.1% of low-risk controls ($P = 0.135$). DIS was reported among 22.9% of high-risk controls compared to 13.2% of low-risk controls ($P = 0.027$). Both DIS and DMS were most frequent among subjects with the highest MAP score (0.75–1.0). Symptoms of DIS are particularly common among subjects with MAP score between 0.75 and 1.0 compared to subjects with a lower MAP score ($P < 0.05$) (Fig. 3). High-risk controls reported poorer physical life qualities compared to low-risk controls ($P < 0.001$), but the difference in mental life qualities was not significant.

DISCUSSION

In our study, the majority of the OSA patients (57.6%) had DMS compared to one-third of controls. The prevalence of DIS and DIS + DMS was significantly higher only among women with OSA compared to women without OSA. This is not surprising, as 80% of the OSA patients in this study were men and DIS is generally more common among women (Li *et al.*, 2002; Subramanian *et al.*, 2010).

The OSA patients with insomnia reported poorer physical and mental quality of life compared to patients without insomnia. Furthermore, the OSA patients with DMS were older and sleepier than other OSA patients. Patients with DIS were not sleepier than patients without DIS, which is consistent with the idea of insomnia as a state of hyperarousal.

Poor physical and mental health as measured by the SF-12, RLS and hypertension were related significantly to an increased risk of insomnia in the general population. Overall, 12% of the general population had a high risk for OSA when using the 0.75 cut-off point in the MAP index. This is a very high prevalence, which might suggest that OSA is often undiagnosed. Being at high risk for OSA as measured by the MAP was an independent risk factor for DMS among controls.

Among the OSA patients, female gender, smoking history and poor mental and/or physical life qualities were independent risk factors for DIS, while age, RLS and poor mental life qualities were independent risk factors for DMS. It is

Table 5 Age, daytime sleepiness, SF-12 and BMI in controls without and with DIS and DMS

	No DIS (n = 635)	*DIS (n = 103)*	P-*value*	*No DMS (n = 503)*	*DMS (n = 235)*	P-*value*
Age (years)	55.6 ± 11.4	61.0 ± 12.8	**< 0.001**	54.9 ± 11.4	59.1 ± 11.5	**< 0.001**
ESS	6.1 ± 3.8	5.1 ± 4.1	**0.026**	5.9 ± 3.8	6.1 ± 4.0	0.452
Short Form-12						
Mental score	51.6 ± 4.4	49.9 ± 6.3	**< 0.001**	51.6 ± 4.4	50.8 ± 5.2	**0.038**
Physical score	51.7 ± 7.1	47.0 ± 10.0	**< 0.001**	51.8 ± 7.2	49.3 ± 8.6	**< 0.001**
BMI (kg m^{-2})	27.7 ± 4.8	28.9 ± 5.6	**0.017**	27.6 ± 4.8	28.5 ± 5.1	**0.029**
Hypertension	31.9%	41.8%	**0.049**	28.6%	43.2%	**< 0.001**
Diabetes	4.6%	5.8%	0.608	4.2%	5.9%	0.303
RLS	15.3%	34.6%	**< 0.001**	14.7%	26.1%	**< 0.001**

BMI, body mass index; DIS, difficulties initiating sleep; DMS, difficulties maintaining sleep; ESS, Epworth Sleepiness Scale; RLS, restless legs syndrome; SF-12, Short Form-12. Significance is shown in bold type. Data shown as mean ± standard deviation.

Table 6 Age, daytime sleepiness, Short Form-12 and BMI in OSA patients without and with DIS and DMS

	No DIS (n = 695)	*DIS (n = 127)*	P-*value*	*No DMS (n = 343)*	*DMS (n = 480)*	P-*value*
Age (years)	54.5 ± 10.6	54.2 ± 10.8	0.723	53.1 ± 10.7	55.5 ± 10.4	**0.002**
ESS	11.8 ± 5.0	11.2 ± 5.4	0.212	10.9 ± 5.0	12.2 ± 5.0	**< 0.001**
Short Form-12						
Mental score	49.2 ± 10.5	43.2 ± 12.0	**< 0.001**	49.4 ± 10.7	47.6 ± 11.0	**0.022**
Physical score	41.0 ± 10.7	36.3 ± 10.9	**< 0.001**	42.2 ± 10.5	38.9 ± 11.0	**< 0.001**
BMI (kg m^{-2})	33.4 ± 5.8	33.9 ± 5.3	0.349	33.1 ± 5.3	33.7 ± 6.0	0.116
Hypertension	56.1%	61.9%	0.224	54.6%	58.8%	0.227
Diabetes	10.7%	11.9%	0.696	11.4%	10.5%	0.673
RLS	22.9%	33.1%	**0.014**	17.2%	29.7%	**< 0.001**

BMI, body mass index; DIS, difficulties initiating sleep; DMS, difficulties maintaining sleep; ESS, Epworth Sleepiness Scale; RLS, restless legs syndrome; OSA, obstructive sleep apnea. Significance is shown in bold type. Data shown as mean ± standard deviation.

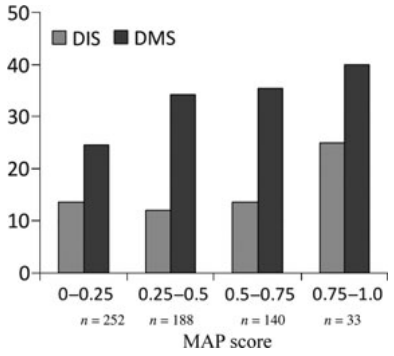

Figure 3. Prevalence (%) of difficulties initiating sleep (DIS) and difficulties maintaining sleep (DMS) based on multivariable apnea index (MAP).

important to note, however, that poor quality of life can be the result of insomnia rather than a predictor of the disorder. The association we have demonstrated does not allow us to distinguish between these possibilities. Some components of quality of life, such as pain and anxiety, are probable risk factors for the onset of insomnia while other components such as being inactive and depressed can be the result of insomnia (Hartz *et al.*, 2007; LeBlanc *et al.*, 2009). As there was no evaluation of depression and anxiety besides the SF-12 in this study, the use of other tools would have been beneficial in order to understand this association more clearly.

One explanation for the high rate of insomnia in patients with OSA is that the apnea may serve as a precipitating factor for DIS and DMS and may co-occur in such a manner as to exacerbate these conditions. It is possible that when falling asleep some OSA patients may be disrupted repeatedly from light sleep by an apnea event, causing them not to perceive sleeping in between the disruptions. These events could recur many times before sleep is established, and as a result the patient experiences long sleep latency. The same pattern could happen when patients wake up in the middle of the night and are having difficulty falling back to sleep. Alternatively, apneic events may lead to full awakenings from sleep, but then the individual is not able to fall back to sleep due to sleep-related anxiety and conditioned arousal.

Symptoms of insomnia may have a negative effect on CPAP treatment in that it is probably difficult for those insomnia patients who have DIS to spend a long time awake in order to adapt properly to the CPAP device. Conversely, those OSA patients who wake up frequently because of apneic episodes and complain of difficulty maintaining sleep might experience more refreshing sleep and adjust favorably

to CPAP. It would therefore be interesting to study the prevalence of insomnia subtypes among OSA patients before and after CPAP.

It has been suggested that the best treatment results are obtained when patients are treated for both disorders separately (Wickwire and Collop, 2010). There is clearly a co-occurrence of these disorders which could have important clinical implications. Compliance to CPAP treatment is relatively poor, but only around 50% of patients are compliant with treatment over time (Haynes, 2005). Insomnia could have a negative effect on CPAP compliance, and therefore it could be important to adjust treatment of these conditions when they co-exist in order to minimize the negative impact on quality of life and avoid a vicious cycle where these conditions intensify the severity of each other.

Comparing the prevalence of insomnia among studies is often difficult due to the differences in the definition of insomnia and the different populations studied. Some studies have reported a similar prevalence of insomnia among sleep apnea patients (Krakow *et al*., 2001; Krell and Kapur, 2005; Luyster *et al*., 2010; Subramanian *et al*., 2010) as we did here, but others have found a slightly lower prevalence (Smith *et al*., 2004; Wickwire and Collop, 2010). However, it is a shared conclusion that symptoms of insomnia are more prevalent among OSA patients than in the general population. Theoretically, this is surprising, as one of the main symptoms of OSA is daytime sleepiness and therefore one might think that these patients would be protected against insomnia. The fact that insomnia is so prevalent among OSA patients points strongly to a mechanistic link between these conditions.

In our study, there was no relationship between OSA severity and insomnia even though having OSA was a strong risk factor for DMS. This is surprising, and one possible explanation might be that patients with more severe sleep apnea have greater hypercapnia because of the severity of their disease, their increased weight and the possible co-occurrence of obstructive pulmonary disease (COPD). This could mean that they are sleepier at bedtime and less likely to wake up during the night (Kaw *et al*., 2009; Witzenblum *et al*., 2008). Similar results were found in a recent study (Hagen *et al*., 2009), which indicated that even though OSA and insomnia often coexist, insomnia is still independent of the degree of OSA. Another study by Kapur *et al.* (2005) suggested that DMS and sleep apnea severity were independent of each other, but it is clear that prospective studies are needed to further clarify the issue.

Our study is the first one to look systematically at a high MAP index as an independent risk factor for insomnia in a general population sample. Having a high MAP index (≥ 0.75) was a significant predictor for DMS. This is not surprising, given the high prevalence of DMS among OSA patients. However, having DMS was not more prevalent among high-risk subjects compared to low-risk subjects ($P = 0.135$). Conversely, DIS was more prevalent among those in the high-risk group ($P = 0.027$).

The current study has several limitations. The insomnia definition was based on two questions answered in a self-report, whereas having a more accurate insomnia evaluation would have been beneficial. Subjects from the general population sample were all aged 40 years or older and therefore results from this study cannot be generalized to younger people. This study was cross-sectional, and therefore we could not assess whether the variables associated with the presence of insomnia were risk factors or consequences of insomnia. Finally, OSA was not assessed objectively in the control group, so the prevalence and associations with insomnia in the general population cannot be determined accurately from these data.

In summary, we found that OSA and DMS coexist frequently and patients with both conditions are older, sleepier and report poorer life qualities than other OSA patients. There are a number of clinical implications of these results. First, providers should screen routinely for the presence of insomnia in OSA patients, given that it is associated with greater impairment in quality of life than OSA alone and the possible negative impact on CPAP treatment. Assessment of insomnia should take into account the insomnia subtypes among these patients, as different subtypes have different rates, consequences and risk factors. Providers should consider treating both conditions together when they co-occur in order to maximize clinical outcomes. This may lead to both direct improvement in symptoms by reducing the severity of insomnia, and indirectly by influencing adherence to CPAP treatment. Further studies are needed to explore whether pharmacological or cognitive–behavioral treatment of insomnia optimizes outcomes in this population when combined with CPAP.

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REFERENCES

Allen, R. P., Picchietti, D., Hening, W. A., Trenkwalder, C., Walters, A. S. and Montplaisi, J. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology. A report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. *Sleep Med*., 2003, 4: 101–119.

Benediktsdottir, B., Janson, C., Lindberg, E. *et al.* Prevalence of restless legs syndrome among adults in Iceland and Sweden: lung function, comorbidity, ferritin, biomarkers and quality of life. *Sleep Med*., 2010, 11: 1043–1048.

Benetó, A., Gomez-Siurana, E. and Rubio-Sanchez, P. Comorbidity between sleep apnea and insomnia. *Sleep Med. Rev*., 2009, 13: 287–293.

Buysse, D. J., Reynolds, C. F., Kupfer, D. J. *et al.* Effects of diagnosis on treatment recommendations in chronic insomnia—a report from the APA/NIMH DSM-IV field trial. *Sleep*, 1997, 20: 542–552.

Chung, K. F. Insomnia subtypes and their relationships to daytime sleepiness in patients with obstructive sleep apnea. *Respiration*, 2005, 72: 460–465.

Hagen, C., Patel, A. and McCall, W. V. Prevalence of insomnia symptoms in sleep laboratory patients with and without sleep apnea. *Psychiatry Res.*, 2009, 170: 276–277.

Hartz, A. J., Daly, J. M., Kohatsu, N. D., Stromquist, A. M., Jogerst, G. J. and Kukoyi, O. A. Risk factors for insomnia in a rural population. *Ann. Epidemiol.*, 2007, 17: 940–947.

Haynes, P. L. The role of behavioral sleep medicine in the assessment and treatment of sleep disordered breathing. *Clin. Psychol. Rev.*, 2005, 25: 673–705.

Johns, M. W. Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep*, 1992, 15: 376–381.

Kapur, V. K., Baldwin, C. M., Resnick, H. E., Gottlieb, D. J. and Nieto, F. J. Sleepiness in patients with moderate to severe sleep-disordered breathing. *Sleep*, 2005, 28: 472–477.

Kaw, R., Hernandez, A. V., Walker, E., Aboussouan, L. and Mokhlesi, B. Determinants of hypercapnia in obese patients with obstructive sleep apnea. A systematic review and metaanalysis of cohort studies. *Chest*, 2009, 136: 787–796.

Klink, M. E., Quan, S. F., Kaltenborn, W. T. and Lebowitz, M. D. Risk factors associated with complaints of insomnia in a general adult population. Influence of previous complaints of insomnia. *Arch. Intern. Med.*, 1992, 152: 1634–1637.

Krakow, B., Melendrez, D., Ferreira, E. *et al.* Prevalence of insomnia symptoms in patients with sleep-disordered breathing. *Chest*, 2001, 120: 1923–1929.

Krell, S. B. and Kapur, V. K. Insomnia complaints in patients evaluated for obstructive sleep apnea. *Sleep Breath.*, 2005, 9: 104–110.

LeBlanc, M., Merette, C., Savard, J., Ivers, H., Baillargeon, L. and Morin, C. M. Incidence and risk factors of insomnia in a population-based sample. *Sleep*, 2009, 32: 1027–1037.

Li, R. H., Wing, Y. K., Ho, S. C. and Fong, S. Y. Gender differences in insomnia—a study in the Hong Kong Chinese population. *J. Psychosom. Res.*, 2002, 53: 601–609.

Luyster, F. S., Buysse, D. J. and Strollo, P. J., Jr. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. *J. Clin. Sleep Med.*, 2010, 6: 196–204.

Maislin, G., Pack, A. I., Kribbs, N. B. *et al.* A survey screen for prediction of apnea. *Sleep*, 1995, 18: 158–166.

Morphy, H., Dunn, K. M., Lewis, M., Boardman, H. F. and Croft, P. R. Epidemiology of insomnia: a longitudinal study in a UK population. *Sleep*, 2007, 30: 274–280.

Pack, A. I. and Gislason, T. Obstructive sleep apnea and cardiovascular disease: a perspective and future directions. *Prog. Cardiovasc. Dis.*, 2009, 51: 434–451.

Partinen, M. and Gislason, T. Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints. *J. Sleep Res.*, 1995, 4: 150–155.

Roth, T., Roehrs, T. and Pies, R. Insomnia: pathophysiology and implications for treatment. *Sleep Med. Rev.*, 2007, 11: 71–79.

Smith, S., Sullivan, K., Hopkins, W. and Douglas, J. Frequency of insomnia report in patients with obstructive sleep apnoea hypopnea syndrome (OSAHS). *Sleep Med.*, 2004, 5: 449–456.

Subramanian, S., Murugan, T. and Chanamolu, S. Gender and ethnic differences in prevalence of self-reported insomnia among patients with obstructive sleep apnea. *Sleep Breath.*, 2010, in press.

Ware, J., Jr, Kosinski, M. and Keller, S. D. A 12-item Short-Form health survey: construction of scales and preliminary tests of reliability and validity. *Med. Care*, 1996, 34: 220–233.

Wickwire, E. M. and Collop, N. A. Insomnia and sleep-related breathing disorders. *Chest*, 2010, 137: 1449–1463.

Witzenblum, E., Chaouat, A., Kessler, R. and Canuet, M. Obstructive sleep apnea in patients with chronic obstructive pulmonary disease. *Proc. Am. Thorac. Soc.*, 2008, 5: 237–241.

Young, T., Peppard, P. E. and Gottlieb, D. J. Epidemiology of obstructive sleep apnea: a population health perspective. *Am. J. Respir. Crit. Care Med.*, 2002, 165: 1217–1239.

Paper II

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Symptoms of Insomnia among Patients with Obstructive Sleep Apnea Before and After Two Years of Positive Airway Pressure Treatment

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Study Objectives: To assess the changes of insomnia symptoms among patients with obstructive sleep apnea (OSA) from starting treatment with positive airway pressure (PAP) to a 2-y follow-up.

Design: Longitudinal cohort study.

Setting: Landspitali—The National University Hospital of Iceland.

Participants: There were 705 adults with OSA who were assessed prior to and 2 y after starting PAP treatment.

Intervention: PAP treatment for OSA.

Measurements and Results: All patients underwent a medical examination along with a type 3 sleep study and answered questionnaires on health and sleep before and 2 y after starting PAP treatment. The change in prevalence of insomnia symptoms by subtype was assessed by questionnaire and compared between individuals who were using or not using PAP at follow-up. Symptoms of middle insomnia were most common at baseline and improved significantly among patients using PAP (from 59.4% to 30.7%, P < 0.001). Symptoms of initial insomnia tended to persist regardless of PAP treatment, and symptoms of late insomnia were more likely to improve among patients not using PAP. Patients with symptoms of initial and late insomnia at baseline were less likely to adhere to PAP (odds ratio [OR] 0.56, P = 0.007, and OR 0.53, P < 0.001, respectively).

Conclusion: Positive airway pressure treatment significantly reduced symptoms of middle insomnia. Symptoms of initial and late insomnia, however, tended to persist regardless of positive airway pressure treatment and had a negative effect on adherence. Targeted treatment for insomnia may be beneficial for patients with obstructive sleep apnea comorbid with insomnia and has the potential to positively affect adherence to positive airway pressure.

Keywords: Adherence, CPAP, insomnia, obstructive sleep apnea

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INTRODUCTION

Chronic insomnia and obstructive sleep apnea (OSA) are two of the most common sleep disorders. Several studies have documented extensive comorbidity with these disorders, with the prevalence of insomnia symptoms in patients with OSA (40-60%) far exceeding that in the general population.[1-6] When these disorders coexist, not only is there an increase in cumulative morbidity, but it is likely that these two diseases interact to promote overall greater illness severity and influence each other in negative ways.[3] Further, the co-occurrence of OSA and insomnia symptoms may complicate OSA treatment and reduce PAP adherence. Recent reviews have called for more research on the comorbidity between insomnia and OSA.[7-10]

Insomnia is not, however, a homogenous disorder. There are a variety of types and subtypes. The subtypes of insomnia are typically characterized as difficulties initiating sleep (initial insomnia), difficulties maintaining sleep (middle insomnia), and early morning awakenings (late insomnia).[1] OSA may serve as a predisposing and/or a precipitating factor for each of the subtypes of insomnia. It also may be the case that one or more of the insomnia subtypes respond differently to OSA treatment and/or are associated with different levels of OSA treatment adherence.

Treatment with positive airway pressure (PAP) is the first-line treatment for OSA, but it can be difficult for patients to tolerate PAP and studies have shown that as few as 50% of patients adhere to the treatment over time.[11,12] Currently, few studies have (1) assessed the relative prevalence of insomnia subtypes in patients with OSA, (2) explored how PAP affects insomnia that is comorbid with OSA (both overall and by subtype), and (3) evaluated how insomnia affects PAP adherence. Of the studies that exist, the findings are mixed.[13-15] Nguyen et al.[13] showed that even though insomnia symptoms were highly prevalent among patients with OSA, they had no effect on PAP adherence. In contrast, Wickwire et al.[14] showed that symptoms of middle insomnia were related to poor PAP adherence; in addition, a recent study by Pieh et al.[15] found a negative effect of psychological factors related to insomnia symptoms on PAP adherence.

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In our previous study,[2] we found that most patients with untreated OSA had symptoms of middle insomnia but the prevalence of initial insomnia was the same as in the general population. Another study found symptoms of middle insomnia to be the most common subtype among patients with OSA.[16] Theoretically, it is surprising that patients with OSA might find it difficult to fall asleep at night because excessive daytime sleepiness (EDS) is a common symptom of untreated OSA. However, it seems likely that repeated breathing disturbances could result in sleep fragmentation and hence middle or late insomnia. Therefore, patients who wake up frequently because of apneic episodes may experience more refreshing sleep when using PAP and as a result adjust favorably to the treatment. Initial insomnia may be expected to diminish adherence to PAP because patients are awake longer and thus more likely to experience the adverse aspects of this treatment (e.g., mask or airflow discomfort) for longer periods of time.[12]

The purpose of the current study was to compare the prevalence of symptoms of initial, middle, and late insomnia in patients with OSA prior to and following the start of PAP treatment, as well as to explore the changes in insomnia symptoms by subtype in individuals who were or were not using PAP at follow-up. It was hypothesized that symptoms of middle insomnia would have the strongest association with untreated OSA and would therefore improve significantly among patients on PAP treatment. However, we expected that symptoms of initial and late insomnia would be more resistant to change despite successful treatment of OSA and that patients with these symptoms would more likely not be using PAP at follow-up.

PATIENTS AND METHODS

Patients in whom OSA had been diagnosed in Iceland and who were referred for PAP treatment to Landspitali—The National University Hospital of Iceland in Reykjavik (the only site in Iceland providing PAP treatment) from September 2005 through December 2009 were invited to participate in the study. They are part of the Icelandic Sleep Apnea Cohort (ISAC).[3] OSA had been recently diagnosed in all enrolled participants (minimum apnea-hypopnea index [AHI] of 15 events/h) and these patients were about to begin PAP treatment. Two y after treatment initiation, participants were invited for a follow-up visit where treatment adherence was examined and baseline assessments were repeated.

Questionnaire and Procedures

All participants were invited to the outpatient clinic at Landspitali—The National University Hospital of Iceland in Reykjavik. The study was approved by Iceland´s National Bioethics Committee, the Data Protection Authority of Iceland, and the Institutional Review Board of the University of Pennsylvania. After a written informed consent was obtained from the research participants, they answered standardized questionnaires about their health and sleep. Additional details are provided in the study by Bjornsdottir et al.[2]

Insomnia Definition

Insomnia symptoms were defined using answers to three questions from the Basic Nordic Sleep Questionnaire. "I have difficulties falling asleep at night" (initial insomnia), "I wake up often during the night" (middle insomnia), and "I wake up early in the morning and can't fall back asleep" (late insomnia).[17] Patients were not asked to refer to a specific time period when answering these questions. Answers were rated on a five-point scale: never/almost never (1); less than once a week (2); once or twice a week (3); three to five times a week (4); every day or almost every day of the week (5). Those who scored ≥ 4 on one or more of these items were defined as having insomnia of that subtype. A patient with insomnia could be classified as having one or more subtype.

Quality of Life

Participants completed the 12-Item Short Form Health Survey (SF-12) questionnaire to assess quality of life. Two summary component scores were derived from the SF-12: physical and mental health summary scores.[18] These scores range from 0-100, where a score of zero indicates the lowest life quality and 100 indicates the highest life quality.

Excessive Daytime Sleepiness

Daytime sleepiness was evaluated using the Epworth Sleepiness Scale (ESS), a brief questionnaire that measures daytime sleepiness.[19] Participants with ESS score ≥ 10 were considered to have excessive daytime sleepiness.

Sleep Apnea Assessment

All participants had a sleep study while untreated with a type 3 portable sleep monitor (Natus Medical Inc, San Carlos, CA, USA or NoxMedical, Reykjavik, Iceland). The same signals were recorded by each monitor. To test for systematic differences in the measurement of OSA severity by the Embla (available from Natus Medical) versus NoxMedical monitors, simultaneous overnight recordings were obtained in 12 patients. No significant differences were found in the AHI or oxygen desaturation index (ODI) measured with the different devices. A two-way random effect model for Intraclass Correlation Coefficient (ICC) for consistency showed that the ICC for AHI was 0.99 ($P < 0.001$) and the ICC for ODI was 0.97 ($P < 0.001$).

The sleep recordings were rescored in a uniform manner by a centralized scoring laboratory using the Somnologica Studio (Natus) software. Scoring of a hypopnea required a $\geq$ 30% decrease in airflow with $\geq$ 4% oxygen desaturation or a $\geq$ 50% decrease in airflow for $\geq$ 10 sec with a sudden increase in flow at the end of the event. Scoring of an apnea required a $\geq$ 80% decrease in flow for $\geq$ 10 sec. The ODI was calculated as the number of falls in oxygen saturation of $\geq$ 4% per h of recording. Additional details are provided in the study by Arnardottir et al.[20]

PAP Use

All patients prescribed PAP were taken care of at the Department of Respiratory Medicine and Sleep, Landspitali University Hospital. Patients on PAP had direct access to the outpatient clinic where trained staff helped them to find the type of device and settings they needed. Various mask types and heated humidifiers were available. PAP users were all in a constantly updated register and they paid a monthly service fee.

PAP adherence at follow-up was estimated based on downloads of usage in the previous 4 w from memory cards (objective data), if available, from ResMed S8 machines (ResMed

Corp. San Diego, CA, USA). Some patients had older PAP devices that did not allow for this type of download. Self-reported data from all patients (subjective data) was also collected at the follow-up visit, based on three multiple choice questions about average PAP use: (1) Do you use PAP for your sleep apnea? (Response alternatives: yes, no, or don't know) (2) How many nights/w do you use PAP? (Response alternatives: 1, 2, 3, 4, 5, 6, or 7 nights/w) and 3) How much of the sleeping time each night do you use PAP? (Response alternatives: all the sleeping time [100%]; almost all the sleeping time [80-99%]; most of the sleeping time [60-79%]; about half of the sleeping time [40-59%], about one third of the sleeping time [20-39%]; almost none of the sleeping time [1-19%]; none of the sleeping time [0%]; don´t know).

Statistical Analyses

All statistics were calculated with STATA 11.0 for Windows (Stata Corporation, College Station, TX, USA). Change in the prevalence of insomnia symptoms with PAP treatment was estimated using population-averaged generalized estimating equations for binomial outcome. The Wald test was used to examine differences in change of prevalence by level of PAP use. Logistic regression was used to analyze risk factors for PAP nonusers at follow up. A P value ≤ 0.05 was deemed statistically significant.

RESULTS

Population Characteristics

At baseline, 822 patients with untreated OSA were enrolled in the study and 90% (n = 741) came to the 2-y follow-up (average ± standard deviation [SD] time between baseline and follow-up visit was 774 ± 135 days). Of these patients, three did not answer the insomnia questions and were therefore excluded from the analyses. In addition, 33 were excluded because they were using a mandibular device instead of PAP at the follow-up. The final study cohort was therefore n = 705 (568 males [80.6%] and 137 females [19.4%]). Additional details are presented in Figure 1.

There was no baseline difference in the distribution of insomnia symptoms, OSA severity, or other main characteristics between the 117 patients who were excluded or did not finish the follow-up and the final study cohort.

Table 1 provides the baseline characteristics of the study population while untreated. The women were on average 4 y older and were more likely to report symptoms of initial insomnia.

Prevalence of Insomnia at Baseline

The prevalence of the three different insomnia subtypes was assessed prior to and 2 y after starting PAP treatment. At baseline, 15.5% of patients exhibited symptoms of initial insomnia, 59.3% had symptoms of middle insomnia, and 27.7% exhibited symptoms of late insomnia. The prevalence of having some type of insomnia symptoms at baseline was 68.3%, but there was considerable overlap between the three different insomnia subtypes, with most patients having more than one symptom of insomnia (Figure 2). Almost half of those who had symptoms of initial insomnia at baseline also had symptoms of middle and late insomnia. Most of those with symptoms of late insomnia at baseline also had symptoms of middle insomnia. Interestingly, most of those with symptoms of middle insomnia did not present with one or the other subtypes. As a result, 33% of the sample had symptoms of isolated middle insomnia at baseline

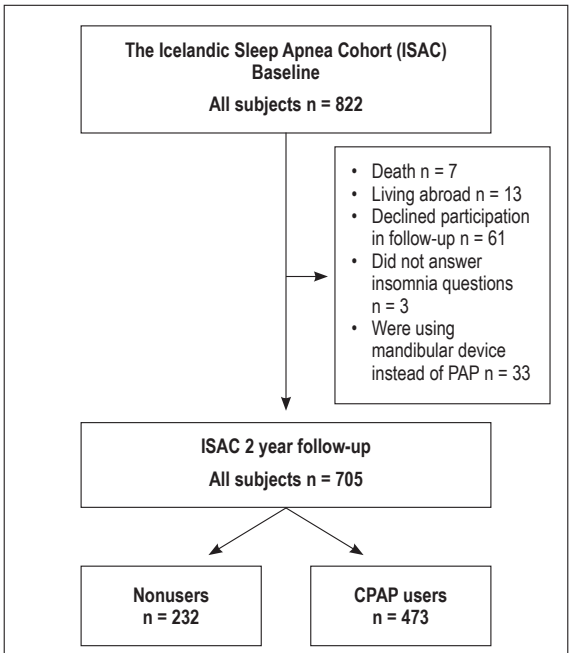

Figure 1—Flow chart of participants.

Table 1—Baseline characteristics of the study population

	All patients (n = 705)	Men (n = 568)	Women (n = 137)	P value for sex difference
Age	54.9 ± 10.2	54.1 ± 10.3	58.4 ± 8.9	**< 0.001**
Body mass index	33.7 ± 5.6	33.6 ± 5.5	32.3 ± 6.0	0.18
AHI	45.5 ± 20.5	46.0 ± 20.5	43.1 ± 20.4	0.15
ODI	36.3 ± 20.0	36.9 ± 19.8	33.9 ± 20.8	0.12
ESS	11.9 ± 5.0	11.9 ± 5.0	11.7 ± 5.3	0.60
Smoking history				
Never smoker	27.3%	26.0%	30.7%	0.27
Ex-smoker	53.0%	53.3%	51.8%	0.76
Current smoker	20.1%	20.7%	17.5%	0.40
Hypertension	46.5%	45.5%	50.4%	0.30
Diabetes	8.5%	8.6%	8.1%	0.84
Initial insomnia	15.5%	12.5%	27.9%	**< 0.001**
Middle insomnia	59.3%	57.8%	65.7%	0.09
Late insomnia	27.7%	26.6%	32.1%	0.20

AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale score; ODI, oxygen desaturation index. Significance is indicated in bold.

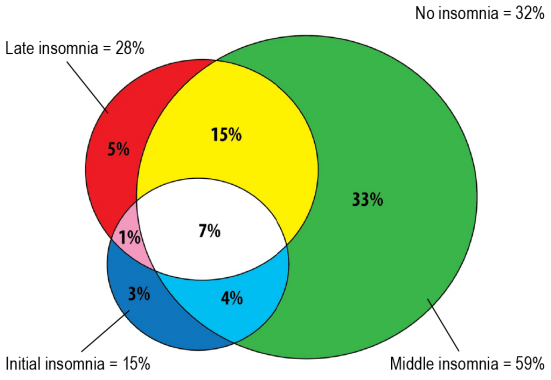

Figure 2—Baseline prevalence of insomnia symptoms among all patients.

and these patients were more obese, had more severe OSA (i.e., a higher AHI) and better mental quality of life compared with patients with other symptoms of insomnia (initial, late, or mixed insomnia) (Table 2).

PAP Use and Estimate of Adherence

Among the 705 patients who completed the follow-up, 473 reported current PAP use and 232 reported being nonusers. Objective data were available for 77.6% of PAP users (367 of 473), and based on these data the average (± SD) use per night was 6.2 (± 2.0) h for the last 4 w. Only 46 of those individuals used the device less than 4 h per night on average. At baseline all patients were prescribed automatic positive airway pressure (autoPAP) and treatment was changed to continuous positive airway pressure (CPAP) if the pressure requirements over the night were stable. Of the PAP users, 53% were on autoPAP and 43% were on fixed CPAP, 3% on bilevel pressure (BiPAP), and 1% on adaptive servoventilation. Treatment was only changed to BiPAP or adaptive servoventilation if treatment efficacy was inadequate. The average (± SD) PAP pressure was 10.9 (± 1.5) cm H_2O and the pressure below which participants on autoPAP spent 95% of the time over the last 7 days was 11.1 (± 1.9) cm H_2O.

Full Versus Partial Users

Patients using PAP for ≥ 5 days/w and ≥ 4 h/night on average for the past 4 w were considered full users (n = 287 of 367 with objective data). On average, full users were using their device for 26.7 ± 2.0 nights for the last 4 w and 6.8 ± 1.2 h per night based on objective data.

Among the 367 with both objective (memory cards) and self-reported data on frequency of CPAP use, we compared those reporting PAP usage ≥ 5 nights/w and ≥ 60% of the night with those fulfilling criteria for full PAP use based on memory cards (≥ 5 days/w and ≥ 4 h/night). Self-reported data had 98.6% sensitivity and 45.1% specificity in distinguishing full versus partial users. Consequently, objective data were used when available, but for the remaining patients, the self-reported data were used to define patients as full, partial, and non-PAP users. Therefore, a total of n = 372 were classified as full users and n = 101 as partial users (367 and 106 were classified based on objective and subjective data, respectively).

Table 2—Baseline differences between those with isolated middle insomnia and those with other symptoms of insomnia (initial, late or mixed)

	Isolated middle insomnia (n = 244)	Other type of insomnia (n = 258)	P value
Age	55.2 ± 10.7	55.5 ± 9.6	0.77
BMI	34.2 ± 6.1	33.1 ± 5.5	**0.04**
AHI	48.4 ± 21.1	41.6 ± 20.0	**< 0.001**
ODI	39.1 ± 21.2	32.5 ± 18.2	**< 0.001**
ESS	12.5 ± 5.0	11.8 ± 5.0	0.11
SF-12 PS	39.3 ± 11.1	39.0 ± 11.0	0.77
SF-12 MS	49.1 ± 10.0	45.7 ± 11.2	**< 0.001**

AHI, apnea-hypopnea index; BMI, body mass index; ESS, Epworth Sleepiness Scale score; ODI, oxygen desaturation index; SF-12 MS, mental quality of life; SF-12 PS, physical quality of life. Significance is indicated in bold.

On average, partial users were using their device for 14.3 ± 7.2 nights for the last 4 w and 3.5 ± 2.2 h per night (for all 28 nights) based on objective data.

Among the 232 nonusers, n = 60 (26.0%) returned their devices within 3 mo from starting PAP. Most of the nonusers (n = 133) had a repeat sleep study at the 2-y follow-up. On average, AHI in these individuals increased from baseline to follow-up (mean increase ± SD = 10.7 ± 22.2 events per hour). There were 98% of the 133 patients who still had an AHI > 15 at the 2-y follow-up. A few of the nonusers (n = 11) had lost more than 10 kg from baseline to follow-up but they were not different in insomnia status or OSA severity at follow-up compared with that at baseline. Of these 11 patients, seven had a repeat sleep study at follow-up and they were all still affected with OSA (AHI ≥ 15) despite their weight loss. In total, the nonusers (n = 133) lost on average 0.2 ± 8.2 kg from baseline to follow-up.

The primary analyses of this paper were conducted by comparing all PAP users (full and partial) with nonusers. Additional sensitivity analysis was performed by assessing the three use designations for group differences (full users, partial users, and nonusers). Using three groups of PAP users did not affect the significance of the results. Partial users were not significantly different from full users and therefore we used only two groups for analysis, all PAP users and nonusers. Furthermore, all analysis were repeated using only PAP users with objective data (n = 367), which did not affect the significance of any of the results.

Changes in Insomnia Symptoms from Baseline to Follow-up among PAP Users and Nonusers

Symptoms of Initial Insomnia

The baseline prevalence of symptoms of initial insomnia was 12.9% among those who were PAP users at follow-up, compared with 20.8% among nonusers (P = 0.007). At follow-up, 9.3%

of PAP users had symptoms of initial insomnia compared with 17.7% of nonusers (P = 0.001). Improvement in these symptoms from baseline to follow-up was of the same magnitude for PAP users and nonusers (Table 3 and Figure 3).

In total, 45.9% of those who had symptoms of initial insomnia at baseline also had these symptoms at follow-up. However, there was no baseline difference in regard to age, body mass index (BMI), or OSA severity between those whose initial insomnia improved and those with persistent symptoms of initial insomnia. There was, however, more improvement in daytime sleepiness among those without symptoms of initial insomnia at follow-up (Table 4).

Patients who reported symptoms of initial insomnia at baseline were more likely to be PAP nonusers at follow-up and this effect remained significant after adjusting for age, sex, BMI, smoking, and OSA severity (Table 5).

Table 3—The difference in changes of insomnia symptoms from baseline to follow-up between positive airway pressure users and nonusers

	Baseline (%)	Follow-up (%)	P_{change}	P*
Initial insomnia				
Nonusers	20.8	17.7	0.25	
PAP users	12.9	9.3	0.03	0.75
Middle insomnia				
Nonusers	59.1	43.5	< 0.001	
PAP users	59.4	30.7	< 0.001	**0.001**
Late insomnia				
Nonusers	36.6	26.0	0.001	
PAP users	23.3	21.2	0.34	**0.05**

*P for difference in change between PAP users and nonusers. PAP, positive airway pressure. Significance is indicated in bold.

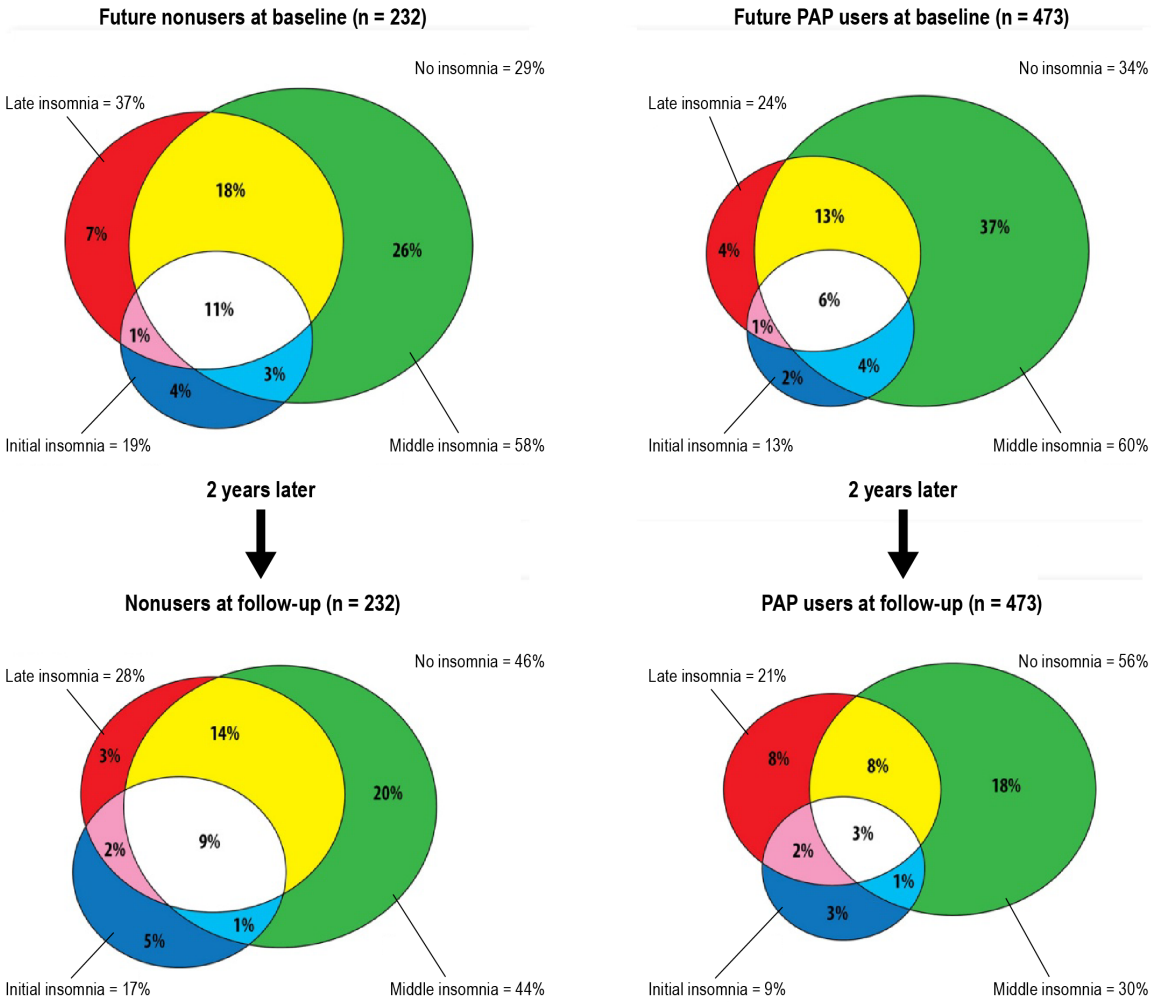

Figure 3—The changes and overlap of insomnia subtypes for both positive airway pressure (PAP) users and nonusers.

Table 4—Change in daytime sleepiness and quality of life among those whose insomnia improved and persisted

	Initial insomnia			Middle insomnia			Late insomnia		
	persisted (n = 50)	improved (n = 59)	P	persisted (n = 199)	improved (n = 219)	P	persisted (n = 91)	improved (n = 103)	P
ESS change	-1.0 ± 4.3	-3.5 ± 4.8	**0.006**	-2.6 ± 4.5	-4.6 ± 5.0	**< 0.001**	-1.8 ± 4.8	-3.9 ± 4.5	**0.002**
SF-12 MS change	-0.5 ± 10.2	1.5 ± 9.9	0.34	1.3 ± 10.0	3.5 ± 9.4	**0.02**	1.4 ± 10.6	2.9 ± 10.0	0.29
SF-12 PS change	3.0 ± 14.3	2.2 ± 13.9	0.78	2.5 ± 11.8	3.3 ± 11.8	0.48	0.3 ± 12.3	4.2 ± 11.7	**0.03**

ESS, Epworth Sleepiness Scale; SF-12 MS, mental quality of life; SF-12 PS, physical quality of life. Significance is indicated in bold.

Table 5—Unadjusted and adjusted effects of insomnia symptoms on PAP nonuse

	Unadjusted odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)[a]	P value[a]
Initial insomnia (n = 109)	0.56 (0.37-0.86)	**0.007**	0.59 (0.38-0.91)	**0.01**
Middle insomnia (n = 418)	1.01 (0.73-1.40)	0.93	0.98 (0.70-1.37)	0.89
Late insomnia (n = 194)	0.53 (0.37-0.74)	**< 0.001**	0.55 (0.39-0.79)	**< 0.001**
Isolated middle insomnia (n = 244)	1.61 (1.14-2.27)	**0.007**	1.48 (1.04-2.12)	**0.03**

[a]Adjusted for sex, age, body mass index, and obstructive sleep apnea severity (apnea-hypopnea index and oxygen desaturation index). Significance is indicated in bold. CI, confidence interval; PAP, positive airway pressure.

Table 6—Baseline characteristics among those whose middle insomnia symptoms improved and persisted

	Middle insomnia persisted (n = 199)	Middle insomnia improved (n = 219)	P value
Male (%)	81.0	76.3	0.23
Age	57.3 ± 9.4	54.8 ± 10.2	**0.01**
BMI	32.8 ± 5.1	35.1 ± 6.4	**< 0.001**
AHI	43.4 ± 20.1	47.3 ± 20.9	**0.05**
ODI	33.3 ± 18.5	39.9 ± 20.5	**< 0.001**

AHI, apnea-hypopnea index; BMI, body mass index; ODI, oxygen desaturation index. Significance is indicated in bold.

Symptoms of Middle Insomnia

The baseline prevalence of middle insomnia symptoms was 59.1% among those who were PAP users at follow-up compared with 59.4% among nonusers (P = 0.93). Compared with baseline, there was a significant improvement in symptoms of middle insomnia for both PAP users and nonusers at follow-up (follow-up prevalence was 30.7% among PAP users compared with 43.5% among nonusers; P ≤ 0.001). However, improvement in these symptoms was much more likely to occur among patients who were adherent with PAP treatment (P = 0.001 for difference in change between PAP users and nonusers). See Table 3 and Figure 3 for details.

Patients whose middle insomnia improved (as compared with those with persistent symptoms of middle insomnia) were younger, more obese, and had more severe OSA at baseline (Table 6). There was also greater improvement in physical quality of life and daytime sleepiness among those patients (Table 4).

Having symptoms of middle insomnia overall did not affect PAP adherence, but individuals with symptoms of isolated middle insomnia were more likely to be PAP users at follow-up and the effect remained significant after adjusting for age, sex, BMI, smoking, and OSA severity (Table 5).

Symptoms of Late Insomnia

The baseline prevalence of having symptoms of late insomnia was 23.3% among those who were PAP users at follow-up compared with 36.6% among nonusers (P < 0.001). Nonusers were more likely to experience improvement in late insomnia compared with PAP users (P = 0.05), improving to levels comparable to those of PAP users (PAP users: 21.2%, nonusers: 26%) (Table 3 and Figure 3).

In total, 46.7% of those who had symptoms of late insomnia at baseline also had these symptoms at follow-up, but there was no baseline difference in regard to age, BMI, or OSA severity between those whose late insomnia improved compared with those with persistent symptoms of late insomnia. Patients whose late insomnia improved did, however, show a greater improvement in mental quality of life and daytime sleepiness (Table 4).

Patients who reported symptoms of late insomnia at baseline were more likely to be PAP nonusers at follow-up and this effect remained significant after adjusting for age, sex, BMI, smoking, and OSA severity (Table 5).

When looking at how long the mask is worn based on objective PAP data, PAP users with symptoms of late insomnia at follow-up had on average 36 min shorter mask-on time than those without late insomnia (P = 0.02). This difference in mask-on time was not seen for patients with other types of insomnia.

No Insomnia Symptoms

Having no symptoms of insomnia at baseline was equally prevalent among those who were PAP users and nonusers at follow-up (PAP users: 33.3%, nonusers: 28.5%, P = 0.20). At follow-up, 55.7% of PAP users had no insomnia compared with 47.4% of nonusers (P = 0.04). Most patients who reported no symptoms of insomnia at baseline were also without insomnia symptoms at follow-up. However, 22.4% of them reported some insomnia symptoms at follow-up. Developing symptoms of middle and late insomnia were much more prevalent

than developing symptoms of initial insomnia among these patients (12.6%, 13.1%, and 2.7%, respectively). Among those who reported symptoms of insomnia at follow-up, PAP users were most likely to report symptoms of late insomnia whereas nonusers were more likely to report symptoms of middle insomnia ($P < 0.05$) (Figure 4).

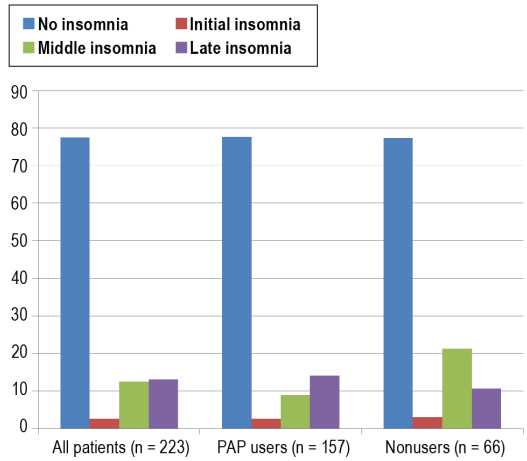

Figure 4—Insomnia status (%) at follow-up among those who had no insomnia symptoms at baseline.

DISCUSSION

The current study shows that insomnia symptoms are common among patients with OSA, especially symptoms of middle insomnia, and these types of symptoms generally improve with PAP treatment. Symptoms of initial insomnia, however, tend to persist even though patients adhere to PAP and can also negatively affect adherence to PAP treatment. Symptoms of late insomnia are (surprisingly) more likely to improve among patients with OSA who are PAP nonusers. Furthermore, some patients with OSA develop insomnia symptoms over the course of treatment. PAP users were more likely to develop symptoms of late insomnia whereas the new onset of middle insomnia symptoms was more common among nonusers.

The high prevalence of middle insomnia among patients with OSA and the indication that these symptoms improve significantly with successful PAP treatment suggests that symptoms of middle insomnia are a consequence of sleep disordered breathing. Our results show that untreated patients with OSA with symptoms of isolated middle insomnia are more obese and have more severe OSA, which supports this theory. This difference in BMI and OSA severity was not present for patients with other types of insomnia symptoms. Another study examining the relationship between insomnia subtypes and daytime sleepiness among patients with OSA also found that those with symptoms of middle insomnia had more severe OSA as well as increased daytime sleepiness compared with patients with symptoms of initial insomnia.[5] The increase in OSA severity among nonusers could therefore possibly cause symptoms of middle insomnia in some patients. The fact that nonusers who had no insomnia at baseline were most likely to develop symptoms of middle insomnia over the study period supports this idea.

In the current study, we saw that patients with symptoms of isolated middle insomnia were more likely to adhere to PAP treatment. A possible explanation is that patients who are waking up frequently during the night while untreated may experience relief both from OSA and insomnia symptoms while being treated with PAP and therefore adjust favorably to the treatment. Conversely, it seems that other mechanisms contribute to symptoms of initial and late insomnia in these patients. Given the negative effects of these subtypes of insomnia on PAP adherence and the indication that these patients do not experience relief from their insomnia despite PAP treatment suggests that some additional intervention is necessary.

We are aware of only one previous study that evaluated the association between insomnia subtypes and PAP adherence. Wickwire et al.[14] conducted a retrospective medical record review of 232 patients with OSA and found that only symptoms of middle insomnia predicted poor adherence to PAP,[14] which contradicts our findings. This discrepancy could partly be explained by the different methods performed, in our study the insomnia assessment was performed at both baseline and follow-up.

Interestingly, symptoms of late insomnia were more likely to improve among nonusers in comparison with PAP users. In general, sleep is not as sound early in the morning as in the beginning of the night when delta sleep is dominant.[21,22] Because of this, patients may be more likely to wake up because of environmental noises, light, or the need to use the bathroom early in the morning. Patients who are using PAP may therefore become more aware of their device when their sleep gets lighter in the morning and for some patients this may disrupt their sleep and cause persistence of late insomnia symptoms. This could also explain why PAP users who had no insomnia at baseline were most likely to develop symptoms of late insomnia. The fact that 13.1% of them had new onset of late insomnia symptoms is noteworthy, especially because the overall prevalence of these symptoms among patients with OSA in this study is not nearly as high as symptoms of middle insomnia, for example.

This study had a number of strengths including the large sample size, the length of the follow-up period, the high response rate at follow-up (> 90%), the use of standardized and validated procedures and instruments, and most importantly being by far the largest study that has looked prospectively at insomnia symptoms among patients with OSA before and following PAP treatment. In addition, this is a clinical sample with various comorbidities, representing the entire spectrum of patients with OSA. Our results have important clinical implications and highlight the need for more studies on additional treatment interventions for patients with OSA and comorbid insomnia.

This study is not, however, without limitations. First, the insomnia definition was based on three questions from the Basic Nordic Sleep Questionnaire describing symptoms; having more detailed questions on insomnia would have been beneficial. However, the definitions we used proved to be very instructive in the context of OSA and we have a previous publication using the same definitions of insomnia.[2] Although the 2-y follow-up is a strength of the study, evaluating the long-term effects of PAP treatment, it can also be considered a limitation. We did not have short-term follow-up results to evaluate the acute effects of

PAP treatment. However, in terms of comparative effectiveness research, what matters to patients is not what happens to them in 1 mo but over the long term. Because this is a cohort study there are many factors that can change in the 2-y study period that may affect insomnia other than the use of PAP treatment. Second, it would have been beneficial to have more detailed information on those patients with initial and late insomnia who stopped using PAP. Did they stop using their device purely because of their insomnia or were there some other underlying reasons? We did not have objective PAP data for all patients but we are confident with the way we estimated PAP use. The lack of objective PAP data on all participants prevented our inclusion of the AHI on the PAP download, a measure of treatment efficacy, as a covariate in our analyses.[23] It is possible that the ability of PAP treatment to reduce AHI to clinically acceptable levels may affect adherence to treatment. Patient-reported nonusage at follow-up was consistent with the patient PAP register, and the results did not change if those without objective PAP data were excluded from the analyses. Finally, this is an observational study, not a randomized controlled trial (RCT), which may be considered a limitation. However, a RCT with such long-term follow-up of severely affected patients with OSA would be difficult to perform for ethical reasons. The importance of observational studies was highlighted in a recent publication of a National Institutes of Health workshop on comparative effectiveness research.[24]

To summarize, our results show approximately 50% reduction in middle insomnia following 2 y of PAP treatment, which suggests that frequent awakenings are a symptom of untreated OSA. Initial and late insomnia, however, did not improve on PAP treatment and these symptoms may negatively affect PAP adherence. These results suggest that initial and late insomnia in patients with OSA are comorbid but unrelated disorders and highlight the importance of including assessment of insomnia subtypes in the management of OSA. Future studies should focus on exploring the benefits of additional interventions prior to or during PAP for patients with OSA and insomnia. For example, it may be useful to undertake a trial of cognitive behavioral treatment for insomnia (CBT-I) prior to or during treatment with PAP to assess whether this intervention not only improves the insomnia in the context of OSA, but whether such treatment increases compliance with PAP, especially in cases of initial and late insomnia. This said, symptoms of initial and/or late insomnia may be undiagnosed advanced sleep phase syndrome or delayed sleep phase syndrome. In these instances, CBT-I may be less helpful and chronotherapeutic strategies may be more useful.

ABBREVIATIONS

AHI, apnea hypopnea index
BMI, body mass index
BPAP, bilevel pressure
CPAP, continuous positive airway pressure
EDS, excessive daytime sleepiness
ESS, Epworth sleepiness scale
ICC, intraclass correlation coefficient
ISAC, Icelandic sleep apnea cohort
ODI, oxygen desaturation index
OR, odds ratio
OSA, obstructive sleep apnea
PAP, positive airway pressure
SF-12, short form 12
SF-12 MS, short form 12 mental score
SF-12 PS, short form 12 physical score

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DISCLOSURE STATEMENT

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REFERENCES

1. Morin CM, Benca R. Chronic insomnia. Lancet 2012;379:1129-41.
2. Bjornsdottir E, Janson C, Gislason T, et al. Insomnia in untreated sleep apnea patients compared to controls. J Sleep Res 2012;21131-8.
3. Krakow B, Melendrez D, Ferreira E, et al. Prevalence of insomnia symptoms in patients with sleep-disordered breathing. Chest 2001;120:1923-9.
4. Smith S, Sullivan K, Hopkins W, Douglas J. Frequency of insomnia report in patients with obstructive sleep apnoea hypopnea syndrome (OSAHS). Sleep Med 2004;5:449-56.
5. Chung KF. Insomnia subtypes and their relationships to daytime sleepiness in patients with obstructive sleep apnea. Respiration 2005;72:460-5.
6. Krell SB, Kapur VK. Insomnia complaints in patients evaluated for obstructive sleep apnea. Sleep Breath 2005;9:104-10.
7. Luyster FS, Buysse DJ, Strollo PJ. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. J Clin Sleep Med 2010;6:196-204.
8. Wickwire EM, Collop NA. Insomnia and sleep-related breathing disorders. Chest 2010;137:1449-63.
9. Beneto A, Gomez-Siurana E, Rubio-Sanchez P. Comorbidity between sleep apnea and insomnia. Sleep Med Rev 2009;13:287-93.
10. Al-Jawder SE, Bahammam AS. Comorbid insomnia in sleep-related breathing disorders: an under-recognized association. Sleep Breath 2012:16:295-304.
11. Kribbs NB, Pack AI, Kline LR, et al. Objective measurement of patterns of nasal CPAP use by patients with obstructive sleep apnea. Am Rev Respir Dis 1993;147:887-95.
12. Weaver T, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc 2008;5:173-8.
13. Nguyen XL, Chaskalovic J, Rakotonanahary D, Fleury B. Insomnia symptoms and CPAP compliance in OSAS patients: a descriptive study using data mining methods. Sleep Med 2010;11:777-84.
14. Wickwire EM, Smith MT, Birnbaum S, Collop NA. Sleep maintenance insomnia complaints predict poor CPAP adherence: a clinical case series. Sleep Med 2010;11:772-6.
15. Pieh C, Bach M, Popp R, et al. Insomnia symptoms influence CPAP compliance. Sleep Breath 2012;39:280-5.

16. Chung KF. Relationships between insomnia and sleep-disordered breathing. Chest 2003;123:310-1.
17. Partinen M, Gislason T. Basic Nordic Sleep Questionnaire (BNSQ): a quantitative measure of subjective sleep complaints. J Sleep Res 1995;4:150-5.
18. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey - construction of scales and preliminary tests of reliability and validity. Med Care 1996;34:220-33.
19. Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 1992;15:376-81.
20. Arnardottir ES, Maislin G, Schwab RJ, et al. The interaction of obstructive sleep apnea and obesity on the inflammatory markers C-reactive protein and interleukin-6: The Icelandic Sleep Apnea Cohort. Sleep 2012;35:921-32.
21. Markov D, Goldman M. Normal sleep and circadian rhythms: neurobiologic mechanisms underlying sleep and wakefulness. Psychiatr Clin North Am 2006;29:841-53.
22. Pivik RT, Busby K, Mercier L, Campbell K. Ontogenetic variations in auditory arousal threshold during sleep. Psychophysiology 1988;25:474-5.
23. Berry RA, Kushida CA, Kryger MH, Soto-Calderon H, Staley B, Kuna ST: Respiratory event detection by a positive airway pressure device. Sleep 2012;35:361-7.
24. Lieu TA, Au D, Krishnan JA, et al. Comparative effectiveness research in lung diseases and sleep disorders: recommendations from the National Heart, Lung, and Blood Institute workshop. Am J Respir Crit Care Med 2011;184:848-56.

Paper III

J Sleep Res. (2014) Regular Research Paper

Quality of life among untreated sleep apnea patients compared with the general population and changes after treatment with positive airway pressure

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Keywords
Personalized medicine, compliance, Icelandic sleep apnea cohort (ISAC), mental and physical health

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SUMMARY

Obstructive sleep apnea leads to recurrent arousals from sleep, oxygen desaturations, daytime sleepiness and fatigue. This can have an adverse impact on quality of life. The aims of this study were to compare: (i) quality of life between the general population and untreated patients with obstructive sleep apnea; and (ii) changes of quality of life among patients with obstructive sleep apnea after 2 years of positive airway pressure treatment between adherent patients and non-users. Propensity score methodologies were used in order to minimize selection bias and strengthen causal inferences. The enrolled obstructive sleep apnea subjects (n = 822) were newly diagnosed with moderate to severe obstructive sleep apnea who were starting positive airway pressure treatment, and the general population subjects (n = 742) were randomly selected Icelanders. The Short Form 12 was used to measure quality of life. Untreated patients with obstructive sleep apnea had a worse quality of life when compared with the general population. This effect remained significant after using propensity scores to select samples, balanced with regard to age, body mass index, gender, smoking, diabetes, hypertension and cardiovascular disease. We did not find significant overall differences between full and non-users of positive airway pressure in improvement of quality of life from baseline to follow-up. However, there was a trend towards more improvement in physical quality of life for positive airway pressure-adherent patients, and the most obese subjects improved their physical quality of life more. The results suggest that co-morbidities of obstructive sleep apnea, such as obesity, insomnia and daytime sleepiness, have a great effect on life qualities and need to be taken into account and addressed with additional interventions.

INTRODUCTION

Obstructive sleep apnea (OSA) is a disorder characterized by recurrent apneas and hypopnoeas during sleep associated with oxygen desaturation and arousals (Punjabi, 2008). OSA affects almost every system in the body, resulting in an increased incidence of hypertension, cardiovascular disease (CVD), stroke, pulmonary hypertension, cardiac arrhythmias and systemic inflammation (McNicholas and Bonsigore, 2007). Sleep fragmentation due to OSA may also result in decreased energy, impaired cognition and altered mood (Soldatos and Paparrigopoulos, 2005), and OSA increases

the risk of traffic and work accidents (Sassani *et al*., 2004). However, symptoms and the presence of co-morbidities vary among patients with OSA (McNicholas and Bonsigore, 2007).

The daytime consequences of OSA are usually more important to the patient than the nocturnal events. Patients may be unaware of their snoring and breathing pauses during sleep, but acutely aware of the consequent daytime sleepiness, impaired work performance, irritability and reduced participation in everyday activities (Chervin, 2000). As a result of these symptoms and functional impairments, patients with OSA often report a poor quality of life in social, emotional and physical domains (Akashiba *et al*., 2002; Baldwin *et al*., 2001; Lacasse *et al*., 2000).

The most effective treatment of OSA is positive airway pressure (PAP), which has been shown to decrease sleepiness, and improve neurocognitive function and vigilance (Gay *et al*., 2006). PAP treatment is mostly beneficial for patients who use PAP for at least 4 h per night (Kohler *et al*., 2010). Studies have shown that untreated patients with severe OSA have reduced quality of life compared with normal controls (Bjornsdottir *et al*., 2012; Yang *et al*., 2000), and a few weeks of PAP treatment improves daytime function and quality of life (Ballester *et al*., 1999; D'Ambrosio *et al*., 1999; Jenkinson *et al*., 1999; Weaver *et al*., 2012). A study by D'Ambrosio *et al.* (1999) found that 8 weeks of PAP treatment by adherent patients improved aspects of quality of life related to vitality, social functioning and mental health. In their study, the magnitude of improvement was, however, most strongly related to the degree of impairment in quality of life at baseline. In a randomized controlled trial by Jenkinson *et al.* (1999), improvements were seen in vitality scores and social function after 1 month of PAP treatment. Ballester *et al.* (1999) found positive effects on social isolation and energy subscales of quality of life after 3 months of PAP treatment. Furthermore, Weaver *et al.* (2012) found that 8 weeks of PAP treatment improved functional outcomes among sleepy patients with mild to moderate OSA.

Despite the evidence discussed above, there are few large studies with long-term follow-up periods that have assessed: (i) the difference in quality of life among patients with OSA and the general population; and (ii) how quality of life changes with long-term PAP treatment between adherent patients and non-users. Given this, the aims of this study were twofold. First, we compared health-related quality of life between the general population and a large group of patients with moderate to severe OSA prior to PAP treatment initiation. Second, we examined differences in the changes of quality of life after 2 years of PAP treatment between adherent patients and non-users.

MATERIALS AND METHODS

OSA cohort

All patients diagnosed with moderate to severe OSA [apnea–hypopnea index (AHI) $\geq$15 events·h^{-1}] who were referred to the Pulmonary Department, Landspitali – The National University Hospital of Iceland for treatment with PAP from September 2005 to December 2009 were invited to participate in the Icelandic Sleep Apnea Cohort (ISAC) study (Arnardottir *et al*., 2012; Bjornsdottir *et al*., 2012, 2013). No other inclusion or exclusion criteria were used. Over 90% of eligible and approached subjects agreed to participate in the study, resulting in 822 subjects included in the prospective cohort at baseline. A total of 793 (96.5%) subjects (642 males and 151 females) had available information on quality of life. Two years after treatment initiation, participants were invited for a follow-up visit where treatment adherence to PAP was examined and baseline assessments were repeated. This follow-up was completed in 741 (90.1%) subjects from October 2007 to January 2012; 655 (88.4%) responded to questions regarding quality of life at follow-up and were not prescribed a mandibular advancement device instead of PAP treatment (Fig. 1).

General population cohort

The general population cohort was primarily invited to participate in the Burden of Obstructive Lung Diseases

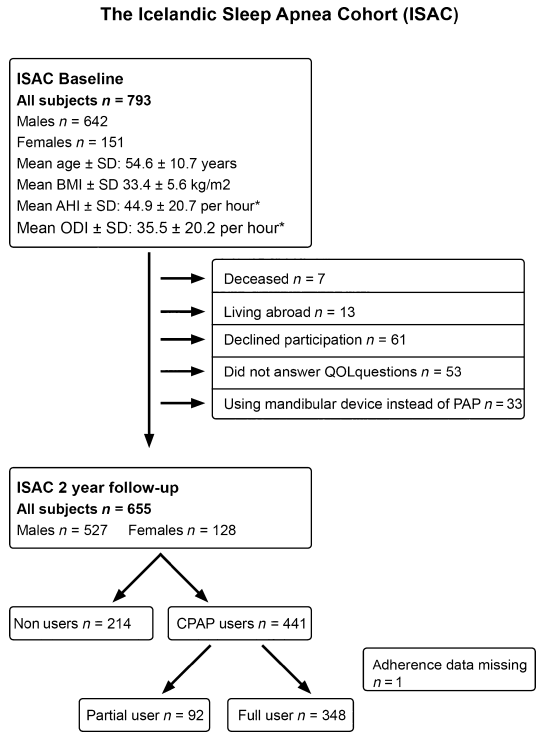

Figure 1. Flow chart of the study population. AHI, apnea – hypopnoea index; BMI, body mass index; CPAP, continuous positive airway pressure; ODI, oxygen desaturation index; PAP, positive airway pressure; QOL, quality of life.

(BOLD) initiative; a multi-centre international study aiming to estimate the burden of chronic obstructive pulmonary disorder worldwide (Buist *et al*., 2007). This was a random sample of Icelanders, ≥40 years living in Reykjavik. Altogether 762 (404 males and 358 females) of the 939 eligible subjects (81.2%) responded. The mean age in this cohort was 57.0 ± 11.8 years and the mean body mass index (BMI) was 27.9 ± 4.9 kg m^{-2}.

General health questionnaire

All participants were invited to the outpatient clinic at Landspitali – The National University Hospital of Iceland in Reykjavik. The study was approved by the National Bioethics Committee and the Data Protection Authority of Iceland, as well as the Institutional Review Board of the University of Pennsylvania. After written informed consent was obtained, participants answered standardized questionnaires about their health and sleep, including questions about smoking and whether they had hypertension and/or diabetes (medical diagnosis and medication), or CVD, which was defined as a medical diagnosis of coronary artery occlusion (myocardial infarction or heart attack), heart failure and/or stroke. Subjects in both cohorts listed their medication, which was subsequently coded according to the Anatomical Therapeutic Chemical (ATC) drug classification system (www.whocc.no/atcddd), and OSA subjects were asked whether they were taking medication to help them sleep.

Quality of life

Participants completed the Short Form 12 (SF-12) questionnaire to assess quality of life. Two summary component scores are derived from the SF-12, the physical component score (PCS) and mental component score (MCS). These scores range from 0 to 100, where 0 indicates the lowest life quality and 100 indicates the highest life quality (Ware *et al*., 1996). The SF-12 is derived from the SF-36, and has been widely used and demonstrated to be reliable and valid in assessing quality of life in large group comparisons (Gandek *et al*., 1998).

Excessive daytime sleepiness

Daytime sleepiness was evaluated using the Epworth Sleepiness Scale (ESS), a brief questionnaire that measures daytime sleepiness. Participants with ESS score ≥10 were considered to have excessive daytime sleepiness (Johns, 1992).

Symptoms of sleep disorders

Sleep symptoms were assessed using the Basic Nordic Sleep Questionnaire, which includes questions on sleep quality, insomnia symptoms, snoring, nocturnal sweating, gastro-oesophageal reflux and daytime sleepiness (Partinen and Gislason, 1995). Three subtypes of insomnia symptoms were defined: difficulty initiating sleep (initial insomnia); difficulty maintaining sleep (middle insomnia); and early morning awakenings (late insomnia; for more details, see Bjornsdottir *et al*., 2013). However, the questionnaire for the general population only included questions on two of those subtypes (initial and middle insomnia). Answers were rated on a five-point scale: never/almost never (1); less than once a week (2); once or twice a week (3); three-five times a week (4); every day or almost every day of the week (5).

Sleep recording in the ISAC

Prior to referral for PAP treatment, all patients with OSA had a sleep study with an Embletta type 3 portable monitor or an Embla 12 channel system (Natus Medical, Ontario, Quebec, Canada), or a T3 device (Nox Medical, Reykjavik, Iceland). The same signals were recorded on all studies; nasal airflow by cannula, oxygen saturation, heart rate, respiratory movements by respiratory inductance plethysmography belts, body position and activity by accelerometer. Trained sleep technologists scored all sleep studies, and the studies had to have ≥4 h of a scorable O_2 saturation signal. Scoring of a hypopnoea required a ≥30% decrease in airflow for ≥10 s with ≥4% oxygen desaturation or ≥50% decrease in airflow for ≥10 s with a sudden increase in flow at the end of the event. Scoring of an apnea required ≥80% decrease in flow for ≥10 s. The AHI was calculated as the mean number of apneas and hypopnoeas per hour of recording (excluding upright time). The oxygen desaturation index (ODI) was calculated as the number of transient drops in oxygen saturation ≥4% per hour of recording (for further details, see Arnardottir *et al*., 2013; Bjornsdottir *et al*., 2013).

PAP use

All patients prescribed PAP received care at the Department of Respiratory Medicine and Sleep, Landspitali University Hospital. Patients on PAP had direct access to the outpatient clinic where trained staff helped them to find the type of device and settings they needed.

Positive airway pressure adherence at the 2-year follow-up was estimated based on downloads of usage in the previous 4 weeks from memory cards (objective data), if available, from ResMed S8 machines (ResMed, San Diego, CA, USA). Some subjects had older PAP devices that did not allow for this type of download. Self-report data from all subjects (subjective data) were collected at the follow-up, based on three multiple-choice questions about average PAP use. Self-reported data had 98.6% sensitivity and 45.1% specificity in distinguishing full users from partial users (for further details, see Arnardottir *et al*., 2013; Bjornsdottir *et al*., 2013).

Participants who used PAP for ≥20 days and ≥4 h day^{-1} on average for the previous 4 weeks based on objective data or ≥5 nights·$week^{-1}$ for ≥60% of the night by questionnaire were considered full users. PAP users not meeting criteria for

full users were classified as partial users; these patients were excluded from the propensity score (PS) sample estimating the effect of PAP treatment on changes in quality of life to allow PS matching between the two primary groups of interest: full users and non-users. Non-users were defined as those who had returned their PAP device within 1 year of therapy initiation, and did not undergo upper airway surgery and were not using the mandibular device.

Statistical analyses

All statistics were calculated with STATA, version 11.0 for Windows (Stata, College Station, TX, USA) or SAS, Version 9.3 (SAS Institute, Cary, NC, USA). For bivariate analysis, the chi-square test and *t*-test were used for nominal and continuous variables, respectively. Linear regression was used in adjusted analyses, and results are presented as adjusted β-estimates and 95% confidence intervals or adjusted least-squares mean estimates and standard errors.

PS sub-classification analyses

Sub-classification using PS quintiles, following an established sequential heuristic described in detail by Maislin and Rubin (2010), was used in two separate analyses: (i) to obtain a comparable sample of patients with OSA and subjects from the general population with respect to relevant covariates; and (ii) to minimize selection bias due to measured covariate imbalance in our non-randomized treatment group comparison between PAP-adherent patients and non-users, thereby allowing for causal inference (Keenan *et al.*, 2014). The importance of using PS and related methodologies within the context of observational studies has been highlighted by a recent working group from the National Heart, Lung and Blood Institute (Lieu *et al.*, 2011; for further details, see supplement).

In order to obtain a comparable sample of patients with OSA and subjects from the general population, we first restricted both populations to participants aged 40–75 years and with BMIs between 25 and 40 kg m^{-2}, based on the obvious distributional differences in age and BMI between the two samples. This restriction resulted in an initial sample of 611 (74.3%) patients with OSA and 471 (61.7%) general population subjects. Within this restricted sample, we used sub-classification by PS quintiles to further match samples on relevant covariates, including age, gender, BMI, smoking status, hypertension, CVD and diabetes. The PS heuristic identified 494 (80.9%) patients with OSA and 418 (88.7%) general population participants from this restricted sample that were included in the final PS designed sample (referred to as the 'OSA-general population PS sample').

Within the OSA cohort only, we then used PS sub-classification to construct a sample of PAP full and non-users in which to obtain an unbiased assessment of the effect of PAP adherence on changes in quality of life. Full and non-users were balanced within subclass with respect to relevant measured covariates at baseline, including: age, gender, BMI, smoking status, hypertension, CVD, diabetes, insomnia symptoms (early, middle and late), sleep medication use, antidepressant use, ESS, OSA severity [AHI, ODI, SaO_2 nadir and hypoxia time (% of sleep time with SaO_2 below 90%)] and baseline levels of PCS and MCS. Of the 348 full and 214 non-users, a total of 308 (89%) and 200 (93%) were included in the PS designed sample (referred to as the 'PAP treatment PS sample'). Comparisons of subjects included and excluded from the PS sample are presented in the online supplement.

RESULTS

Results in all subjects

Baseline characteristics in the overall sample

Overall, patients with OSA were slightly younger, with a higher BMI, more daytime sleepiness, as well as a higher prevalence of hypertension, diabetes and middle insomnia when compared with subjects from the general population (Table 1). OSA subjects were also more likely to be males, have a smoking history, and reported significantly lower mental and physical quality of life. Both MCS and PCS remained significantly lower among patients with OSA after adjusting for age, BMI, gender, smoking and the co-morbidities listed in Table 1; on average, patients with OSA had PCS scores 9.48 points lower [95% confidence interval (CI): −10.53, −8.44; $P < 0.0001$] and MCS scores 3.35 points lower (95% CI: −4.35, −2.35; $P < 0.0001$) than the general population.

Determinants of quality of life in patients with OSA and controls

We ran regression analyses within the overall OSA and general population cohorts to assess potential determinants of physical and mental quality of life. PCS was lower for those with higher BMI, both for patients with OSA and the general population. Furthermore, higher age, female gender and CVD were significantly associated with a lower PCS in both groups; diabetes was associated with worse PCS in controls. Lower MCS was associated with lower age, current smoking and hypertension among controls; and with lower age, current smoking, female gender and lower BMI among patients with OSA (Table 2).

When examining sleep symptoms (Table 3), symptoms of initial and middle insomnia were both associated with lower MCS and PCS among general population subjects. Among patients with OSA, we found no significant relationships between severity of OSA, based on AHI and ODI, and either PCS or MCS. Among patients with OSA, initial insomnia was associated with lower PCS and MCS, and late insomnia was associated with lower MCS. More subjective sleepiness

Table 1 Baseline characteristics of all patients with OSA and the general population cohort

	General population (n = *762)*	*OSA* (n = *793)*	P
Age (years)	57.0 ± 11.8	54.6 ± 10.7	**<0.0001**
BMI (kg m^{-2})	27.9 ± 4.9	33.4 ± 5.6	**<0.0001**
Male (%)	53.0	81.0	**<0.0001**
Smoking history			
Never smoker (%)	39.2	27.3	**<0.0001**
Previous smoker (%)	42.6	51.0	
Current smoker (%)	18.2	21.7	
Hypertension (%)	25.1	45.3	**<0.0001**
CVD (%)	15.1	18.4	0.0781
Diabetes (%)	2.9	8.7	**<0.0001**
ESS	6.0 ± 3.9	11.7 ± 5.1	**<0.0001**
Early insomnia (%)	14.1	15.3	0.5200
Middle insomnia (%)	17.3	34.8	**<0.0001**
Late insomnia (%)	–	27.9	–
MCS	51.4 ± 4.7	48.3 ± 10.9	**<0.0001**
PCS	50.9 ± 7.8	40.3 ± 10.9	**<0.0001**

Values are given as mean ± standard deviation for continuous variables and percentages for nominal variables. BMI, body mass index; CVD, cardiovascular disease; ESS, Epworth Sleepiness Scale; MCS, mental component score; OSA, obstructive sleep apnea; PCS, physical component score. Significance is marked as bold.

Table 2 Independent association with PCS and MCS in the general population cohort and patients with OSA

	General population (n = *762)*		*Patients with OSA* (n = *793)*	
	PCS	*MCS*	*PCS*	*MCS*
Age (years)	**−0.12 (−0.17, −0.07)**	**0.09 (0.05, 0.12)**	**−0.16 (−0.23, −0.08)**	**0.16 (0.07, 0.24)**
Female gender	**−2.21 (−3.25, −1.16)**	−0.52 (−1.2, 0.16)	**−5.17 (−6.99, −3.36)**	**−2.48 (−4.45, −0.51)**
BMI (kg·m^{-2})	**−0.20 (−0.31, −0.10)**	0.04 (−0.03, 0.11)	**−0.53 (−0.66, −0.40)**	**0.15 (0.01, 0.29)**
Smoking history				
Previous smoker	−1.05 (−2.19, 0.09)	−0.71 (−1.46, 0.03)	−1.4 (−3.07, 0.26)	−0.74 (−2.56, 1.07)
Current smokers	**−2.77 (−4.26, −1.28)**	**−1.01 (−1.98, −0.04)**	**−2.62 (−4.61, −0.63)**	**−4.18 (−6.34, −2.01)**
Hypertension	−0.62 (−1.93, 0.69)	**−1.35 (−2.2, −0.49)**	0.25 (−1.31, 1.8)	−0.9 (−2.59, 0.79)
CVD	**−3.54 (−5.20, −1.87)**	0.44 (−0.64, 1.52)	**−5.77 (−7.67, −3.86)**	−1.27 (−3.34, 0.79)
Diabetes	**−6.97 (−10.18, −3.77)**	0.98 (−1.1, 3.06)	0.00 (−2.59, 2.59)	1.1 (−1.71, 3.91)

Values are given as adjusted beta-values (95% CI); estimates are adjusted for all other variables in the table.
BMI, body mass index; CVD, cardiovascular disease; MCS, mental component score; OSA, obstructive sleep apnea; PCS, physical component score. Significance is marked as bold.

was associated with decreased quality of life among patients with OSA; no such relationship was seen among controls. Sleep medication and antidepressant use was associated with poorer PCS and MCS in OSA subjects. These data were not available in the general population sample (Table 3).

OSA and general population cohorts: results in the PS sample

The covariate balance achieved by applying our PS methodology to the patients with OSA and general population subjects is shown in a modified version of a Love plot (Ahmed *et al*., 2006). Prior to implementing the PS heuristic, there were significant differences between patients with OSA and controls for BMI ($P < 0.0001$), gender ($P < 0.0001$), past smoking status ($P = 0.001$), never smoker status ($P < 0.0001$), hypertension ($P < 0.0001$), diabetes ($P = 0.0001$) and CVD ($P = 0.010$). However, after subclassification and controlling for PS quintile, there were no differences between OSA cases and general population subjects (all $P > 0.686$; see Fig. 1 in supplement).

When comparing PCS and MCS within this PS-designed sample of OSA cases and general population subjects (Table 4), patients with OSA had significantly lower quality of life in both measures, with a PCS score 9.5 points lower

Table 3 Independent associations of sleep symptoms with PCS and MCS in general population subjects and patients with OSA

	General population (n = *762)*		*Patients with OSA* (n = *793)*	
	PCS	*MCS*	*PCS*	*MCS*
ESS	0.06 (−0.08, 0.20)	−0.08 (−0.16, 0.01)	**−0.36 (−0.50, −0.22)**	**−0.27 (−0.42, −0.13)**
Difficulties falling asleep	**−2.90 (−4.49, −1.32)**	**−1.94 (−2.94, −0.95)**	**−2.62 (−4.72, −0.51)**	**−2.98 (−5.19, −0.77)**
Difficulties maintain sleep	**−1.49 (−2.94, −0.03)**	**−1.04 (−1.96, −0.13)**	−1.03 (−2.49, 0.43)	0.32 (−1.21, 1.85)
Early morning awakenings	n/a	n/a	−0.26 (−1.89, 1.36)	**−2.24 (−3.94, −0.54)**
Sleep medication use	n/a	n/a	**−2.75 (−5.14, −0.36)**	**−4.37 (−6.87, −1.87)**
Antidepressant use	n/a	n/a	**−3.88 (−5.79, −1.98)**	**−5.88 (−7.88, −3.88)**

Values are given as adjusted beta-values (95% CI). The beta estimates are adjusted for all variables in the table and for gender, age and BMI. ESS, Epworth sleepiness score; MCS, mental component score; OSA, obstructive sleep apnea; PCS, physical component score. Significance is marked as bold.

Table 4 Comparison of baseline quality of life measures in the OSA-general population PS sample

	LS mean ± SE			
	Patients with OSA	*General population*	*Difference (95% CI)*	P*
Physical quality of life	41.4 ± 0.45	50.9 ± 0.48	−9.48 (−10.81, −8.14)	<0.0001
Mental quality of life	48.3 ± 0.40	51.3 ± 0.43	−2.95 (−4.15, −1.75)	<0.0001

**P*-value adjusted for PS subclass.
LS, Least squares; OSA, obstructive sleep apnea.

than controls ($P < 0.0001$) and an MCS score 3.0 points lower ($P < 0.0001$).

Change in quality of life among patients with OSA in OSA-general population PS sample 2 years after initiating PAP treatment

When looking at patients with OSA in the OSA-general population PS sample, both PCS (mean ± SE change: 2.6 ± 0.4; $P < 0.0001$) and MCS (1.9 ± 0.5; $P < 0.001$) increased significantly 2 years after treatment initiation. Despite these significant increases, PCS values in patients with OSA at the 2-year follow-up remained significantly lower than the values seen in the general population at baseline (mean ± SE after 2 years: 43.9 ± 0.5 versus 50.9 ± 0.5; $P < 0.0001$). MCS values were borderline non-significantly lower in the OSA group after 2 years of therapy than the general population at baseline (50.3 ± 0.40 versus 51.3 ± 0.42; $P = 0.072$). In the current PS sample, full PAP users had an average increase in BMI of 0.9 kg m^{-2}, compared with a non-significant increase of 0.09 kg m^{-2} in non-users ($P < 0.001$ comparing full versus non-users). Within the overall observational sample, we observed a significant negative correlation ($\rho = -0.18$, $P < 0.0001$) between BMI change and PCS change, controlling for baseline BMI and PCS; thus, patients with more weight loss had more positive PCS changes.

PAP full versus non-users: results in the PAP treatment PS sample

Prior to implementing the PS heuristic, there were significant differences between full and non-users in terms of BMI ($P = 0.01$), gender ($P = 0.04$), hypertension ($P = 0.001$), initial ($P = 0.004$) and late ($P = 0.001$) insomnia, sleep medication use ($P = 0.02$) and all OSA severity measures (all $P < 0.0001$). After sub-classification and controlling for PS quintile, there were no differences between full and non-users (all $P > 0.677$; see Fig. 2 in supplement).

In the PAP treatment PS sample, significant 2-year increases ($P < 0.05$) in both quality of life measures were observed for full and non-users, separately. When comparing the 2-year changes in physical and mental quality of life between PAP groups, we found only a borderline difference between full and non-users for change in PCS ($P = 0.06$), and no differences in the change in MCS ($P = 0.80$). While we did not observe significant evidence for a PAP by BMI group interaction, we did find a significant difference for PCS when we restricted analysis to BMI >35 kg m^{-2} ($P = 0.02$), such that subjects adherent to PAP had a significantly greater improvement in PCS than non-users. No differences in PAP full and non-users related to BMI groups were found for MCS (Table 5).

Given our previously reported co-morbidity of OSA and insomnia (Bjornsdottir *et al*., 2012, 2013), we also examined

Table 5 Comparison of change in quality of life in PAP treatment PS sample

		LS mean ± SE change		
	BMI group[*,†]	*Adherent*	*Non-users*	P[‡]
Physical quality of life	Overall	3.42 ± 0.53[§]	1.79 ± 0.66[§]	0.0631
	<30	2.91 ± 0.97[§]	1.73 ± 1.15	0.4511
	30–35	2.50 ± 0.89[§]	2.49 ± 1.08[§]	0.9959
	≥35	**4.64 ± 0.88[§]**	**1.05 ± 1.22**	**0.0216**
Mental quality of life	Overall	2.13 ± 0.54[§]	2.35 ± 0.68[§]	0.7988
	<30	2.60 ± 0.97[§]	4.06 ± 1.15[§]	0.3525
	30–35	0.98 ± 0.96	1.32 ± 1.17	0.8313
	≥35	2.80 ± 0.88[§]	1.96 ± 1.22	0.5892

*propensity score sample included 308 adherent users (BMI<30: n=87; BMI 30-35: n=107, BMI ≥35: n=114) and 200 non-users (BMI<30: n=63; BMI 30-35: n=75, BMI ≥35: n=62);
[†]p-value for PAP × BMI group interaction: 0.5266 for PCS and 0.4579 for MCS;
BMI, body mass index; LS, Least squares. Significance is marked as bold.

the effect of PAP treatment within strata defined by baseline subjective sleepiness or insomnia. We did not observe any significant difference in quality of life changes between PAP groups when comparing patients based on ESS at baseline. When looking within patients with and without insomnia at baseline, we observed a significant difference in PCS change between full users and PAP non-users for those who did not have initial ($P = 0.02$), middle ($P = 0.01$) or late ($P = 0.02$) insomnia at baseline; full users had greater increases in PCS (see Table 3 in supplement).

While we observed statistically significant results within these strata, we note that we did not observe significant interactions between PAP group and any of these cut points; thus, results should be considered suggestive and replicated within independent populations.

Given the established relationship between quality of life and depression, we also examined the effect of PAP in patients stratified by antidepressant use at baseline. We did not observe a significant interaction between PAP adherence and antidepressant medication use for either PCS ($P = 0.498$) or MCS ($P = 0.327$), and there were no significant differences between PAP groups in PCS or MCS change within strata (see Table 4 in supplement).

DISCUSSION

The main findings of this study are that untreated patients with OSA have impaired physical and mental quality of life when compared with a general population sample. This effect remains significant after using PSs to select a sample of patients with OSA and a general population sample, balanced with regard to age, BMI, gender, smoking status, diabetes, hypertension and CVD. A significant improvement after a 2-year follow-up was seen in all patients, but full users of PAP do not appear to improve their quality of life more than non-users.

Among patients with OSA, age, gender, BMI, CVD, sleepiness, initial insomnia, sleep medication and antidepressant use were all significant determinants of decreased quality of life. The fact that quality of life was decreased among those who reported sleep medication and antidepressant use could reflect that those who have impaired physical and mental health are more likely to use these medications than those who are more healthy.

We did not find significant overall differences between full and non-users of PAP in improvement of physical and mental quality of life from baseline to follow-up within our overall PS-matched sample. However, we did observe a significantly larger improvement in PCS for adherent patients compared with non-users within the most obese patients (BMI>35 kg m^{-2}); this stronger effect of PAP in the most obese has been seen previously for other outcomes (Pak *et al.*, 2014). We also observed a significant effect of PAP on PCS in patients with no insomnia symptoms at baseline, although this result needs to be replicated within independent samples. Taken together, results suggest that PAP may have a significant impact on physical quality of life within specific subsets of patients with OSA. No differences were found in mental quality of life in these subgroups.

Reduced quality of life among patients with OSA

Our results show that OSA significantly impairs quality of life and, even though we observed significant increases in quality of life after 2 years, these patients still have lower life qualities, particularly physical quality of life, when compared with subjects from the general population. Others have reported similar associations of OSA and poor life quality (Akashiba *et al.*, 2002; Baldwin *et al.*, 2001; Lacasse *et al.*, 2000). Finn *et al.* (1998) assessed self-reported general health status in 421 men and 316 women aged 30–60 years in a general community sample, and reported that OSA was independently related to lower general health. The association remained significant after adjustment for age, gender, BMI, smoking status, alcohol use and cardiovascular conditions.

In our study, sleep parameters, such as symptoms of insomnia, daytime sleepiness and sleep medication use, were more related to quality of life than OSA severity measured by apneas per hour of sleep or hypoxaemia. Others have found similar results. For example, a population-based study by Baldwin *et al.* (2001) suggested that mild OSA was related to reduced vitality, while more severe OSA was more broadly associated with reduced quality of life. That study also indicated that subjective sleep symptoms (sleepiness and disturbed sleep) are widely associated with poor quality of life (Baldwin *et al*., 2001). A study by Silva *et al.* (2009) found that changes in quality of life over a 5-year period were not related to changes in OSA severity, but rather to worsening of difficulties initiating and maintaining sleep, as well as daytime sleepiness. Akashiba *et al.* (2002) found that mood or depression has more effect on quality of life than OSA severity and excessive daytime sleepiness. Others have reported similar results regarding the association of depression and quality of life (Diamanti *et al*., 2013; Kawahara *et al*., 2005). Unfortunately, measures of depression were unavailable in our study, but we did ask about antidepressant use and found a strong relationship with worse quality of life. Furthermore, we controlled for insomnia symptoms in our analysis, which are highly correlated to symptoms of depression (Lustberg and Reynolds, 2000).

The effect of PAP treatment

We did not find a statistically significant difference in the improvement in quality of life between full and non-users of PAP, with both groups showing significant improvements from baseline to follow-up. However, we note that the *P*-value for a difference in the change in PCS between full and non-users was borderline significant ($P = 0.063$), with full users showing a larger increase on average compared with non-users. Previous studies have not assessed the difference in improvement in quality of life between full and non-PAP users. Others have, however, reported improvement in quality of life among patients with OSA who adhere to PAP treatment (Avlonitou *et al*., 2012; Diamanti *et al*., 2013). In the study by Diamanti *et al.* (2013), only patients with more than 5 h of PAP use were included, and the study by Avlonitou *et al.* (2012) also excluded patients who were not adherent to PAP treatment. Furthermore, a study by D'Ambrosio *et al.* (1999), reporting positive effects of PAP treatment on quality of life, assessed change from baseline in a small sample of adherent patients ($n = 29$), and the magnitude of improvement was most strongly related to the degree of impairment in quality of life at baseline. In order to assess whether PAP treatment had an effect on changes in quality of life independent of baseline levels, adherent patients and non-users were matched for baseline quality of life in our PS sample.

A study by Jenkinson *et al.* (1997) showed positive effects of 5–7 weeks of continuous PAP (CPAP) on quality of life, measured by the SF-36, with effect sizes in the Energy/Vitality dimension of 0.98, and 0.76 for the MCS and 0.57 for the PCS. They concluded that CPAP treatment returns patients with OSA to a quality of life similar to the normal population, which we did not see for physical quality of life in the present study. The study by Jenkinson *et al.* (1997) did not assess differences in improvement between patients with different adherence to CPAP. Furthermore, Sanner *et al.* (2000) concluded that long-term CPAP treatment had a positive effect on quality of life. They did not, however, find a significant correlation between CPAP use and change in the quality of life measures. These studies may therefore have methodological issues that impacted their results. If we had only assessed changes in quality of life among full users in our study, we would have observed similar associations as found in previous studies (Avlonitou *et al*., 2012; D'Ambrosio *et al*., 1999; Diamanti *et al*., 2013; Jenkinson *et al*., 1997; Sanner *et al*., 2000).

A randomized controlled study by Montserrat *et al.* (2001) of the effectiveness of CPAP treatment, using a sham CPAP as a placebo for the control group, found positive effects of CPAP on daytime sleepiness and vitality. In this study, there was, however, no difference found in quality of life scores, measured by the SF-36, between those who were treated with CPAP as compared with placebo. Similar results were found in another randomized controlled trial using sham CPAP, with no significant benefits of CPAP over placebo on quality of life measured by the SF-36 (Barnes *et al*., 2002;). Jenkinson *et al.* (1999) did, however, find a positive effect on quality on life when comparing therapeutic CPAP with sub-therapeutic CPAP in a randomized study, and Ballester *et al.* (1999) reported similar results when comparing conservative treatment (sleep hygiene and weight loss therapy) alone with conservative treatment plus CPAP.

In a meta-analysis conducted by Jing *et al.* (2008), it was concluded that PAP treatment does not improve general quality of life scores, but does improve physical domains and vitality. It is possible that some subgroups of patients improve their quality of life on PAP, as we saw for obese subjects and those without insomnia.

Even though quality of life is significantly improved from baseline to follow-up for all patients with OSA (both PAP users and non-users) in our study, these patients still have much poorer physical health than subjects from the general population even after 2 years of therapy. Patients with OSA have various co-morbidities, such as obesity, high blood pressure and disturbed sleep, and these symptoms are often still apparent even though the OSA is well treated. In our observational sample, full users showed a higher increase in BMI from baseline to follow-up as compared with non-users. This increase in BMI while on PAP is likely to limit the benefit that would have occurred had patients who were adherent to PAP not gained weight. This indicates a need for more personalized medicine including broader therapeutic interventions that target co-morbidities such as obesity and sleep difficulties. In our previous study (Bjornsdottir *et al*., 2013), we found that symptoms of initial insomnia tend to persist in spite of successful PAP treatment. Therefore, it

may well be that some of these patients have another untreated disorder and/or health condition besides OSA that impacts their quality of life. The existence of these underlying co-morbidities could help explain why quality of life is still significantly impaired, despite successful PAP treatment. Long-term follow-up studies are needed to explore how PAP treatment affects co-morbid symptoms related to quality of life and wellbeing of patients with OSA. Particularly, there is a need for studies on more personalized treatment interventions for these patients, for example additional interventions for those suffering from co-morbid insomnia.

The major strengths of this study include the large clinical cohort of patients with OSA, the comparison with a general population cohort using propensity matching and the comparison between patients with OSA with different degrees of PAP use, as well as the extensive 2-year follow-up with a high response rate (>90%). Furthermore, this study included detailed questionnaire assessments of co-morbid conditions as well as sleep studies in all OSA subjects. The major limitations were that we did not have measures of depression, which is an important indicator of quality of life. We did, however, control for insomnia symptoms and the use of antidepressants. Although a majority of patients (75%) using PAP had objective adherence information, a subset of patients included in this manuscript was classified based on subjective data only. As described in previous publications (Arnardottir *et al.*, 2013; Bjornsdottir *et al.*, 2013), our subjective criteria have high sensitivity (98.6%) and moderate specificity (45.1%) for classifying full versus partial users. This combination of high sensitivity and low specificity means that full users are likely to be correctly classified, but also that a proportion of patients meeting our subjective criteria of full usage are actually partial users. While not ideal, the misclassification of partial users as full users in this minority of patients is expected to bias us towards the null, i.e. against observing a strong PAP effect. Moreover, we observed no significant changes in our estimates or results when restricting to only the subset of PAP users that had objective data. Furthermore, we did not have short-term follow-up results to evaluate the acute effects of PAP treatment on mental and physical health, and we used the SF-12 to measure quality of life whereas using SF-36 could have potentially provided better discrimination. PS methodologies create balance with respect to measured covariates included in the matching; however, we cannot rule out the potential for unknown or unrecognized confounding. Moreover, we note that in order to obtain a well-matched sample of patients with OSA and general population subjects, we necessarily excluded patients with higher obesity and the most co-morbidities, while simultaneously including less healthy and more obese general population subjects. While this restriction may reduce the scope of our inference, we note that our sample is more inclusive of 'real-world' patients than typical randomized trials. Finally, while we recognize that there is likely a subset of the general population with undiagnosed OSA, including these patients as controls is expected to bias our results towards the null, suggesting that the significant differences observed in this study may be even greater.

Taken together, the results of the current study show that patients with OSA have impaired quality of life compared with the general population, and, although a significant improvement after a 2-year follow-up was seen in all patients, full users of PAP do not appear to significantly improve their quality of life more than non-users. Despite the lack of statistical significance, there was a trend towards more improvement in PCS for PAP-adherent patients compared with non-users in the overall population. Moreover, we found significant differences in specific subsets, including the most obese and those without insomnia; full users in these subgroups showed more improvement in physical quality of life compared with non-users. Co-morbidities of OSA such as obesity, insomnia symptoms and daytime sleepiness have a great effect on quality of life, and these factors need to be taken into account and addressed with additional treatment interventions.

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DECLARATION OF CONTRIBUTION

E. B. designed the study with T. G., B. B., E. S. A. and A. I. P. E. B. performed the literature search, and statistical analyses with the help of B. K. and C. J. E. B. drafted the paper and participated in all revisions of the paper with the co-authors. B. K. performed the propensity matching analyses, and participated in data interpretation and all revisions of the manuscript. B. E. participated in the data collection, the literature review and in all revisions of the manuscript. E. S. A. participated in the study design, data collection and all revisions of the manuscript. C. J. participated in statistical analyses, data interpretation and all revisions of the manuscript. T. G. co-supervised the work, designed the study, and participated in data interpretation and all revisions of the manuscript. J. F. S. participated in all revisions of the manuscript and co-supervised the work. S. T. K. participated in data interpretation and all revisions of the manuscript. A. I. P. co-supervised the work, designed the study, and participated in data interpretation and all revisions of the manuscript. B. B. co-supervised the work, designed the study, and

participated in data interpretation and all revisions of the manuscript.

CONFLICT OF INTEREST

The authors declare no competing interests with regard to the submitted work. Dr Arnardottir is a consultant for Nox Medical, Inc. Dr Kuna receives grant support from Philips Respironics. Other authors do not report a conflict of interest.

REFERENCES

Ahmed, A., Husain, A., Love, T. E. *et al.* Heart failure, chronic diuretic use, and increase in mortality and hospitalization: an observational study using propensity score methods. *Eur. Heart J.*, 2006, 27: 1431–1439.

Akashiba, T., Kawahara, S., Akahosni, T. *et al.* Relationship between quality of life and mood or depression in patients with severe obstructive sleep apnea syndrome. *Chest*, 2002, 122: 861–865.

Arnardottir, E. S., Maislin, G., Schwab, R. J. *et al.* The interaction of obstructive sleep apnea and obesity on the inflammatory markers C-reactive protein and interleukin-6: the Icelandic Sleep Apnea Cohort. *Sleep*, 2012, 35: 921–932.

Arnardottir, E. S., Janson, C., Bjornsdotttir, E. *et al.* Nocturnal sweating – a common symptom of obstructive sleep apnoea: the Icelandic sleep apnoea cohort. *BMJ Open*, 2013, 3(5).

Avlonitou, E., Kapsimalis, F., Varouchakis, G., Vardavas, C. and Behrakis, P. Adherence to CPAP therapy improves quality of life and reduces symptoms among obstructive sleep apnea syndrome patients. *Sleep Breath.*, 2012, 16: 563–569.

Baldwin, C. M., Griffith, K. A., Nieto, F. J., O'Connor, G. T., Walsleben, J. A. and Redline, S. The association of sleep disordered breathing and sleep symptoms with quality of life in the Sleep Heart Health Study. *Sleep*, 2001, 24: 96–105.

Ballester, E., Badia, J. R., Hernández, L. *et al.* Evidence of the effectiveness of continuous positive airway pressure in the treatment of sleep apnea/hypopnea syndrome. *Am. J. Respir. Crit. Care Med.*, 1999, 159: 495–501.

Barnes, M., Houston, D., Worsnop, C. *et al.* A randomized controlled trial of continuous positive airway pressure in mild obstructive sleep apnea. *Am. J. Respir. Crit. Care Med.*, 2002, 165: 773–780.

Bjornsdottir, E., Janson, C., Gislason, T. *et al.* Insomnia in untreated sleep apnea patients compared to controls. *J. Sleep Res.*, 2012, 21: 131–138.

Bjornsdottir, E., Janson, C., Sigurdsson, J. *et al.* Symptoms of insomnia among OSA patients before and after 2 years of PAP treatment. *Sleep*, 2013, 36: 1901–1909.

Buist, A. S., McBurnie, M. A., Vollmer, W. M. *et al.* International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet*, 2007, 370: 741–750.

Chervin, R. D. Sleepiness, fatigue, tiredness and lack of energy in obstructive sleep apnea. *Chest*, 2000, 118: 372–379.

D'Ambrosio, C., Bowman, T. and Mohsenin, V. Quality of life in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure – a prospective study. *Chest*, 1999, 115: 123–129.

Diamanti, C., Manali, E., Ginieri-Coccossis, M. *et al.* Depression, physical activity, energy consumption, and quality of life in OSA patients before and after CPAP treatment. *Sleep Breath.*, 2013, 17: 1159–1168.

Finn, L., Young, T., Palta, M. and Fryback, D. G. Sleep-disordered breathing and self-reported general health status in the Wisconsin Sleep Cohort Study. *Sleep*, 1998, 21: 701–708.

Gandek, B., Ware, J. E., Aaronson, N. K. *et al.* Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. *J. Clin. Epidemiol.*, 1998, 51: 1171–1178.

Gay, P., Weaver, T., Loube, D. and Iber, C. Evaluation of positive airway pressure treatment for sleep related breathing disorders in adults: a review by the positive airway pressure task force of the standards of practice committee of the American Academy of Sleep Medicine. *Sleep*, 2006, 29: 381–401.

Jenkinson, C., Stradling, J. and Petersen, S. Comparison of three measures of quality of life outcome in the evaluation of continuous positive airways pressure therapy for sleep apnoea. *J. Sleep Res.*, 1997, 6: 199–204.

Jenkinson, C., Davies, R. J., Mullins, R. *et al.* Comparison of therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: a randomised prospective parallel trial. *Lancet*, 1999, 353: 2100–2105.

Jing, J., Huang, T., Cui, W. and Shen, H. Effect on quality of life of continuous positive airway pressure in patients with obstructive sleep apnea syndrome: a meta-analysis. *Lung*, 2008, 186: 131–144.

Johns, M. W. Reliability and factor analysis of the Epworth Sleepiness Scale. *Sleep*, 1992, 15: 376–381.

Kawahara, S., Akashiba, T., Akahoshi, T. and Horie, T. Nasal CPAP improves the quality of life and lessens the depressive symptoms in patients with obstructive sleep apnea syndrome. *Intern. Med.*, 2005, 44: 422–427.

Keenan, B. T., Maislin, G., Sunwoo, B. Y. *et al.* Obstructive sleep apnea treatment and fasting lipids: a comparative effectiveness study. *Eur. Respir. J.*, 2014, 2: 405–414. May 15 (Epub ahead of print).

Kohler, M., Smith, D., Tippett, V. and Strading, J. R. Predictors of long-term compliance with continuous positive airway pressure. *Thorax*, 2010, 65: 829–832.

Lacasse, Y., Godbout, C. and Sériés, F. Health-related quality of life in obstructive sleep apnoea. *Eur. Respir. J.*, 2000, 19: 499–503.

Lieu, T. A., Au, D., Krishnan, J. A. *et al.* Comparative effectiveness research in lung diseases and sleep disorders recommendations from the National Heart, Lung, and Blood Institute Workshop. *Am. J. Respir. Crit. Care Med.*, 2011, 184: 848–856.

Lustberg, L. and Reynolds, C. F. III Depression and insomnia: questions of cause and effect. *Sleep Med. Rev.*, 2000, 4: 253–262.

Maislin, G. and Rubin, D. B. Design of non-randomized medical device trials based on sub-classification using propensity score quintiles. In: J. S. M. Proceedings (Ed.) *Biopharmaceutical Section.* VA, American Statistical Association, Alexandria, 2010: 2182–2196.

McNicholas, W. T. and Bonsigore, M. R. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. *Eur. Respir. J.*, 2007, 29: 156–178.

Montserrat, J. M., Ferrer, M., Hernandez, L. *et al.* Effectiveness of CPAP treatment in daytime function in sleep apnea syndrome: a randomized controlled study with an optimized placebo. *Am. J. Respir. Crit. Care Med.*, 2001, 164: 608–613.

Pak, V. M., Keenan, B. T., Jackson, N.. *et al.* Adhesion molecule increases in sleep apnea: beneficial effect of positive airway pressure and moderation by obesity. *Int. J. Obes.*, 2014, doi: 10.1038/ijo.2014.123.

Partinen, M. and Gislason, T. Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints. *J. Sleep Res.*, 1995, 4: 150–155.

Punjabi, N. M. The epidemiology of adult obstructive sleep apnea. *Proc. Am. Thorac. Soc.*, 2008, 5: 136–143.

Sanner, B. M., Klewer, J., Trumm, A., Randerath, W., Kreuzer, I. and Zidek, W. Long-term treatment with continuous positive airway

pressure improves quality of life in obstructive sleep apnoea syndrome. *Eur. Respir. J.*, 2000, 16: 118–122.

Sassani, A., Findley, L. J., Kryger, M., Goldlust, E., George, C. and Davidson, T. M. Reducing motor-vehicle collisions, costs, and fatalities by treating obstructive sleep apnea syndrome. *Sleep*, 2004, 27: 453–458.

Silva, G. E., An, M. W., Goodwin, J. L. *et al*. Longitudinal evaluation of sleep disordered breathing and sleep symptoms with change in quality of life: the Sleep Heart Health Study. *Sleep*, 2009, 32: 1049–1057.

Soldatos, C. R. and Paparrigopoulos, T. J. Sleep physiology and pathology: pertinence to psychiatry. *Int. Rev. Psychiatry*, 2005, 17: 213–228.

Ware, J. Jr, Kosinski, M. and Keller, S. D.. A 12-item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med. Care*, 1996, 34: 220–233.

Weaver, T. E., Mancini, C., Maislin, G. *et al*. Continuous positive airway pressure treatment of sleepy patients with milder obstructive sleep apnea. *Am. J. Respir. Crit. Care Med*., 2012, 186: 677–683.

Yang, E. H., Hla, K. M., McHorney, C. A., Havighurst, T., Badr, M. S. and Weber, S. Sleep apnea and quality of life. *Sleep*, 2000, 23: 535–541.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Method and Results

Table S1. Comparison of patients included in and excluded from PS designed observational study.

Table S2. Comparison of patients included in and excluded from PS designed observational study.

Table S3. Comparison of change in quality of life between full and non-users in *propensity score* matched sample stratified by sleepiness and insomnia symptoms at baseline.

Table S4. Association between PAP Adherence and PCS and MCS change, stratified by antidepressant medication use.

Figure S1. Modified Love plot comparing OSA patients (n = 494) and general population subjects (n = 418) before and after PS matching.

Figure S2. Modified Love Plot Comparing PAP Full (n = 308) and Non-users (n = 200).

Paper IV

The prevalence of depression among untreated OSA patients using a standardized psychiatric interview

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Abstract

Study objectives: The aims of this study were: 1) to use a standardized psychiatric interview, conducted by a trained psychologist to assess the prevalence of depression among untreated OSA patients, and 2) to identify if OSA severity or other co morbid disorders (insomnia, hypertension and diabetes) are related to depression among untreated OSA patients.

Methods: Participants were newly diagnosed OSA patients (n=284) waiting to start positive airway pressure (PAP) treatment. The Mini International Neuropsychiatric Interview (MINI) was used to assess depression.

Results: Overall, 15.5% of the sample met the diagnosis for dysthymia. Women had a significantly higher prevalence (29.5% vs. 11.7% among men, $p<0.001$). The prevalence of major depression was 6% in the overall sample and there was no difference in the prevalence among genders (5.8% among men vs. 6.6 % among women) Those who suffered from depression reported lower quality of life and were more likely to report symptoms of insomnia and use sleep medication and antidepressants.

Conclusions: Sleep medication use, daytime sleepiness and symptoms of initial insomnia were independently related to depression but OSA severity was not. Increased awareness of the relationship between depression and OSA and the appropriate use of assessment tools might significantly improve diagnostic accuracy as well as treatment outcome for both disorders.

Key words: Depression, obstructive sleep apnea, psychiatric interview

Introduction

Obstructive sleep apnea (OSA) is a disorder characterized by loud snoring and recurrent apneas and hypopneas during sleep, associated with oxygen desaturation and arousals[1]. Fragmented sleep and poor sleep quality are common among OSA patients and often result in decreased energy, excessive sleepiness, impaired cognition and altered mood[2]. This disrupted sleep pattern affects the stress system of the body and makes those suffering from OSA more vulnerable for developing depression[3].

Prevalence studies have shown high rates of depression among OSA patients in both community and clinical populations, ranging from 7-63% (for reviews, see[4-6]). Furthermore, several studies have shown that OSA patients with high levels of depression have the lowest quality of life and suffer most from daytime sleepiness and fatigue[7-9]. It has also been suggested that, among depressive OSA patients, daytime sleepiness is more strongly related to depression than OSA severity[8-10].

In addition to daytime sleepiness and fatigue, the high co-morbidity of insomnia among OSA patients reported in our previous studies[11,12] could also partially explain elevated levels of depression among this population as epidemiological studies have reported that individuals with insomnia have nearly four times higher risk for developing a new depressive disorder in the following 3.5 years after insomnia diagnosis[13].

Some studies have reported improvements in depressive symptoms after PAP treatment [14,15] but others have not [16,17]. Therefore, evidence to date suggests that depressive symptoms may persist in at least some patients receiving PAP treatment.

While depression seems to play a role in the overall expression of OSA, the true nature of this relationship remains uncertain. It can be difficult to identify the cause and effect in the relationship of depression and OSA. Previous studies on OSA and mental health have focused on the level of depression in the OSA population. Symptoms such as fatigue, loss of

interest, decreased libido and poor concentration are common to both depression and OSA, which means that commonly used depression scales may not be valid in assessing depressive symptoms among OSA patients[6]. Most standardized self-report questionnaires used to evaluate depression among OSA patients have not been specifically designed for assessment in this population[18] and may therefore be inappropriate to use. As a result it is unclear if OSA and depression express a real co-morbidity or only share similar symptoms[19].

Due to the frequent symptom overlap between depression and OSA, it is important to carefully select the instruments used to measure depression in this population. In order to do so, the aims of the current study were: 1) to use a standardized psychiatric interview, conducted by a trained psychologist to assess the prevalence of depression among untreated OSA patients, and 2) to identify if OSA severity or other co-morbid disorders (insomnia, hypertension and diabetes) are related to depression among untreated OSA patients.

Subjects and Methods

Participants in this study were 284 patients diagnosed with OSA in Iceland and referred for positive airway pressure (PAP) treatment to the Landspitali University Hospital in Reykjavik from February 2010 – December 2013. Altogether 104 among the 284 participants were also taking part in an ongoing study of the relationship between OSA and cardiovascular diseases and response to PAP treatment in lean and obese patients. Subjects who had been excluded from the above study were invited to take part in the current study with no other inclusion/exclusion criteria than having AHI>15 (n=180). All 284 subjects in the current study went through the same protocol for data collection.

All participants had initially been diagnosed with OSA as defined by an apnea-hypopnea index (AHI) ≥15 events/hr and oxygen desaturation index (ODI) of ≥10 events/hr. When sleep studies were rescored, there were however some subjects (n = 9) who had AHI

between 10-15 events/hr but they were not excluded from the study. Altogether, over 90% of approached subjects agreed to participate in the study. The study protocol was approved by the National Bioethics Committee of Iceland and the Data Protection Authority of Iceland (10-048).

General health questionnaire

Participants were invited to the outpatient clinic at the Landspitali University Hospital in Reykjavik, Iceland before initiating OSA treatment. After written informed consent was obtained, they answered self-administered standardized questionnaires about their current sleep-wake problems and health condition and underwent a standardized psychiatric diagnostic interview. The general health questionnaire included questions about whether subjects had hypertension and/or diabetes (medical diagnosis and medication). Women were asked if they were postmenopausal and all patients were asked if they exercised on a regular basis (yes/no). Furthermore, subjects were asked to list all medication they were taking which were subsequently coded according to the Anatomical Therapeutic Chemical (ATC) drug classification system (www.whocc.no/atcddd). Those who listed medications in the ATC code N05C were registered as using sleep medications and those who listed medications in the ATC code N06 were registered as using antidepressants.

Depression

Depression was evaluated with the Mini International Neuropsychiatric Interview (MINI), a short and structured diagnostic interview that contains 120 questions and screens 17 axis I disorders according to the Diagnostic and statistical manual (DSM) IV criteria for 24 current and lifetime diagnosis [20]. The MINI interview was developed to meet the increasing demand for a short, reliable and valid diagnostic tool. A trained psychologist with experience

in working with OSA patients and training in administrating the MINI conducted all the interviews. The average administration time of the MINI is 15-20 minutes[20]. Only depressive disorders (major depression and dysthymia; part A and B from the MINI) were investigated in this study. The MINI is based on yes or no answers and has two to four screening questions per disorder. When the screening questions are answered positively, additional symptom questions within each disorder section are asked.

Studies have showed that the MINI provides a reliable DSM III-R diagnosis within a short time frame [21]. For the English version of the MINI, excellent inter-rater and test-retest reliability, and moderate validity of MINI versus the World Health Organization Composite International Diagnostic Interview (CIDI) have been reported [21]. The Icelandic version of the MINI has not been extensively studied but one preliminary study supports its validity [22].

A diagnosis of dysthymia according to the DSM-IV includes depressed mood for most of the day for two or more years and at least two of the following symptoms causing distress in life or interfering with functional ability: poor appetite or overeating, sleep problems, tiredness or lack of energy, low self-esteem, hopelessness, poor concentration, and trouble making decisions. A diagnosis of major depression includes having five or more of the following symptoms over a two-week period, most of the day, nearly every day: depressed mood, such as feeling sad, empty or tearful, significantly diminished interest or feeling no pleasure in almost all activities, significant weight loss when not dieting, weight gain, or decrease or increase in appetite, insomnia or increased desire to sleep, restlessness or slowed behavior that can be observed by others, fatigue or loss of energy, feelings of worthlessness, or excessive guilt, trouble making decisions, or trouble thinking or concentrating, recurrent thoughts of death or suicide, or a suicide attempt. At least one of the symptoms must be either a depressed mood or a loss of interest or pleasure. The symptoms must be severe enough to

cause noticeable problems in day-to-day activities, such as work, school, social activities or relationships with others [23].

Quality of life

Participants completed the Short Form 12 (SF-12) questionnaire to assess quality of life[24]. Two summary component scores are derived from the SF-12, the physical component score (PCS) and mental component score (MCS). These scores range from 0-100, where a zero score indicates the lowest life quality and 100 indicates the highest life quality.

Excessive daytime sleepiness

Daytime sleepiness was evaluated using the Epworth Sleepiness Scale (ESS), a brief questionnaire that measures subjective daytime sleepiness[25]. Participants with ESS score $\geq$10 were considered to have excessive daytime sleepiness.

Symptoms of sleep disturbances

Sleep symptoms were assessed using the Basic Nordic Sleep Questionnaire, which includes questions on sleep quality, insomnia symptoms, snoring, nocturnal sweating, and daytime sleepiness[26]. Three subtypes of insomnia symptoms were defined: difficulty initiating sleep (initial insomnia), difficulty maintaining sleep (middle insomnia) and early morning awakenings (late insomnia), for more details see previous publication[12]. Answers were rated on a five point scale: never/almost never (1); less than once a week (2); once or twice a week (3); three to five times a week (4); every day or almost every day of the week (5). Those who reported symptoms of insomnia at least three times per week were considered to be suffering from the appropriate subtype of insomnia.

Sleep apnea

All participants had a diagnostic sleep study with an Embletta type 3 portable monitor or an Embla 12 channel system (Embla^{TM}; Flaga Inc., Reykjavik, Iceland) or a T3 device (Nox Medical, Reykjavik, Iceland). The same signals were recorded on all studies: nasal pressure by cannula, oxygen saturation, heart rate, respiratory movements by respiratory inductance plethysmography (RIP) belts, body position, and activity by accelerometer. The sleep recordings were scored at the Landspitali University Hospital in Reykjavik by trained sleep technologists and the studies had to have at least 4 hours of a scorable O_2 saturation signal and respiration by flow or RIP belts. Scoring of a hypopnea required a ≥ 30% decrease in airflow for ≥ 10 sec with ≥ 4% oxygen desaturation or ≥ 50% decrease in airflow for ≥ 10 sec with a sudden increase in flow at the end of the event. Scoring of an apnea required ≥ 80% decrease in flow for ≥ 10 sec. The AHI was calculated as the mean number of apneas and hypopneas per hour of recording (excluding upright time). The ODI was calculated as the number of transient drops in oxygen saturation ≥ 4% per hour of recording.

Statistical analyses

All statistics were calculated with STATA 12.0 for Windows (Stata Corporation, College Station, Texas). For bivariate analysis, the chi-square test and t-test were used for nominal and continuous variables respectively. Multiple logistic regression was used to identify which risk factors had an independent association with depression. A p-value of ≤ 0.05 was determined as statically significant.

Results

Study population characteristics

Baseline characteristics are shown in Table 1. Among the study population, the majority was males (78%) and the mean age was 53.9 ± 9.1 years, with women being on average 2.7 years older than the men. The women were more obese but with less severe OSA as measured by AHI and ODI. Furthermore, women were more likely to report symptoms of initial and middle insomnia and to use sleep medications and antidepressants (Table 1).

Insert table 1 here

The prevalence of depression

Overall, 15.5% of the sample met the diagnosis for dysthymia. Women had a significantly higher prevalence (29.5% vs. 11.7% among men, $p<0.001$). The prevalence of major depression was 6% in the overall sample and no difference in the prevalence among genders (5.8% among men vs. 6.6 % among women). The prevalence of depression overall (dysthymia or major depression) was 20.8%. Women showed significantly higher prevalence, 36.1% vs. 16.6% among men, ($p<0.001$) but this difference was driven by the dysthymia results (Figure 1). Furthermore, 82% of the women were postmenopausal, and depression was more common among them as compared to premenopausal women (31.8% vs. 10.3%; $p=0.04$).

Insert Figure 1 here

Subjects who met the diagnosis for depression (dysthymia or major depression) were more obese, sleepier, and less likely to exercise on a regular basis. In addition, they had lower mental and physical quality of life, were more likely to suffer from initial and late insomnia, but had no significant difference in the prevalence of middle insomnia (Table 2). Furthermore, those who met diagnosis for depression were more likely to use sleep medications and antidepressants.

Insert table 2 here

Table 3 shows the results of logistic regression where several variables were tested for their independent associations to depression. Apart from the variables listed in table 3, diabetes, hypertension, OSA severity (AHI and ODI), exercise and the other subtypes of insomnia (yes/no) were tested but results were not significant. The results are presented in stepwise order. Sleep medication use was most strongly related to depression but sleepiness as measured by the ESS score and symptoms of initial insomnia were also independently related to depression (dysthymia or major depression). Other subtypes of insomnia were not independently related to depression (Table 3). This was also examined separately for the genders and the results did not change for men, but for women, depression was only independently related to initial insomnia (daytime sleepiness as measured by the ESS was no longer significant).

Discussion

The main findings of the current study were that 20.8% of untreated OSA patients meet the diagnosis for depression (dysthymia or major depression) according to a structured diagnostic interview carried out by a trained psychologist. This is considerably higher than reported in the general population in Iceland. In a study from 2009, the lifetime prevalence of depression in Iceland, assessed by The Composite International Diagnostic Interview (core version 1.1) was 13%[27], which is similar or lower than reported in other European countries[28]. Altogether, 18.3% of subjects in the current study used antidepressants and, as expected, this was more common among those who met the diagnosis for depression according to the MINI. Similar to previous findings, depression was more common among women [6,9] but 82% of the women in the current study were postmenopausal and studies have shown a higher prevalence of depression in postmenopausal women[29]. Sleep medication use, symptoms of initial insomnia and daytime sleepiness were highly related to depression while OSA severity was not.

Many previous studies have found a much higher prevalence of depression among OSA patients than reported in the current study. For example, in a study by Mosko et al.[30] 58% of OSA patients met the DSM criteria for depression and in a study by Millmann et al.[31] 45% of OSA patients had depressive symptoms. Akashiba et al.[7] reported a 48% prevalence of depression in a sample of sixty male OSA patients compared to controls (n=34). In their study, OSA patients had a much higher prevalence of depression than controls and depression was associated with poorer quality of life as we also found in our study. Furthermore, Aikens et al.[32] showed that 32% of their OSA patients had elevated depression scores on the Minnesota multiphasic personality inventory (MMPI) and there were twice as many OSA patients with elevated depression scores than age and sex matched primary snorers. These

differences in prevalence of depression among OSA patients are probably partially due to different definitions and instruments used to assess depression.

Most previous studies have used self-reported questionnaires to assess depression and as a result, overrepresentation of the prevalence is likely to occur due to the frequent symptom overlap between depression and OSA. An Australian study by Douglas et al.[33] showed that among patients with suspected OSA, the overall rate of depression based on doctor diagnosis, Hospital Anxiety and Depression Scale (HADS), or two screening questions from the MINI was 53%. In that study, the prevalence of depression assessed with the MINI questions was 45% and a significant correlation was reported (0.736; $p<0.001$) between HADS and the MINI depression questions[33]. This is a much higher prevalence of depression than reported in our study but the fact that Douglas et al.[33] only used two screening questions from the MINI has to be considered a limitation and could partially explain the difference in the results. Another recent study indicated that HADS would be an accurate screening tool for assessing major depression among patients in sleep disorder clinics[34] but further studies comparing the use of self report questionnaires and structured clinical interviews in large cohorts of OSA patients are needed.

Patients with untreated OSA have a very high prevalence of insomnia and daytime sleepiness and, as we report here, these factors are related to depression and need to be taken into account when treating OSA. Studies have shown that symptoms of initial insomnia tend to persist even though OSA is successfully treated while middle insomnia improves with PAP treatment[12], indicating that initial insomnia requires additional treatment apart from OSA. Our results further emphasize this point since initial insomnia is strongly related to depression in our study and depression has been associated with lack of compliance with medical treatment[35]. Results regarding the impact of depression on PAP adherence are inconsistent

(see review[6]) but a recent study indicated that depressive OSA patients might have poorer adherence with PAP treatment[36].

Furthermore, a number of studies have indicated a bidirectional relationship between poor sleep and depression and some have suggested that sleep difficulties may lead to or exacerbate depression and that by improving sleep quality it is possible to improve symptoms of depression as well[37,38]. OSA severity was not related to depression in our study and others have reported similar results, suggesting that depression is more related to disrupted sleep and sleepiness than OSA severity per se [9].

The major limitations of the current study are that OSA was evaluated with type 3 sleep study rather than a full PSG. However, the NOX T3, which was used for the majority of patients in the current study, has demonstrated a very good measurement agreement as compares to the PSG[39]. Another limitation is the fact that this is a cross-sectional study and therefore follow-up data regarding changes in depression after PAP treatment and the effect of depression on PAP adherence are missing.

The major strengths of the current study were the large cohort of untreated OSA patients and the use of a standardized psychiatric interview to assess depression. The MINI includes questions regarding symptoms that are highly related to untreated OSA and therefore misdiagnosis of depression is possible. However, structured diagnostic interviews like the MINI have become an essential part of psychiatric medicine. Apart from being the diagnostic gold standard in mental health research, the MINI is also increasingly being used to help ensure diagnostic precision in clinical practice[40]. Even though information collected from open clinical interviews may vary depending on how a particular question is asked or framed, structured diagnostic interviews include questions that are precise and carefully linked to diagnostic criteria, therefore minimizing the risk of imprecise diagnosis. It is however time consuming to assess all patients with standardized interviews and therefore it could be more

realistic to initially screen patients with self report questionnaires and subsequently further assess those who screen positively for depression and have difficulties in adapting to PAP treatment. Additional interventions targeted at depression might by beneficial in such cases.

In conclusion, the prevalence of depression in untreated OSA patients assessed with a standardized clinical psychiatric interview is lower than frequently reported in previous studies. Depression among OSA patients was more common among women and highly related to sleep medication use, daytime sleepiness and symptoms of initial insomnia but not related to OSA severity as measured by AHI and ODI. Increased awareness of the relationship between depression and OSA and the appropriate use of assessment tools might significantly improve diagnostic accuracy as well as treatment outcome for both disorders.

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References

1. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008;5:136-43.
2. Soldatos CR, Paparrigopoulos TJ. Sleep physiology and pathology: pertinence to psychiatry. Int Rev Psychiatry 2005;17:213-28.
3. Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. Sleep Med Rev 2008;12:197-210.
4. Schröder CM, O'Hara R. Depression and Obstructive Sleep Apnea (OSA). Ann Gen Psychiatry 2005;4:13.
5. Saunamäki, T, Jehkonen M. Depression and anxiety in obstructive sleep apnea syndrome: a review. Acta Neurol Scand 2007;116:277-88.
6. Harris M, Glozier N, Ratnavadivel R, Grunstein RR. Obstructive sleep apnea and depression. Sleep Med Rev 2009;13:437-44.
7. Akashiba T, Kawahara S, Akahoshi T, et al. Relationship between quality of life and mood or depression in patients with severe obstructive sleep apnea syndrome. Chest 2002;122:861-5.
8. Sforza E, de Saint Hilaire Z, Pelissolo A, Rochat T, Ibanez V. Personality, anxiety and mood traits in patients with sleep-related breathing disorders: effect of reduced daytime alertness. Sleep Med 2002;3:139-45.
9. Asghari A, Mohammadi F, Kamrava SK, Tavakoli S, Farhadi M. Severity of depression and anxiety in obstructive sleep apnea syndrome. Eur Arch Otorhinolaryngol 2012;269:2549-53.
10. Kjelsberg FN, Ruud EA, Stavem K. Predictors of symptoms of anxiety and depression in obstructive sleep apnea. Sleep Med 2005;6:341-6.
11. Bjornsdottir E, Janson C, Gislason T, et al. Insomnia in untreated sleep apnea patients compared to controls. Journal of Sleep Research 2012;21:131-8.
12. Bjornsdottir E, Janson C, Sigurdsson JF, et al. Symptoms of insomnia among patients with obstructive sleep apnea before and after two years of positive airway pressure treatment. Sleep 2013;36:1901-9.
13. Szelenberger W, Soldatos C. Sleep disorders in psychiatric practice. World Psychiatry 2005;4:186-90.

14. Schwartz DJ, Kohler WC, Karatinos G. Symptoms of depression in individuals with obstructive sleep apnea may be amenable to treatment with continuous positive airway pressure. Chest 2005;128:1304-9.
15. Kuna ST, Gurubhagavatula I, Maislin G, et al. Noninferiority of functional outcome in ambulatory management of obstructive sleep apnea. Am J Respir Crit Care Med 2011;183:1238-44.
16. Munoz A, Mayoralas LR, Barbe F, Pericas J, Agusti AG. Long-term effects of CPAP on daytime functioning in patients with sleep apnoea syndrome. Eur Respir J 2000;15:676-81.
17. Gagnadoux F, Le Vaillant M, Goupil F, et al. Depressive symptoms before and after long-term CPAP therapy in patients with sleep apnea. Chest 2014;145:1025-31.
18. Andrews JG, Oei TP. The roles of depression and anxiety in the understanding and treatment of Obstructive Sleep Apnea Syndrome. Clin Psychol Rev 2004;24:1031-49.
19. Baran AS, Richert AC. Obstructive sleep apnea and depression. CNS Spectr 2003;8:128-34.
20. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59:4-57.
21. Lecrubier Y,, Sheehan, DV, Weiller E, Amorim P, Bonora I, Sheehan K, Janavs J, Dunbar GC. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: reliability and validity according to the CIDI. *European psychiatry* 1997; 12:224-31.
22. Sigurðsson BH. Comparison between two standardized psychiatric interviews and two self-report measures: MINI, CIDI, PHQ and DASS (Cand Psych). University of Iceland. 2008.
23. American Psychiatric Association. Diagnostic and Statistical Manual Of Mental Disorders DSM-IV-TR Fourth Edition (Text Revision). American Psychiatric Association. 2000.
24. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey - Construction of scales and preliminary tests of reliability and validity. Medical Care 1996;34:220-33.

25. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5.
26. Partinen M, Gislason T. Basic Nordic Sleep Questionnaire (BNSQ): a quantitated measure of subjective sleep complaints. *Journal of sleep research* 1995; 4:150-55.
27. Stefánsson JG, Líndal E. Algengi geðraskana á Stór-Reykjavíkursvæðinu. *Læknablaðið 2009; 9*:559-64.
28. Wittchen HU, Jacobi F. Size and burden of mental disorders in Europe--a critical review and appraisal of 27 studies. Eur Neuropsychopharmacol 2005;15:357-76.
29. Frey BN, Lord C, Soares CN. Depression during menopausal transition: a review of treatment strategies and pathophysiological correlates. Menopause Int 2008;14:123-8
30. Mosko S, Zetin M, Glen S, Garber D, DeAntonio M, Sassin J, McAnich, J, Warren S. Self- reported depressive symptomatology, mood ratings, and treatment outcome in sleep disorders patients. *Journal of Clinical Psychology* 1989;45:51-60.
31. Millman RP, Fogel BS, McNamara ME, Carlisle CC. Depression as a manifestation of obstructive sleep apnea: reversal with nasal continuous positive airway pressure. J Clin Psychiatry 1989;50:348-51.
32. Aikens, JE, Mendelson, WB. A matched comparison of MMPI responses in patients with primary snoring or obstructive sleep apnea. *Sleep*, 1999; 22:355-59.
33. Douglas N, Young A, Roebuck T, et al. Prevalence of depression in patients referred with snoring and obstructive sleep apnoea. Intern Med J 2013;43:630-4.
34. Law M, Naughton MT, Dhar A, Barton D, Dabscheck E. Validation of two depression screening instruments in a sleep disorders clinic. J Clin Sleep Med 2014;10:683-8.
35. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med 2000;160:2101-7.
36. Law M, Naughton M, Ho S, Roebuck T, Dabscheck E. Depression may reduce adherence during CPAP titration trial. J Clin Sleep Med 2014;10:163-9.

37. Wiebe ST, Cassoff J, Gruber R. Sleep patterns and the risk for unipolar depression: a review. Nat Sci Sleep 2012;4:63-71.
38. Jansson-Frojmark M, Lindblom K. A bidirectional relationship between anxiety and depression, and insomnia? A prospective study in the general population. J Psychosom Res 2008;64:443-9.
39. Cairns A, Wickwire E, Schaefer E, Nyanjom D. A pilot validation study for the NOX T3(TM) portable monitor for the detection of OSA. Sleep Breath 2014;18:609-14.
40. Nordgaard J, Revsbech R, Sæbye D, Parnas J. Assessing the diagnostic validity of a structured psychiatric interview in a first-admission hospital sample. World Psychiatry 2012;11:181-5.

Table 1: Baseline characteristics of the study population.

	All subjects (n =284)	Men (n = 223)	Women (n = 61)	P value for gender difference
Age (yr)	53.9 ± 9.1	53.3 ± 9.2	56.0 ± 8.2	**0.041**
BMI (kg/m^2)	33.0± 6.0	32.5 ± 5.7	34.8 ± 6.4	**0.006**
AHI (events/hr)	33.1 ± 18.3	34.3 ± 18.9	28.6 ± 15.3	**0.036**
ODI (events/hr)	29.8 ± 18.1	30.9 ± 18.7	25.6 ± 15.0	**0.049**
ESS	10.3 ± 4.4	10.4 ± 4.3	9.8 ± 4.7	0.401
Hypertension (%)	59.4	57.2	67.2	0.159
Diabetes (%)	9.2	9.1	9.8	0.851
Initial insomnia (%)	18.5	13.6	36.1	**<0.001**
Middle insomnia (%)	55.5	50.0	75.4	**<0.001**
Late insomnia (%)	28.0	26.7	32.8	0.348
Sleep medication (%)	15.1	10.3	32.8	**<0.001**
Antidepressant use (%)	18.3	15.7	27.9	**0.029**

BMI: body mass index; AHI: apnea-hypopnea index, ODI: oxygen desaturation index, ESS: Epworth Sleepiness Scale. Significance ($p<0.05$) is marked as **bold.**

Table 2. Characteristics of OSA patients with and without depression (dysthymia or major depression)

	Subjects without depression (n=225)	Subjects with depression (n=59)	P value
Women (%)	17.3	37.3	
Age (yr)	54.2±9.0	52.7±9.4	0.281
BMI (kg/m^2)	32.6±5.8	34.5±6.3	**0.023**
ESS	9.9±4.5	11.5±3.5	**0.017**
AHI (events/hr)	33.5±18.7	31.7±16.9	0.527
ODI (events/hr)	29.8±18.2	29.7±18.0	0.956
PCS	41.9±9.4	36.5±10.0	**<0.001**
MCS	45.4±11.0	36.7±8.5	**<0.001**
Hypertension (%)	58.0	64.4	0.375
Diabetes (%)	9.0	10.2	0.777
Exercise (%)	66.1	50	**0.047**

Initial insomnia (%)	13.5	37.3	**<0.001**
Middle insomnia (%)	53.6	62.7	0.211
Late insomnia (%)	24.2	42.4	**0.006**
Sleep medication (%)	8.9	39.0	**<0.001**
Antidepressant use (%)	12.4	40.7	**<0.001**

BMI: body mass index, ESS: Epworth Sleepiness Scale, AHI: apnea-hypopnea index, ODI: oxygen desaturation index, PCS: physical component score from the SF-12, MCS: mental component score from the SF-12. Significance ($p<0.05$) is marked as **bold**.

Table 3. Factors associated with depression among untreated OSA patients. The association is expressed as adjusted odds ratio with a 95% confidence interval (OR (95% CI)).

	Depression (dysthymia + major depression)
	OR (95% CI)*
STEP 1	
Gender	**3.07 (1.61-5.86)**
Age	0.97 (0.94-1.01)
	$R^2 = 0.04$
STEP 2	
Gender	**2.99 (1.53-5.82)**
Age	0.98 (0.95-1.02)
BMI	1.03 (0.98-1.08)
ESS score	**1.09 (1.01-1.17)**
	$R^2= 0.07$
STEP 3	
Gender	1.94 (0.89-4.20)
Age	0.98 (0.94-1.01)
BMI	1.00 (0.95-1.06)
ESS score	**1.12 (1.04-1.22)**
Initial insomnia	**3.02 (1.37-6.67)**
Sleep medications	**4.89 (2.25-10.64)**
	$R^2 = 0.17$

ESS: Epworth Sleepiness Scale * adjusted for all the variables in the table. Significance is marked as **bold**.

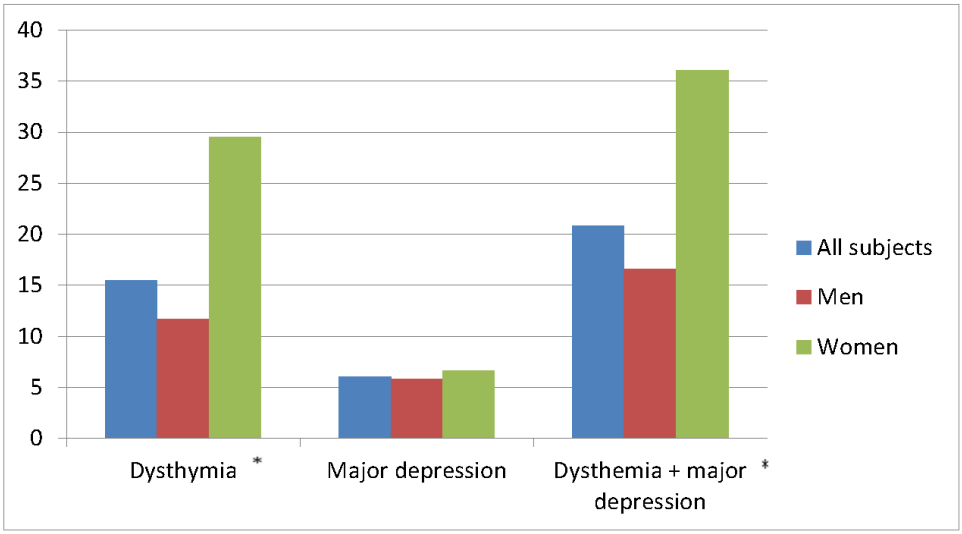

Figure 1. The prevalence (%) of dysthymia and major depression in the overall sample and by gender. * Gender difference p<0.001.