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Treatment success with continuous positive airway pressure or mandibular advancement splints in non-severe obstructive sleep apnea

A randomized controlled clinical trial on sleep quality, health-related quality of life and clinical predictors of treatment success

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«Husk det, barn: Kunnskap er aldri tungt å bære»

Sitat fra sogneprest Gustav Ludvig Kullerud (1852-1936)
til sin datter, min bestemor,
Dagrunn Flatås, f. Kullerud (1925-2017)

Til mine foreldre

Mari-Ann & Einar M. Berg

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Acronyms and abbreviations

AHI	Apnea-Hypopnea-Index
BPAP	Bilevel Positive Airway Pressure
BMI	Body mass index
CPAP	Continuous Positive Airway Pressure
ENT	Ear-Nose-Throat
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-related quality of life
HSAT	Home sleep apnea testing
ICSD-3	International classification of sleep disorders, version 3
ITT	Intention-to-treat
LOCF	Last observation carried forward
MAD	Mandibular advancement device
MAS	Mandibular advancement splint
OR	Odds ratio
OSA	Obstructive sleep apnea
PP	Per protocol
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomized controlled clinical trial
RCI	Reliable Change Index
REI	Respiratory Event Index
RIP	Respiratory inductance plethysmography
SF36	Medical Outcomes Study Short-Form 36-Element Health Survey
SpO_2	Peripheral blood oxygen saturation
T-90%	Percentage of total sleep time spent having SpO_2 less than 90%
95% CI	95% Confidence interval

List of papers

This thesis is based on the following papers, respectively referred to as Paper I, Paper II, and Paper III in the text.

Paper I

Berg, L.M., Ankjell, T.K.S., Trovik, T.A., Sjögren, A., Rikardsen, O.G., Moen, K., Sun, Y-Q., Bugten, V. (2020) 'Self-reported sleep quality with mandibular advancement device or continuous positive airway pressure: A randomized clinical trial on patients with mild and moderate obstructive sleep apnea', *Journal of Dental Sleep Medicine,* 7(2), 10 pages.

Paper II

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Paper III

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Summary

Obstructive sleep apnea (OSA) is a respiratory sleep-disorder characterized by repeated breathing cessations (respiratory events) due to pharyngeal soft tissue collapse, resulting in nocturnal hypoxia and fragmented sleep. If left untreated, OSA increases the risk of cardiovascular, metabolic, neurocognitive, and mental disorders and is associated with premature death. The most common non-surgical treatment alternatives for OSA are continuous positive airway pressure (CPAP) and mandibular advancement splints (MAS). The CPAP reliably reduces the number of respiratory events, but compliance to CPAP treatment is challenging in the treatment of non-severe OSA. The MAS is associated with better compliance, but the ability to reduce the number of respiratory events is unpredictable compared to the CPAP treatment.

The impact on subjective sleep quality and health-related quality of life (HRQoL) from CPAP and MAS treatment is believed to affect the treatment compliance. However, few studies have assessed the association between CPAP and MAS treatment and the subjective sleep quality, and the relationship between subjective sleep quality and HRQoL in non-severe OSA. Moreover, predicting success and compliance in the treatment of non-severe OSA with CPAP and MAS is difficult. Based on anatomical OSA risk factors, the Friedman tongue position is a promising, but insufficiently studied, predictive tool for CPAP and MAS efficacy and compliance.

The overall aim of this clinical trial was to compare CPAP and MAS treatment regarding efficacy, compliance to treatment and the impact on self-reported sleep quality and HRQoL among patients with non-severe OSA.

Between 2014 and 2018, 104 adult patients with non-severe OSA were recruited to this clinical trial in Northern- and Mid-Norway. The patients were randomly allocated to CPAP or MAS treatment and evaluated after 4- and 12 months of treatment. Data were obtained from a medical examination, questionnaires, type 3 home sleep apnea testing, and CPAP recordings. The treatment groups were compared according to the aim of the study and associations between Friedman tongue position, compliance to treatment, and respiratory event improvements were investigated. The correlation between improvements in subjective sleep quality and HRQoL was also investigated. Both intention-to-treat and per protocol analyses were performed for comparisons between the treatment groups. Comparisons after 12 months of treatment were adjusted for baseline variables.

The patients studied in this clinical trial had worse self-reported general health and higher body mass index (kg/m^2) but had no more symptoms of anxiety and depression than the average

Norwegian adult population. Subjective sleep quality and HRQoL were worse than the average non-OSA population at baseline. After 4 and 12 months of treatment both treatment groups significantly improved the number of respiratory events and subjective sleep quality. This also applied to HRQoL after 12 months of treatment. While the number of respiratory events were lower in the CPAP treatment group compared to the MAS treatment group, the subjective sleep quality and HRQoL were not found to differ between the treatment groups at follow-up. Improvements in the subjective sleep quality correlated with some aspects of the HRQoL. Compliance to MAS treatment was significantly better than compliance to CPAP treatment at follow-up. Friedman tongue position was not predictive for treatment success nor compliance to treatment. The findings in this clinical trial coincide with the current evidence in OSA research.

In conclusion, there were no conclusive differences found between CPAP and MAS treatment regarding subjective sleep quality and HRQoL after 12 months of treatment, despite differences in the ability to improve the number of respiratory events. CPAP remains the primary choice of treatment, but the comparable effect on patient-reported outcomes between CPAP and MAS treatment combined with the better compliance to MAS treatment suggests that MAS should be available as a treatment option for patients with non-severe OSA. Tongue size according to the Friedman tongue position does not seem to predict compliance and efficacy of CPAP and MAS treatment in patients with non-severe OSA.

Sammendrag

Obstruktiv søvnapné (OSA) er en søvnlidelse som karakteriseres av gjentatte pustestans som følge av mykvevskollaps i svelget. Dette fører til nattlig hypoksi og oppstykket søvn, som ubehandlet kan føre til økt risiko for hjerte-kar-sykdom, metabolsk sykdom, kognitiv svikt og psykisk uhelse. Ubehandlet OSA er også forbundet med for tidlig død. Ikke-kirurgisk behandling av OSA skjer oftest ved hjelp av kontinuerlig luftveisovertrykk (CPAP) eller søvnapnéskinner (MAS). CPAP er svært effektivt for å redusere antallet pustestans, men behandlinga er forbundet med dårlig behandlingsetterlevelse blant pasienter med ikke-alvorlig OSA. Behandling med MAS er forbundet med god etterlevelse, men det er vanskelig å forutsi hvor god reduksjonen av antall pustestans blir med MAS.

Innvirkningen fra behandling med CPAP og MAS på opplevd søvnkvalitet og helserelatert livskvalitet er antatt å påvirke behandlingsetterlevelsen, men sammenhengen mellom behandling med CPAP og MAS og opplevd søvnkvalitet er lite studert. Dette gjelder også sammenhengen mellom opplevd søvnkvalitet og helserelatert livskvalitet. Dessuten, er det utfordrende å forutsi behandlingseffekten og etterlevelsen av CPAP og MAS. Ut fra kjente risikofaktorer for OSA knyttet til anatomiske forhold er det tenkelig at «Friedman tongue position» (Friedman skår) kan forutse vellykkethet og etterlevelse ved behandling med CPAP og MAS, men dette er ikke tidligere undersøkt i kliniske studier.

Hovedmålet med denne kliniske studien var å sammenligne behandling med CPAP og MAS med hensyn til behandlingens evne til å bedre antallet pustestans, behandlingsetterlevelse og virkningen fra behandlinga på opplevd søvnkvalitet og helserelatert livskvalitet blant pasienter med ikke-alvorlig OSA.

Mellom 2014 og 2018 ble 104 voksne pasienter med ikke-alvorlig OSA rekruttert til studien i Nord- og Midt-Norge. Pasientene ble tilfeldig satt til behandling med CPAP eller MAS og fulgt opp med kontroller etter 4- og 12 måneder. Data ble innhentet gjennom medisinsk undersøkelse, spørreskjemaer, type 3-polygrafi og avlesning av CPAP-logg. Behandlingsgruppene ble sammenlignet i tråd med hovedmålet i studien, og sammenhengen mellom Friedman skår og behandlingsetterlevelse og bedring i antall pustestans ble undersøkt. Sammenhengen mellom bedring i opplevd søvnkvalitet og bedring i helserelatert livskvalitet ble også undersøkt. Både «intention-to-treat-analyser» og «per protocol-analyser» ble utført ved sammenligning av behandlingsgruppene. Sammenligningene ved 12-månederskontrollen ble justert for basisvariabler.

Pasientene i denne kliniske studien hadde dårligere selv-rapportert generell helsetilstand og høyere kroppsmasseindeks (BMI, kg/m^2), men ikke flere symptomer på angst og depresjon sammenlignet med gjennomsnittet blant voksne nordmenn. Opplevd søvnkvalitet og helserelatert livskvalitet før behandling var dårligere enn hos nordmenn uten OSA. Etter 4- og 12 måneder hadde behandling med både CPAP og MAS signifikant forbedret antall pustestans og opplevd søvnkvalitet. Ved 12-månederskontrollen var dette også tilfelle for deler av den helserelaterte livskvaliteten i begge behandlingsgruppene. Selv om CPAP-behandlinga var klart best til å redusere antallet pustestans, kunne det ikke påvises forskjell mellom gruppene vedrørende opplevd søvnkvalitet og helserelatert livskvalitet på kontrollene. Bedringen i opplevd søvnkvalitet var dessuten korrelert til deler av forbedringa i helserelatert livskvalitet. Behandlingsetterlevelsen til MAS var betydelig bedre sammenlignet med CPAP. Det var ikke mulig å forutsi hvilke pasienter som hadde vellykket behandling med CPAP og MAS, og hvilke som etterlevde behandlinga ut fra Friedman skår. Funnene i denne kliniske studien samsvarer med gjeldende evidens innen forskningsfeltet.

Det kan konkluderes med at det ikke ser ut til å være forskjell i søvnkvalitet og helserelatert livskvalitet mellom behandlingsgruppene etter 12 måneder med CPAP- og MAS-behandling, til tross for stor forskjell i antall pustestans ved behandling. CPAP er fortsatt førstevalg ved behandling av ikke-alvorlig OSA, men effekten på pasient-rapportert søvnkvalitet og helserelatert livskvalitet sammen med god behandlingsetterlevelse tilsier at MAS burde være et tilgjengelig behandlingsalternativ til CPAP. Det kan også konkluderes med at tungestørrelse i henhold til Friedman skår ikke ser ut til å forutsi etterlevelse og effekt av CPAP- og MAS-behandling hos pasienter med ikke-alvorlig OSA.

1 Introduction

1.1 Classification of sleep apnea

Sleep apnea is a collective term for disorders characterized by abnormal breathing or breathing cessation during sleep. The American Academy of Sleep Medicine has categorized sleep-related breathing disorders into obstructive sleep apnea (OSA) including upper airway resistance syndrome, central sleep apnea, sleep-related hypoventilation disorders, sleep-related hypoxemia disorders, and isolated symptoms and normal variants of respiration during sleep (American Academy of Sleep Medicine, 2014). These sleep related conditions frequently overlap. Patients having OSA may thus experience central apnea events and vice versa. Nevertheless, the disorder is classified as OSA providing most of the apnea events are obstructive. Sleep disorders other than OSA in adults will not be discussed in depth in this thesis.

The severity of OSA is defined by the Apnea-Hypopnea-Index (AHI), describing the average number of apnea- and hypopnea-events per hour during sleep. Apnea events are defined as ≥ 90% reduction in respiratory flow lasting ≥ 10 seconds. Hypopnea events are defined as ≥ 30% reduction in respiratory flow lasting ≥ 10 seconds combined with a change in sleep stage (arousal) or ≥ 3% drop in peripheral blood oxygen saturation (SpO_2) from baseline (Berry et al., 2012). In the international classification of sleep disorders, version 3 (ICSD-3), OSA is defined as AHI ≥ 5 combined with associated symptoms of OSA, or AHI ≥ 15 with or without associated symptoms (American Academy of Sleep Medicine, 2014). In 2005, version 2 of the international classification of sleep disorders abandoned the requirement for all patients to have symptoms associated with OSA (American Academy of Sleep Medicine, 2005). Consequently, the name of the disorder was changed from “obstructive sleep apnea syndrome” to OSA. However, the OSA severity is still divided into three categories based on AHI (Table 1), as described by an American Academy of Sleep Medicine Task Force in 1999 (American Academy of Sleep Medicine., 1999).

Table 1 Grading of obstructive sleep apnea (OSA) severity.

Severity	*Apnea-Hypopnea-Index (AHI)*
Mild OSA	AHI ≥ 5 < 15
Moderate OSA	AHI ≥ 15 < 30
Severe OSA	AHI ≥ 30

1.2 Epidemiology

The Akershus Sleep Apnea Project (2006-2008) estimated the total prevalence of OSA at 16% in a Norwegian population aged 30-65. Among these, 50% were estimated to be mild cases of OSA (Hrubos-Strom et al., 2011). This estimate is within the range of international prevalence studies varying from 9 % to 38 % in the general adult population (Senaratna et al., 2017). OSA seems to be approximately twice as prevalent in middle-aged men compared to women, but with increasing age, the sex differences tend to diminish due to higher OSA prevalence in postmenopausal women (American Academy of Sleep Medicine, 2014, Franklin et al., 2013, Senaratna et al., 2017). Overall, OSA prevalence increase with increasing age and increasing body mass index (BMI) (Beiske and Stavem, 2018, Gottlieb and Punjabi, 2020).

1.3 Pathophysiology and comorbidities associated with obstructive sleep apnea

Obstructive apnea- and hypopnea events arise from a soft tissue collapse in the upper airways, typically in the velo- and oropharyngeal region (Ryan and Bradley, 2005). These events completely or partially block the airflow during inspiration. The mechanisms behind collapsing airways vary between patients, but the cross-section and possibly the shape of the pharyngeal lumen play an essential role (Gottlieb and Punjabi, 2020). Reduced patency in the upper airways increases the negative intraluminal air pressure during inspiration. In OSA patients, the magnitude of this negative airway pressure reaches the critical closing pressure, i.e., the pressure where the soft tissues can no longer withstand a collapse, typically in the order of -5 cm H_2O (Dempsey et al., 2010, White, 2005). When awake, the soft tissue collapse is prevented by pharyngeal dilator muscle activity, which keeps the airways patent beyond the critical closing pressure. However, during sleep and especially in stage R sleep, this muscle activity is minimal, allowing apnea- and hypopnea events to occur (Leung et al., 2012, Ryan and Bradley, 2005, White, 2005).

Apnea- and hypopnea events usually last 10-50 seconds but can in some cases last more than a minute (Leppanen et al., 2017). During this time the O_2-levels drop, and CO_2-levels in the blood rises. With the changes in O_2- and CO_2-levels, mucosal mechanoreceptor stimulation and changes in lung volume trigger an increased pharyngeal muscle tone, ending the apnea- or hypopnea event. This increased muscle activity is frequently accompanied with an arousal, which disrupts sleep and is thought to be detrimental to sleep quality (Eckert and Malhotra, 2008, Leung et al., 2012, Ryan and Bradley, 2005).

1.3.1 Etiology

The etiological factors of OSA can be split into two categories: 1) anatomical factors, affecting the cross-section and shape of the pharyngeal lumen, and 2) non-anatomical factors, concerning factors other than the physical size of the upper airways. Some commonly acknowledged factors predisposing to OSA are listed in Table 2.

Table 2 Selection of factors predisposing to OSA, no specific order.

Anatomical factors	*Non-anatomical factors*
Retrognath mandible	High age
Small palatal height and width	High loop gain
Inferior hyoid bone position	Caudal traction forces on the airways
Nasal obstructions	Smaller lung volume
Increased volume of adipose tissues	Allergic rhinitis
Enlarged adenoids and tonsils	More type II muscle fibers in the tongue
Enlarged tongue	High testosterone levels or menopause
Edema in the pharyngeal walls	Sedative drugs or alcohol

A small or retrognath mandible, small palatal height and width, and inferior hyoid bone position are commonly found skeletal restrictions that directly affect the size of the pharyngeal lumen (Avci et al., 2019, Barrera et al., 2017, Leung et al., 2012, Ryan and Bradley, 2005, Saboisky et al., 2009). Narrowing of the nasal- and nasopharyngeal lumen from bony- and soft tissues may contribute to a more negative intraluminal pressure during inspiration and promote mouth breathing. Thus, predisposing to pharyngeal collapsibility (Eckert and Malhotra, 2008, Ryan and Bradley, 2005), which is indirectly observed through nasal characteristics in OSA patients (Barrera et al., 2017, Leung et al., 2012, Moxness et al., 2017, Varendh et al., 2018). Regardless of the skeletal features, an enlarged soft tissue volume in the pharyngeal region contributes to narrowing of the pharyngeal lumen. More adipose tissues, enlarged adenoids, enlarged palatal- and lingual tonsils, enlarged tongue or macroglossia, and edema in the soft palate and pharyngeal walls due to snoring and repeated soft tissue collapse, all give rise to increased pharyngeal soft tissue volumes (Barrera et al., 2017, Camacho et al., 2016, Eckert and Malhotra, 2008, Friedman et al., 1999, Jara and Weaver, 2018, Leung et al., 2012, Ryan and Bradley, 2005, Saboisky et al., 2009). The way bony restrictions and soft tissue volumes affect the pharyngeal lumen is illustrated in Figure 1.

Non-anatomical factors such as decreased activity in pharyngeal dilator muscles, higher representation of glossal type II muscle fibers, less rigid para-pharyngeal soft tissues (increasing age and caudal traction forces on the airways), smaller lung volume (obesity), ventilatory instability (high loop gain), hormonal changes (menopause), male gender (high testosterone levels), allergic rhinitis, and use of sedative drugs and alcohol, all increase the risk of developing OSA (American Academy of Sleep Medicine, 2014, Eckert and Malhotra, 2008, Leung et al., 2012, Liu et al., 2020, Saboisky et al., 2009).

Various combinations of anatomical and non-anatomical factors are found in each OSA patient, influenced and determined by age, gender, ethnicity, genetics, and associated comorbidities such as metabolic syndrome, coronary heart disease, chronic obstructive pulmonary disease, neuro-muscular disorders, hypothyroidism, renal failure, and Down's syndrome (American Academy of Sleep Medicine, 2014, Lavigne et al., 2009, Leung et al., 2012).

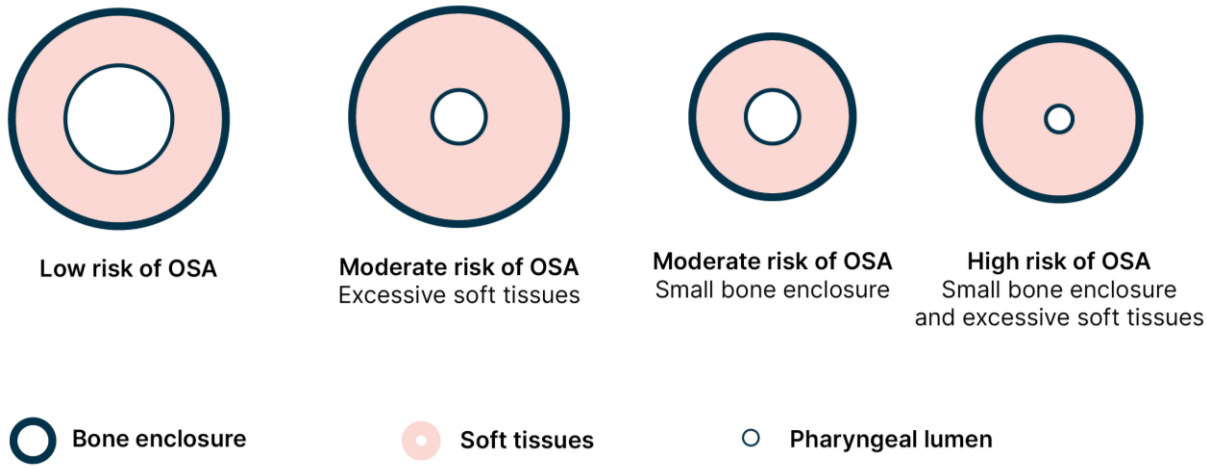

Figure 1 The way hard and soft tissues affect the pharyngeal lumen size. Modified from Watanabe et al. (2002). Illustration by Brett Guise, TkMidt.

1.3.2 Associated symptoms

Symptoms of OSA span from none through unspecific symptoms associated with poor sleep quality to very specific symptoms of pharyngeal soft tissue collapse. A selection of typical symptoms of OSA is presented in Table 3. The most predictive symptom of OSA is witnessed obstructive apnea events, most often observed by a bed partner, but may also manifest as waking up during nocturnal choking (Gottlieb and Punjabi, 2020). Snoring and excessive daytime sleepiness may be the most universally presented symptoms in OSA patients. Although the majority of OSA patients experience snoring and excessive daytime sleepiness, both symptoms have poor sensitivity since they are much more prevalent than OSA (Arnardottir et al., 2016). Unrefreshing sleep and poor sleep quality may be symptoms of OSA, but may as well be a symptom of depression (Douglas et al., 2013, Kjelsberg et al., 2005, Saunamaki and Jehkonen,

2007) or other sleep disorders such as insomnia, sleep-related movement disorders, circadian rhythm disruptions, or poor sleep hygiene (Lusic Kalcina et al., 2017, Schroeder and Gurenlian, 2019). Some sleep-related conditions are associated with OSA and can be considered symptoms of OSA themselves, although possible causality may be unclear. Examples of such conditions are sleep-related movement disorders, insomnia, nocturia, xerostomia, and nocturnal esophageal reflux (Bjorvatn et al., 2014, Gottlieb and Punjabi, 2020, Lavigne et al., 2009, Oksenberg et al., 2006).

Table 3 Common OSA symptoms, adapted from American Academy of Sleep Medicine (2014) and Lavigne et al. (2009).

Daytime sleepiness	Impaired concentration	Motor parasomnias
Depression and anxiety	Impotence	Nocturia
Esophageal reflux	Insomnia	Snoring
Fatigue	Morning headaches	Unrefreshing sleep
Hypertension resistant to treatment	Morning xerostomia	Witnessed apneas

1.3.3 Short- and long-term consequences

Compared to the general adult population, OSA patients report worse general health status on a group level (Beiske and Stavem, 2018, Fornas et al., 1995). This can be attributed to the OSA itself but may as well be a consequence of the various risk factors of OSA, or the medical conditions associated with OSA. It is a complex relationship between OSA and various comorbidities, since medical conditions associated with OSA are confounded by factors such as age, obesity, and gender. Nevertheless, several conditions are also independently related to OSA (Tveit et al., 2018). Conditions frequently associated with OSA are listed in Table 4.

Table 4 Selection of health conditions associated with untreated OSA

Cardiovascular	*Metabolic*	*Neurocognitive*	*Mental health and pain*
Hypertension	Obesity	Sleepiness	Anxiety
Coronary heart disease	Glucose intolerance	Reduced executive function	Depression
Cerebral stroke	Type 2 diabetes	Memory loss	Primary headaches
Arrhythmias	Systemic inflammation	Dementia	Oro-facial pain
Cardiovascular death		Fatal accidents	

A middle-aged population with daytime sleepiness, snoring and no/mild OSA is previously shown to likely develop/worsen OSA when left untreated for 10 years (Lindberg et al., 1999). This indicates that not only does the prevalence of OSA increase with age, but the severity of untreated OSA also increases with age. This is probably related to both age-dependent risk factors and comorbid conditions with bilateral associations with OSA, such as obesity and less rigid pharyngeal walls (Patel, 2015, Saboisky et al., 2009). Since patients with OSA experience frequent and sometimes prolonged periods of hypoxia, several mental and physical conditions are potentially modified by OSA (American Academy of Sleep Medicine, 2014, Dewan et al., 2015, Veasey and Rosen, 2019).

1.3.3.1 Cardiovascular conditions

Cardiovascular conditions such as hypertension (Peppard et al., 2000), stroke (Yaggi et al., 2005), coronary heart disease (Peker et al., 2006), and nocturnal arrhythmias (Mehra et al., 2006) are shown to be independently associated with OSA. Sleep fragmentation, sympathetic activation due to arousals, and intrathoracic pressure fluctuations due to apnea events may predispose for cardiovascular diseases. However, repeated episodes of nocturnal hypoxia may be the most important mechanism linking OSA to cardiovascular disease (Dewan et al., 2015). The nocturnal hypoxaemic burden is also shown to predict time to death in OSA patients with stable heart failure, which underline the importance of reducing the duration of nocturnal hypoxia through OSA treatment (Oldenburg et al., 2016). The impact on cardiovascular conditions is significantly contributing to the increased risk of all-cause mortality observed in patients with severe OSA (Gami et al., 2013, Ge et al., 2013, Marshall et al., 2008, Yaggi et al., 2005).

1.3.3.2 Metabolic disease

High BMI and obesity is a significant risk factor for developing and worsening OSA (Schwartz et al., 2008), but the association is likely to be bidirectional since OSA seems to worsen obesity. Moreover, OSA is considered an independent risk factor for glucose intolerance and type 2 diabetes (Botros et al., 2009, Ong et al., 2013, Patel, 2015). There are complex mechanisms behind the relationship between OSA and metabolic disease, but hypoxemia seems to be an important factor in glucose intolerance (Dewan et al., 2015). Hypoxemia related to OSA also seems to worsen the risk of cardiovascular mortality in patients with metabolic syndrome, suggesting that treatment of OSA is particularly important in obese patients (Drager et al., 2013).

1.3.3.3 Neurocognitive sequelae

Neurocognitive consequences from OSA span from daytime sleepiness to irreversible loss of memory. Daytime sleepiness is an obvious result of poor sleep quality associated with OSA but

may also be a result of hypoxia. Sleep fragmentation, intermittent hypoxia, and hormonal changes in OSA patients are believed to cause neurocognitive impairment, but the mechanisms are not fully understood (Dewan et al., 2015). Focal loss of grey matter and structural changes in the brain are shown in OSA patients, through neuroimaging (Lal et al., 2012). Daytime sleepiness may be effectively reversed through adequate OSA treatment. However, long-term sequelae such as an earlier onset of age-related dementia and faster progression of dementia in elders are suspected to be consequences associated with inadequately treated OSA, and severe OSA in particular (Dewan et al., 2015, Richards et al., 2019). A short-term risk with OSA is the reduced executive function, which impairs reaction time, planning and problem solving (Lavigne et al., 2009). This may be closely linked to daytime sleepiness and pose an increased risk of occupational or traffic accidents (George, 2007, Lindberg et al., 2001, Terán-Santos et al., 1999). The increased risk of accident may even contribute to the all-cause mortality in OSA patients.

1.3.3.4 Chronic pain

Patients with OSA are more likely to experience facial pain (Olmos, 2016), tension-type headache (Chiu et al., 2015), increased pain intensity, and lower pain tolerance (Athar et al., 2020, Charokopos et al., 2018). Although the causal relationship between OSA and headaches is somewhat elusive (Kristiansen et al., 2012, Russell et al., 2014), nocturnal hypoxia induces inflammatory pathways which may lead to hyperalgesia and poor pain tolerance. Sleep fragmentation on the other hand, is hypothesized to cause hypoalgesia, counteracting the effect of hypoxia regarding pain sensitivity in OSA patients (Charokopos et al., 2018). Besides independent associations between OSA features and pain, OSA is also associated with sleep-related movement disorders such as bruxism. Thus, OSA may aggravate orofacial pain related to bruxism and temporomandibular dysfunction (Olmos, 2016).

1.3.3.5 Mental health

A selection of psychiatric conditions may be associated with OSA, but the mechanism behind this is unclear. Some studies indicate a higher prevalence of depression and anxiety among OSA patients but increasing OSA severity does not correlate with increasing severities of these conditions (Bjornsdottir et al., 2016, Bjorvatn et al., 2017, Diaz and Brown, 2016, Douglas et al., 2013, Shapiro et al., 2014). Nevertheless, the total burden of OSA symptoms, which seems unrelated to OSA severity and the way the patient cope with OSA, may have an adverse effect on mental health (Arnardottir et al., 2016, Macey et al., 2010, Saunamaki and Jehkonen, 2007). Adverse effects on mental health may be associated with OSA patients reporting worse health-related quality of life (HRQoL) than the general population (Beiske and Stavem, 2018, Lacasse et al., 2002, Lee et al., 2015).

1.3.3.6 Cancer

In vitro and animal studies have shown an association between sleep fragmentation, intermittent hypoxia, and accelerated tumor growth (Dewan et al., 2015, Owens et al., 2016). These findings are not yet found in humans, but epidemiological studies have shown a higher cancer incidence and cancer mortality among OSA patients compared to the general population (Martinez-Garcia et al., 2014, Nieto et al., 2012). However, literature studies have so far not presented evidence for an independent association between OSA and increased cancer risk and mortality (Martinez-Garcia et al., 2016, Owens et al., 2016, Zhang et al., 2017).

1.4 Treatment alternatives for obstructive sleep apnea

1.4.1 Continuous Positive Airway Pressure

Since first described in 1981, the continuous positive airway pressure (CPAP) has been the primary treatment alternative for OSA (Gottlieb and Punjabi, 2020, Patil et al., 2019b, Sullivan et al., 1981). The CPAP creates a pneumatic splint in the airways, which reduces the intraluminal negative pressure responsible for soft tissue collapses in OSA. The pressure required to maintain airway patency vary between patients but is automatically titrated in modern CPAP devices for optimal effect with minimal discomfort (Patil et al., 2019a). The positive pressure is generated by a compressor unit and is delivered to the patient via a hose and mask (Figure 2). The mask covers the nose or both nose and mouth (Sullivan et al., 1981). The CPAP is highly effective at reducing the AHI and improving nocturnal hypoxia in most patients regardless of the OSA severity (Giles et al., 2006, Patil et al., 2019b). In OSA treatment, CPAP is known to improve daytime sleepiness, executive function, the risk of accidents, HRQoL, hypertension, and possibly cardiovascular- and all-cause mortality (Ge et al., 2013, Gottlieb and Punjabi, 2020, Kuhn et al., 2017, Lisan et al., 2019, Qaseem et al., 2013, Patil et al., 2019b).

Figure 2 Demonstration of a CPAP device.
Photo by Dr. Vegard Bugten, St. Olavs Hospital.

The challenge with CPAP treatment is establishing and maintaining good compliance to treatment (Crawford et al., 2014, Weaver and Grunstein, 2008). Suboptimal compliance reduces the effectiveness of the CPAP treatment and may be responsible for conflicting findings regarding health benefits associated with CPAP (McEvoy et al., 2016, Patil et al., 2019b, Weaver et al., 2007). The OSA severity and thus the risk of sequelae from OSA immediately worsen after CPAP withdrawal and do probably return to baseline levels after prolonged time without CPAP treatment (Phillips et al., 2007, Sutherland and Cistulli, 2019, Young et al., 2013). This demonstrates that CPAP is only effective at treating OSA when it is used. Despite the commonly used cut-off for adequate compliance being 4 hours usage, at least 70% of nights on average (Kribbs et al., 1993, Jacobsen et al., 2017), the CPAP should be used all night, every night for optimal efficacy (Crawford et al., 2014, Patil et al., 2019b). More symptoms and more severe OSA are associated with better compliance to CPAP treatment (Jacobsen et al., 2017, Madbouly et al., 2014). The number and severity of side effects associated with CPAP, such as a dry or congested nose, mask leaks, eye irritation, sleep fragmentation, pressure on the face, problems with spontaneous intimacy with the bed partner, claustrophobia, and noise from the CPAP device are associated with poor CPAP compliance (Olsen et al., 2008, Giles et al., 2006, Schwartz et al., 2018). CPAP equipment that minimizes side effects are therefore advised, thus the choice of mask type and CPAP humidification should be adapted to the individual patient's preference. Manually or automatically CPAP titration does not seem to impact the compliance (Patil et al., 2019a).

1.4.1.1 Bilevel Positive Airway Pressure

In the treatment of central sleep apnea, obesity hypoventilation syndrome, or OSA combined with respiratory diseases such as asthma or chronic obstructive pulmonary disorder, the use of bilevel positive airway pressure (BPAP) may be preferred over CPAP (Aurora et al., 2012, Kushida et al., 2006a). In contrast to CPAP, the BPAP device reduces the positive airway pressure during expiration. This is beneficial for patients with reduced lung capacity and apnea/hypopnea events with reduced respiratory effort. Moreover, the BPAP may also be effective in patients with congestive heart failure combined with central sleep apnea who are unsuccessfully treated with CPAP (Aurora et al., 2012). However, the BPAP device is more expensive than the CPAP device and is regarded as a second-line treatment in cases where CPAP are expected to provide adequate treatment. There is no evidence suggesting that BPAP is superior to CPAP in routine OSA treatment in patients without daytime hypercapnia or restrictive lung diseases (Patil et al., 2019b). Nevertheless, since the BPAP device allows higher positive pressures than the CPAP device, BPAP may be attempted in OSA patients requiring inspiratory positive pressures exceeding 20 cm H_2O (Patil et al., 2019a).

1.4.2 Mandibular advancement splints

Intraoral devices in OSA treatment were first described in case-series during the 1980s (Schmidt-Nowara et al., 1995). Since then, the extent of research on intraoral devices, and the mandibular advancement splint (MAS) in particular, have increased rapidly alongside with its popularity in OSA treatment (Ferguson et al., 2006). The MAS consist of occlusal splints placed in the upper and lower jaw respectively, which reposition and fixate the mandible in an anterior position (Figure 3). The mechanisms by which the MAS improves OSA are not fully elucidated, but the forward shifting of the mandible increases the velopharyngeal lumen and bring the hyoid bone forward, thus stabilizing the airways and reducing collapsibility of the pharyngeal walls (Chan et al., 2010, Marklund et al., 2012, Serra-Torres et al., 2016). Activation of pharyngeal dilator muscles and the genioglossal musculature when wearing a MAS may also improve airway collapsibility (Heidsieck et al., 2016, Serra-Torres et al., 2016), but the clinical significance of this effect is not clear (Bamagoos et al., 2019, Sutherland and Cistulli, 2019).

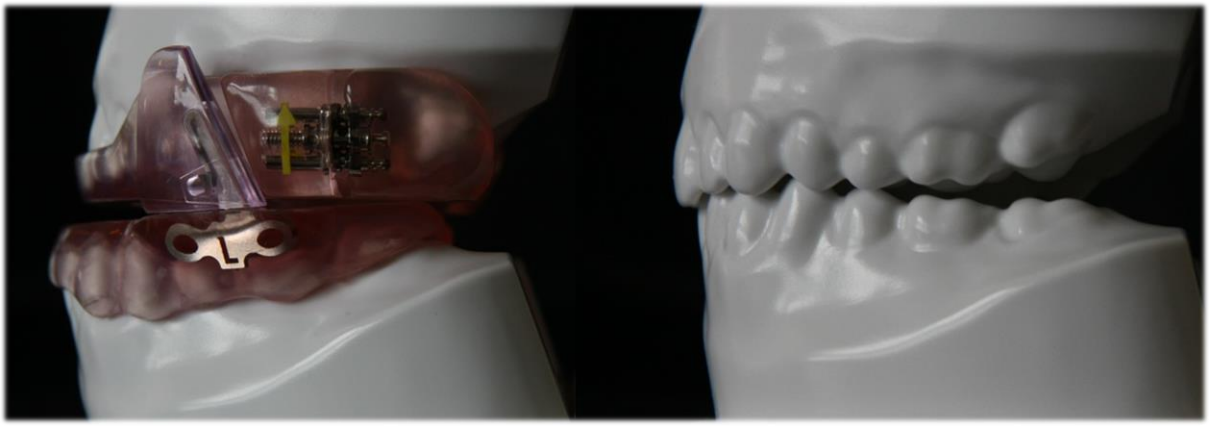

Figure 3 Mandibular repositioning from a mandibular advancement splint.

The MAS share some similarities with a simple occlusal stabilizing splint, but the latter is ineffective in OSA treatment since occlusal stabilizing splints do not advance the mandible (Ahrens et al., 2011, Marklund et al., 2012). Dose-dependent efficacy of the mandibular advancement has been demonstrated (Aarab et al., 2010, Bamagoos et al., 2019), but the optimal mandibular position in MAS treatment may not be the maximally protruded position in all patients (Sutherland and Cistulli, 2019). More mandibular advancement is associated with more adverse effects in MAS treatment (Aarab et al., 2010), which may lead to poor compliance to treatment (Mullane and Loke, 2019). However, typical adverse effects such as pressure on teeth, temporomandibular joint and muscle discomfort, dry mouth, and excessive salivation, are usually mild and transient (Doff et al., 2013b, Schwartz et al., 2018, Sutherland et al., 2014). Patients with exaggerated gag reflex may however be MAS intolerant. The most severe long-term side effect in MAS treatment is related to bite changes, which in most patients are clinically insignificant (Battagel and Kotecha, 2005, Marklund, 2017, Serra-Torres et al., 2016).

All MAS either belong to a mono-block or twin-block design. In the mono-block design, the two splints for the upper and lower jaws are fused into one piece and the mandibular protrusion usually cannot be adjusted chair-side. The twin-block design consists of two separate splints, which allow limited movement of the mandible when in place. Most modern twin-block MAS are fitted with mechanisms for chair-side titration and are regarded as more comfortable to wear compared to older mono-block designs. The ability to open the mouth when wearing the MAS may reduce the MAS efficacy, but little is known about differences in efficacy between the various custom-made MAS designs (Marklund, 2017).

MAS treatment reduces AHI and improves nocturnal hypoxia (Lim et al., 2006, Qaseem et al., 2013), but patients with severe OSA are less likely to achieve adequate AHI reduction by using a MAS (Marklund et al., 2012). Indeed, MAS treatment is less predictable and often less effective at reducing AHI compared to CPAP in both non-severe and severe OSA. MAS is thus considered a second-line alternative in OSA treatment (Marklund, 2017, Ramar et al., 2015, Gagnadoux et al., 2009, Doff et al., 2013b, Hoekema et al., 2008). However, MAS treatment improves daytime sleepiness, the risk of accidents, HRQoL, and cardiovascular health including hypertension, at a level comparable to CPAP treatment (Andren et al., 2013, Bratton et al., 2015, de Vries et al., 2018, Doff et al., 2013b, Iftikhar et al., 2013, Kuhn et al., 2017, Phillips et al., 2013, Schwartz et al., 2018, Sharples et al., 2016, Sutherland et al., 2015). Better compliance to MAS treatment than CPAP treatment is the likely mechanism behind the comparable health outcomes in the two treatments, despite more residual AHI in MAS treatment (Iftikhar et al., 2017, Sutherland and Cistulli, 2019). General compliance to MAS treatment is superior to CPAP treatment (Schwartz et al., 2018), and patients prefer MAS over CPAP in most crossover trials (Gagnadoux et al., 2009, Phillips et al., 2013, Sutherland et al., 2015). The overall effectiveness of MAS treatment is therefore comparable to CPAP treatment at group level, particularly in non-severe OSA patients. MAS is regarded a viable alternative to CPAP treatment in non-severe OSA and severe OSA when patients are non-compliant to CPAP (Doff et al., 2013b, Marklund, 2017, Ramar et al., 2015, Sutherland et al., 2015).

1.4.2.1 Non-customized splints and tongue-stabilizing devices

Although MAS is the prevailing oral appliance used in OSA treatment, other oral appliances exist, such as non-customized splints and tongue stabilizing devices. In contrast to customized devices manufactured by dental technicians, a non-customized splint is adapted by the patient at home, known as a “boil-and-bite splint”. These devices are cheap and may be more accessible than MAS for some patients, but they are largely non-effective at improving OSA, and are not recommended for treating OSA (Friedman et al., 2012, Ngiam et al., 2013, Serra-Torres et al., 2016).

Since MAS require dental support for retention, the tongue-stabilizing device has been proposed as an alternative for edentulous patients. A tongue-stabilizing device anteriorly repositions the tongue and fixates it using suction, thus preventing the tongue from blocking the airway. Few studies have investigated the effect of tongue-stabilizing devices, but a small crossover randomized controlled trial (RCT) showed similar AHI improvement compared to MAS. However, the treatment period in that RCT was 1 week, and the compliance to treatment was poor, suggesting that the tongue-stabilizing device is not a viable alternative to the MAS for most patients (Deane et al., 2009).

1.4.3 Surgical interventions

Several surgical procedures have been established as treatment options for OSA, but most of them have limited efficacy or is only suitable for specific subgroups of adult OSA patients (Camacho et al., 2013). Surgical interventions are however considered the primary choice of treatment in most pediatric OSA patients (Cielo and Gungor, 2016, Venekamp et al., 2015). In most children and adolescents with sleep-disordered breathing, anatomical obstructions from enlarged tonsils and adenoids are the predominant pathophysiological mechanism (Mitchell et al., 2019). Thus, surgical removal of the tissues obstructing the airway may cure OSA in many pediatric patients (Pereira et al., 2016). Some noteworthy surgical treatment alternatives in patients with OSA are briefly presented next.

1.4.3.1 Tracheostomy

By bypassing the airway regions susceptible to obstructive events, tracheostomy is a highly effective OSA treatment. Prior to the introduction of CPAP treatment, tracheostomy was the only highly effective treatment for severe OSA. However, due to the morbid nature of tracheostomy, the procedure was limited to patients with life-threatening complications to OSA and is now only used as a last resort in OSA treatment (Camacho et al., 2013, Gottlieb and Punjabi, 2020, Sullivan et al., 1981).

1.4.3.2 Uvulopalatopharyngoplasty and tonsillectomy

Since the 1960s, surgical reduction of soft tissues in the upper airways have been used in the treatment of snoring, but in 1981, the uvulopalatopharyngoplasty (UPPP) was introduced as a surgical treatment of OSA (Camacho et al., 2013, Rosvall and Chin, 2017, Fujita et al., 1981). The UPPP seek to enlarge the velo- and oropharyngeal lumen by removal of soft tissues in the soft palate, including the uvula and the palatal tonsils. When performed exclusively, or as a part of a multilevel surgery approach, UPPP may be effective in reducing OSA severity and improving daytime sleepiness in selected groups of OSA patients (Friedman et al., 2009). However, in

patients where excessive soft tissues in the velopharyngeal region are not the primary cause of OSA, UPPP is usually ineffective as a sole treatment approach (Franklin et al., 2009, Friedman et al., 2002). Multilevel surgery, where UPPP is performed in combination e.g., with tongue base reduction or nasal surgery, may thus be a better surgical treatment approach in many OSA patients (Friedman et al., 2004, Mulholland et al., 2019). Regardless of its use as a single or multilevel surgical approach, UPPP is an invasive procedure associated with a multitude of adverse effects, making it suitable only as a second-line treatment in most patients (Camacho et al., 2013, Sutherland et al., 2018, Franklin et al., 2009).

In patients who do benefit from UPPP, a significant part of the treatment success seems to be attributed to the removal of large tonsils (Friedman et al., 2004, Jara and Weaver, 2018, Stuck et al., 2018). Indeed, patients with large palatal tonsils seem to benefit from tonsillectomy without resection of the uvula and posterior soft palate (Smith et al., 2017). Hence, tonsillectomy in selected patients might be regarded a less invasive surgical alternative to UPPP for treating non-severe OSA or at least for improving CPAP compliance in OSA patients (Camacho et al., 2016, Park et al., 2017).

1.4.3.3 Maxillomandibular advancement surgery

Anterior repositioning of the maxilla and mandible following a Le Fort I osteotomy and sagittal split mandibular osteotomy may improve AHI in more than 80% of OSA patients (Sutherland et al., 2018, Zaghi et al., 2016). Nevertheless, the irreversible and invasive nature of this procedure limits the use to a second-line treatment for a limited selection of OSA patients. Serious postoperative complications are rare, but patients are on average hospitalized for 3.5 days after surgery, and all patients experience a temporary injury of facial nerves (Zaghi et al., 2016). Orthognathic surgery also affects facial aesthetics in most patients (John et al., 2018). However, maxillomandibular advancement surgery may be considered in patients with severe OSA and retrognath mandible, who are unable to use CPAP and are not eligible for soft tissue surgery (Sutherland et al., 2018). The treatment mechanism resembles that of MAS treatment, thus treatment success in terms of achieving AHI < 5 is more likely in patients with baseline AHI < 30. Nevertheless, patients with more severe baseline OSA seem to benefit the most from orthognathic surgery (Zaghi et al., 2016).

1.4.3.4 Nasal surgery

Increased nasal resistance and nasal obstructions worsen the negative intraluminal pressure in the pharyngeal region, thus worsening OSA severity (Leung et al., 2012). Nasal obstructions are also shown to reduce CPAP acceptance and compliance (Weaver and Grunstein, 2008, Sawyer et al.,

2011). Nasal surgery, preferably including inferior turbinate reduction, may therefore be performed to reduce OSA severity, and improve both CPAP efficacy and compliance in patients with increased nasal resistance (Friedman et al., 2009, Moxness and Nordgard, 2014, Park et al., 2014).

1.4.4 Weight loss and physical exercise

Since obesity is a well-known risk factor for OSA, all patients being overweight and obese are recommended to lose weight (Ng et al., 2015, Patel and Mehra, 2015). Besides, CPAP treatment seems to increase the risk of weight gain (Drager et al., 2015), and increasing BMI reduces the chance of effective OSA treatment with MAS (Marklund et al., 2004, Ngiam et al., 2013). This further emphasizes the importance of weight loss in OSA therapy. Dietary weight loss is shown to reduce AHI but may not be as effective as CPAP and MAS treatment on a group level. Bariatric surgery in morbidly obese patients may improve OSA more and may have better long-term results than dietary weight loss but may not be a suitable treatment alternative in all cases (Ashrafian et al., 2015, Fredheim et al., 2013, Patel, 2015). One obvious mechanism linking weight loss to OSA improvement is the reduction of pharyngeal soft tissue volumes. However, as previously mentioned, the relationship between obesity, OSA and the metabolic syndrome is complex and possibly bidirectional (Ong et al., 2013, Patel, 2015).

Independent of weight loss, exercise training seems to significantly improve OSA in respect to daytime sleepiness, sleep quality, and reduced AHI levels (Ackel-D'Elia et al., 2012, Awad et al., 2012, Karlsen et al., 2016, Kline et al., 2011). Exercise training may even be as effective as MAS treatment at a group level (Iftikhar et al., 2017). Although the mechanisms behind this are still somewhat unknown, changes in pharyngeal muscle tonus, redistribution of bodily fat depositions, improved lung volumes, change in arousal threshold, and improved sleep-architecture are possible mechanisms for OSA improvement after exercise training (Awad et al., 2012, Iftikhar et al., 2017). Regardless of the treatment mechanisms, changes in lifestyle promoting more physical exercise and weight loss should be supplementary to other treatments in all overweight OSA patients (Gottlieb and Punjabi, 2020, Iftikhar et al., 2017).

1.5 Compliance to obstructive sleep apnea treatment

The efficacy of both CPAP and MAS treatment are fully dependent on patient compliance, but compliance is generally sub-optimal in both treatments at group level (Rotenberg et al., 2016, Sharples et al., 2016, Sutherland et al., 2014). In the quest to improve OSA treatment, studying compliance to treatment and patient variables related to compliance is essential (Kushida et al., 2006b, Schwartz et al., 2018). However, compliance is an intricate and multifaceted subject which

involve both psychological, behavioural, social, as well as biomedical and anatomical aspects (Crawford et al., 2014, Olsen et al., 2008). Evaluating treatment compliance in OSA treatment is not equivalent with studying compliance as a biopsychosocial phenomenon and concept. Nevertheless, when interpreting compliance data and studying predictors for treatment compliance, the multifaceted nature of compliance should be kept in mind. Specific biomedical or behavioural variables studied in relation to treatment compliance should be considered components of a wider, holistic approach to treatment compliance (Crawford et al., 2014).

In this thesis, compliance to treatment is evaluated in terms of time spent actively using the assigned treatment device when sleeping, in relation to the total time sleeping. Thus, treatment compliance in this context reflects on the physical and psychological ability to use a given treatment device, and not the willingness or desire to use the treatment device. The term compliance to treatment in this thesis includes initial acceptance to treatment and the adherence to the user protocol of the assigned treatment device.

1.6 Sleep quality and health-related quality of life

Sleep fragmentation is a signature feature in OSA, leading to less efficient sleep and poor sleep quality (American Academy of Sleep Medicine, 2014). OSA patients assessed by polysomnography (PSG) shows more superficial sleep (stage N1), less rapid eye movements (stage R) and slow-wave sleep (stage N3) and experience more shifts between sleep stages than healthy individuals do (Loredo et al., 2006, Shahveisi et al., 2018). This change in sleep architecture may be associated with OSA patients reporting poor subjective sleep quality (Lusic Kalcina et al., 2017) and in many cases excessive daytime sleepiness (Bjorvatn et al., 2015). Self-reported sleep quality and excessive daytime sleepiness are not necessarily associated with OSA severity based on AHI (Arnardottir et al., 2016, Lusic Kalcina et al., 2017), but sleep quality seems to be associated with short-term compliance to CPAP treatment (Somiah et al., 2012). Moreover, treatment with CPAP seems to restore normal sleep architecture and improve polysomnographic sleep quality (Loredo et al., 2006, Quan et al., 2018). The term “sleep quality” may have several different meanings, and the diverse use of the term is a challenge in sleep research (Krystal and Edinger, 2008). However, “sleep quality” may in general refer to either measured “objective” or self-reported “subjective” sleep quality. In this thesis, the term “sleep quality” encompass self-reported sleep efficiency and the feeling of refreshing sleep.

Subjective sleep quality may affect HRQoL (Kang et al., 2017) and the well documented negative impact from OSA on HRQoL is probably independent of OSA severity (Beiske and Stavem, 2018, Lacasse et al., 2002, Macey et al., 2010). Especially in patients with depression and anxiety,

the HRQoL may be impaired disproportionally to OSA severity (Bjorvatn et al., 2017, Castro et al., 2013, Lee et al., 2015). Nevertheless, both CPAP and MAS treatment are shown to improve HRQoL, or at least aspects of HRQoL in OSA patients (Gagnadoux et al., 2009, Kuhn et al., 2017, Qaseem et al., 2013, Phillips et al., 2013).

There is no consensus on how to define HRQoL, or how it should be measured in OSA (Karimi and Brazier, 2016, Lacasse et al., 2002). HRQoL is generally considered a subcategory of the wider term "quality of life", which is defined by the World Health Organization as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (World Health Organization. Division of Mental and Prevention of Substance, 1997). Thus, the term "quality of life" includes subjects such as politics, economy, and living conditions, in addition to physical and mental health. Narrowing the definition is therefore useful when studying quality of life in the context of a specific health issue. The term HRQoL is commonly used for describing daily functioning in the light of perceived physical, mental, and social wellbeing (Karimi and Brazier, 2016). Although only one of several possible definitions of HRQoL, this is the definition used when discussing HRQoL in this thesis.

1.7 Thesis questions and aims

The poor compliance to CPAP treatment among patients with non-severe OSA is challenging the concept of CPAP being the gold standard treatment for all OSA patients (Ramar et al., 2015, Rotenberg et al., 2016, Sutherland et al., 2015). Combined with an increasing amount of literature questioning the use of AHI as a sole measurement of OSA severity and measure of treatment success (Arnardottir et al., 2016, Azarbarzin et al., 2019, Kulkas et al., 2017, Macey et al., 2010, Oldenburg et al., 2016, Patel and Mehra, 2015, Schwartz et al., 2018), MAS is becoming an increasingly relevant treatment option in non-severe OSA. Indeed, MAS treatment is included as a treatment option for OSA patients unable to use CPAP in Norwegian hospital trusts (Skår et al., 2015). Unfortunately, there is still no convenient and reliable clinical method for predicting treatment success and compliance in CPAP and MAS treatment (Marklund, 2017, Ngiam et al., 2013, Okuno et al., 2016, Sawyer et al., 2011, Sutherland and Cistulli, 2019, Vroegop et al., 2013). More precisely, how to identify those patients who will benefit the most from CPAP or MAS treatment respectively is still unknown (Gulati et al., 2017, Patil et al., 2019b, Saffer et al., 2015, Sutherland et al., 2018). Identifying patient characteristics that predict treatment outcome in non-severe OSA patients is necessary to enable tailored treatment which facilitate treatment success (Eastwood et al., 2010, Engstrøm et al., 2015, Sutherland et al., 2018, Ye et al., 2014).

In cases with small velo- and oropharyngeal volume due to tongue position, the AHI is likely to be high, which in turn is associated with better compliance to CPAP treatment (Friedman et al., 2013, Jacobsen et al., 2017). In MAS treatment, the ability to increase the velo- and oropharyngeal lumen is a key mechanism for achieving treatment success (Bamagoos et al., 2019, Marklund et al., 2012). However, no studies seem to have investigated the direct association between the tongue position in the oral cavity and the compliance to CPAP and MAS treatment. Neither is it known if tongue position is suited as a clinical predictor of treatment success (Sutherland and Cistulli, 2019).

The attitude and motivation to treatment are thought to be important for treatment compliance (Askland et al., 2020). It is thus plausible that the impact on sleep quality and/or HRQoL from treatment is associated with compliance and treatment success (Olsen et al., 2008, Sutherland et al., 2014). Nevertheless, self-reported sleep quality is not studied in a general non-severe OSA population with CPAP and MAS treatment (Lusic Kalcina et al., 2017, El-Solh et al., 2017). Neither is the relationship between self-reported sleep quality and HRQoL extensively studied in CPAP and MAS treated patients (Kang et al., 2017). Hence, little is known about the correlation between self-reported sleep quality and HRQoL, and its relation to compliance and treatment success in a non-severe OSA population.

1.7.1 Overall aim

The overall aim of this clinical trial was to compare the treatment with CPAP to a twin-block MAS regarding efficacy, compliance to treatment and impact on self-reported sleep quality and HRQoL among patients with non-severe OSA.

1.7.2 Specific aims

1.7.2.1 Paper I

To compare self-reported sleep quality, treatment compliance and AHI after 4 months of treatment with MAS or CPAP in non-severe OSA.

1.7.2.2 Paper II

To investigate the association between Friedman score and both treatment compliance and AHI improvement in patients with non-severe OSA receiving CPAP or MAS treatment.

1.7.2.3 Paper III

To compare CPAP and MAS after 12 months of treatment in patients with non-severe OSA, in terms of their HRQoL and self-reported sleep quality, and to investigate the correlation between HRQoL and sleep quality.

2 Patients and methods

2.1 Study design

This thesis is based on the results from a two-centered parallel-arm RCT (Papers I, and III), and a prospective observational study in the clinical trial setting (Paper II). Patients were allocated to either CPAP or MAS treatment by block-randomization with 30 lots per block, per study site, and a 50/50 allocation ratio. The lots were made by paper and concealed in an opaque envelope at each study center. The randomization envelopes were made by one of the researchers in the project (TKSA). The RCT was not blinded due to the nature of the interventions.

2.2 Study locations and recruitment period

All patients in the RCT were recruited and treated in the cities Tromsø and Trondheim, Norway. Patients were residents of Troms and Finnmark County (except southern parts of Troms and eastern parts of Finnmark) in Northern Norway, and Trøndelag County (except the northernmost parts) in Mid-Norway (Figure 4). In total three hospitals screened and recruited patients to the trial: The University Hospital in Northern Norway in Tromsø, and St. Olavs and Aleris Hospitals in Trondheim. Aleris Hospital transferred eligible patients to St. Olavs Hospital for randomization and treatment. Thus, Aleris Hospital was not involved in the treatment and follow-up of patients in the trial. In total, 104 eligible patients were enrolled in the trial between October 2014 and February 2018 in Tromsø (n = 71), and between May 2017 and February 2018 in Trondheim (n = 33).

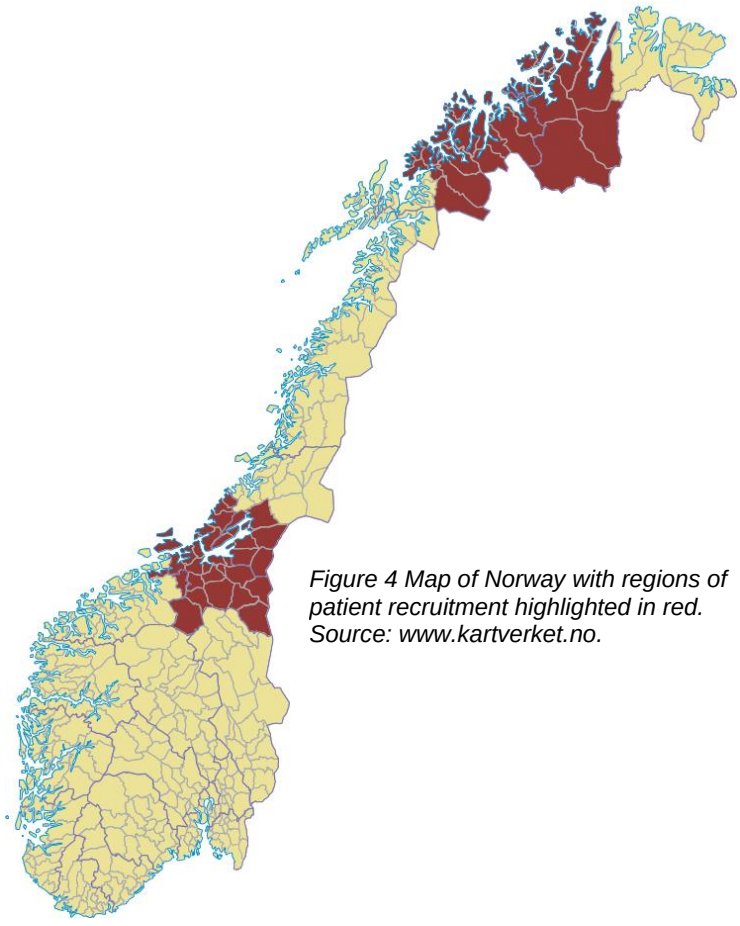

Figure 4 Map of Norway with regions of patient recruitment highlighted in red. Source: www.kartverket.no.

2.2.1 Eligibility criteria

Patients eligible for the trial were 20-75 years of age, had AHI between 10.0 and 29.9 accompanied by subjective symptoms of OSA. Furthermore, all patients had to be able to protrude

the mandible at least 5 millimeters, accept the random allocation to treatment, accept completing questionnaires and attending at the planned consultations and follow-ups. The exclusion criteria for participating were:

- Previous treatment with CPAP or MAS.
- Severe OSA (AHI ≥ 30).
- Primarily central sleep apnea.
- Pregnancy.
- Drug abuse.
- Daily use of sedative medication.
- Pre-existing severe psychiatric disorders or somatic health issues disqualifying or interfering with CPAP or MAS treatment.
- Disorders disqualifying CPAP or MAS treatment including.
    - Claustrophobia.
    - Exaggerated gag reflex.
    - Subjective signs of temporomandibular dysfunction (defined as considerable facial myalgia or arthralgia related to jaw movement).
    - Anatomical abnormalities in the nasal- or oral cavity disqualifying CPAP or MAS treatment including nasal obstructions or hypertrophic tonsils eligible for surgical correction.
    - Inadequate dental support for wearing MAS (< 10 teeth in the mandible).
    - Inadequate periodontal support (no tooth mobility > Miller grade I).
    - Health conditions where BPAP is regarded the primary choice of treatment.

The eligibility and exclusion criteria were assessed at the clinical examination of the patients referred for OSA screening and treatment (described in section 2.3.2).

2.2.2 Patient flow

All patients recruited to the RCT were referred from the primary health care with a suspected OSA diagnosis, for screening at the Ear-Nose-Throat (ENT) Departments at the hospitals involved in the trial. All patients were screened for OSA with home sleep apnea testing (HSAT) before an otorhinolaryngologist performed a medical examination of the patients. All patients who satisfied the eligibility criteria were then invited to participate in the trial and gave a written, informed consent to participate in the trial (Appendix 1). All patients completed a set of questionnaires providing patient-reported baseline data before drawing a lot, allocating them to either CPAP or MAS treatment. Patients had their respective treatment device adapted and were encouraged to use it all night, every night. Patients were called for follow-up visits 4 and 12 months after treatment initiation. At the follow-up visits, efficacy data were retrieved from the CPAP device and a new HSAT was performed in the MAS treatment group. All patients completed identical sets of questionnaires at the follow-up visits and received a personalized motivational talk to advocate optimal treatment compliance. Patients were welcomed to contact the ENT departments at any time during the trial if they had questions or problems regarding the treatment device. A schematic presentation of the patient flow in the RCT is shown in Figure 5.

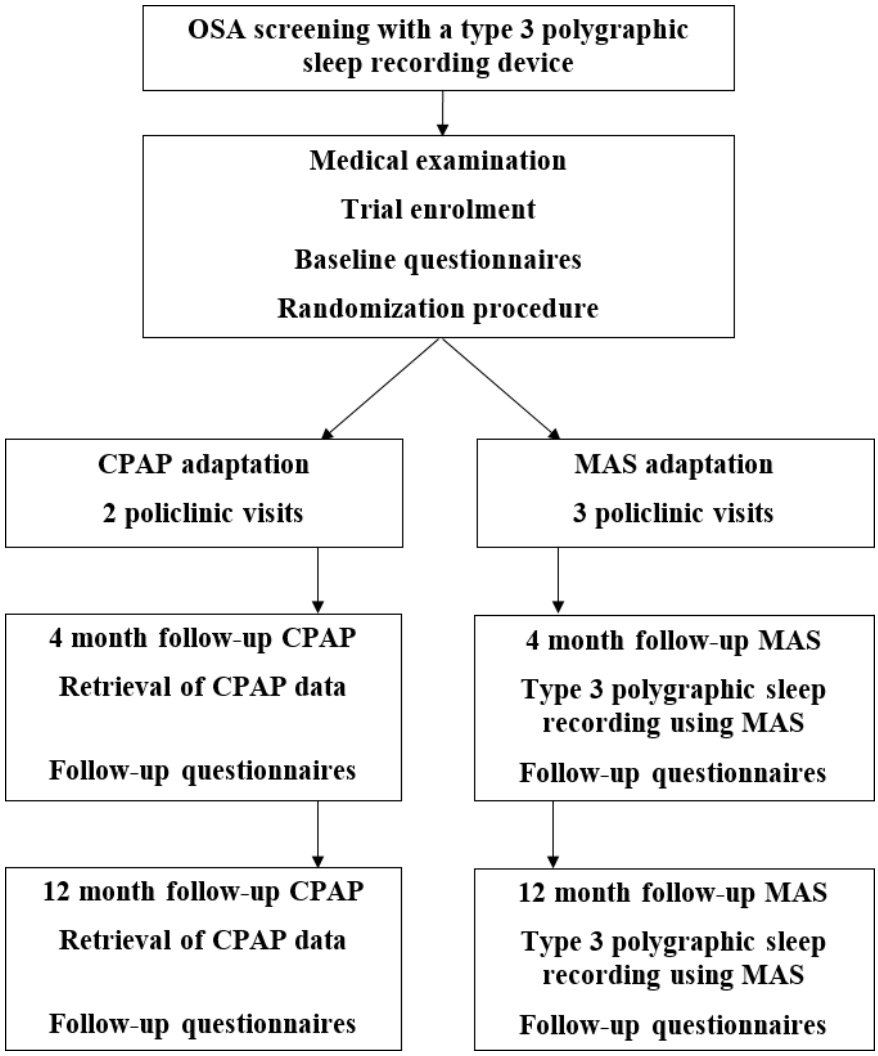

Figure 5 Flow diagram for patients enrolled in the trial.

2.3 Diagnostic process

2.3.1 Home sleep apnea testing

Screening for OSA in this RCT was performed in accordance with the common clinical practice established at the hospitals hosting the RCT. Patients referred from the primary health care to the ENT departments with the suspicion of primary OSA in Northern- and Mid-Norway are screened with an ambulatory type 3 polygraphic sleep recording device without using an oral thermistor (Embletta® or Nox T3™, ResMed Norway AS) (Skår et al., 2015). During the screening night, the patients sleep at home, or at a hotel, hence the term HSAT (Kapur et al., 2017). The OSA screening in this RCT recorded movement in the chest and abdomen (respiratory inductance plethysmography [RIP]), nasal airflow, snoring, bodily position, physical activity, heart rate and peripheral blood oxygen saturation (SpO_2%). The resultant sleep recordings were analyzed by designated software (Noxturnal Software System, Reykjavik, Iceland) and subsequently manually analyzed by sleep technicians according to Berry et al. (2012). The HSAT screening is less labor-intensive but also less accurate than screening performed with polysomnography (PSG).

A desaturation event during the HSAT was defined as a SpO_2%-drop ≥ 3% from baseline. An apnea event was defined as ≥ 90% decrease in nasal- or RIP-flow lasting ≥ 10 seconds. A hypopnea event was defined as ≥ 30% decrease in nasal- or RIP-flow lasting ≥ 10 seconds combined with desaturation event. Patients in the MAS treatment group wore the MAS throughout the HSAT performed at both follow-up visits. This was the only difference between the HSAT performed at baseline and the follow-up visits respectively. Since efficacy data and compliance data were available through the CPAP log, no HSAT was performed in the CPAP treatment group at any follow-up visit.

2.3.2 Clinical examination

The clinical examination was performed by an otorhinolaryngologist as a routine step in the management of patients referred for OSA screening (Skår et al., 2015). The otorhinolaryngologist assessed the weight, height, dental status, morphology of the oral cavity and pharynx, nasal patency, and temporomandibular status according to the eligibility criteria. The size of the palatal tonsils was graded according to Brodsky (1989), and tongue size and position was scored using the 4-grade Friedman score (Friedman et al., 2004). In cases where the dental status required for MAS treatment was difficult to assess, a trained dentist was consulted for the assessment of the oral cavity, dentition, and dental occlusion.

2.3.3 Calibration of health-care personnel

All health-care personnel involved in the examination and patient treatment in the trial were calibrated according to the study protocol by two researchers (LMB and TKSA). Calibration sessions involving all personnel took place prior to the inclusion of the first patient at each study site. All physicians and dentists had the relevant study protocol items demonstrated by the researchers and were briefed on who to properly perform each protocol item in a standardized manner. Following the briefing, all personnel including sleep technicians performed all relevant steps described in the study protocol on pilot patients under close supervision by the researchers. No personnel were included in the study until they had correctly understood and performed all protocol items. The part of the study protocol performed by the sleep technicians were developed in close collaboration between the sleep technicians and the researchers. The sleep technicians were thus not trained by the researchers but were calibrated and instructed to adhere to the study protocol throughout the study period.

Calibration was further performed at least once a year at each study site, ensuring that screening and treatment of patients were as standardized as possible between the hospitals hosting the RCT and amongst the involved personnel. At the calibration sessions, the researchers observed and discussed the execution of the study protocol with every dental team and otorhinolaryngologist separately. During the spring of 2017, a calibration test was performed to ensure similar manual diagnostic HSAT scoring at the study sites. The log from 10 polygraphic sleep recordings from non-severe OSA patients were manually scored by the sleep technicians responsible for the HSAT scoring procedures in Tromsø and Trondheim. No statistically significant deviation was found between the manual scoring performed Tromsø and Trondheim respectively. However, since none of the involved personnel were observed to deviate from the study protocol at any calibration session, no kappa score was calculated from any of the calibration sessions.

In addition to the calibration sessions, all 6 otorhinolaryngologists and the 3 dentists involved in the trial were monitored at least once a year by the researchers TKSA and LMB respectively. The sleep technicians were frequently monitored by the researchers every time completed questionnaires were handed over from the sleep technicians to the researchers for punching in the SPSS statistical software. In cases where any health-care personnel had doubts about the study protocol, the case or issue was immediately discussed, and the treatment protocol clarified accordingly together with all relevant personnel. Both researchers TKSA and LMB were available for consultation to the otorhinolaryngologists, sleep technicians and dental teams during the complete trial period. The otorhinolaryngologists were all experienced registrar physicians or senior physicians. The dental teams consisted of 2 experienced dentists, 1 specialist dentist,

1 experienced dental hygienist and 1 experienced dental nurse. The sleep technicians were all highly experienced in scoring HSATs and evaluating CPAP efficacy and compliance.

2.4 Treatment protocol

A detailed written treatment protocol and clinical checklists were used during screening, treatment, and follow-up visits in both treatment groups. The treatment protocol and the checklists were tested at each study site as part of the training and calibration of personnel before enrollment of the first patient in the RCT. The protocol and checklist testing were performed on pilot patients not enrolled in the trial. The diagnostic process and treatment protocol were in line with the later updated American Academy of Sleep Medicine practice guidelines for diagnostic testing for OSA (Kapur et al., 2017).

2.4.1 Continuous positive airway pressure protocol

Patients allocated to CPAP treatment met a sleep technician on two consecutive days where an auto-CPAP device (Resmed S9 Autoset or Resmed AirSense 10 Autoset, Resmed®, San Diego, CA, USA) was personalized and thereafter tested the night between the two visits. A nasal pillow, nose-mask or full facemask was chosen based on the needs and preferences of the individual patient. Patients were instructed to use the CPAP every night and encouraged to contact the ENT department in case they had any problems associated with the CPAP usage. Approximately 1/3 of the patients in the CPAP treatment group were scheduled for an intermediate follow-up after 3-6 weeks of treatment as recommended by Kushida et al. (2006a). However, this intermediate follow-up was not included as a formal follow-up in the CPAP treatment protocol since most patients had a considerable travel distance between their home and the hospital, and thus preferred to contact the hospitals themselves if they found a follow-up between treatment start and the 4-month follow-up necessary. Besides, a mandatory appointment 3-6 weeks following treatment start would deviate from the standard treatment policies of the hospitals hosting the study, thus compromising the external validity of the RCT. Usage- and efficacy data from the last 90 days were downloaded from the CPAP device's software at both follow-ups. If necessary, the sleep technicians adjusted the CPAP device settings for optimal performance at the follow-up sessions.

2.4.2 Mandibular advancement splint protocol

Patients allocated to MAS treatment met a dental team consisting of a trained dentist and a dental hygienist or dental nurse on three occasions for the manufacturing of a twin-block, adjustable MAS with interlocking protrusion wings and soft fitting surface (Figure 6).

Figure 6 SomnoDent Fusion® mandibular advancement splint. Left: Lower jaw. Right: Upper jaw.

An orthopantomography (exposure time: 11 seconds, voltage: 83 kilovolts) and clinical intraoral examination was performed to rule out any odontogenic pathology requiring treatment prior to the MAS treatment. The dental team recorded data regarding the relationship between the lower and upper jaw, mandibular protrusion ability, condition of the dentition at tooth level, mucosal lining of the whole oral cavity, salivation status, tooth support including periodontal pocket depth, tooth mobility and dental plaque index. The salivation status was tested using a friction test between an examination mirror and the buccal mucosa where pronounced friction was regarded indicative of hyposalivation. Following the examination, registration of the jaw relation was performed with a George Gauge™ (Scheu-dental GmbH, Iserlohn, Germany). Silicone impressions of the dental arches were sent together with the bite registration to one of two dental labs for manufacturing the MAS (Respire Blue, Respire Medical, New York, NY, USA or SomnoDent Fusion®, SomnoMed, Sydney, NSW, Australia). Two weeks later, the MAS returned to the dental team and was set to 60-65% of the maximal mandibular protrusion before the patient received it. The patient was called 2-3 weeks later, and the MAS was titrated to the maximal comfortable protrusion (68% ± 10 on average) by the dental teams (Bartolucci et al., 2016, Marklund et al.,

2012). When necessary, the dentist adjusted the MAS titration at the 4-month follow-up visit after the HSAT was performed.

2.5 Clinical outcomes

2.5.1 Home sleep apnea testing variables

Several clinical parameters are measured with a type 3 polygraphic sleep recording device, but in the context of this RCT, only a selection of the available variables from the HSAT were evaluated. The variables of interest were the:

- Number of minutes asleep, subcategorized in supine and non-supine sleep.
- Number of obstructive apneas during sleep.
- Number of central apneas during sleep.
- Number of mixed apneas during sleep.
- Mean apnea duration in seconds.
- Number of hypopneas during sleep.
- Mean hypopnea duration in seconds.
- AHI, defined as the average number of apnea and hypopnea events per hour.
- Mean SpO_2 during sleep.
- Percentage of total sleep time spent having SpO_2 less than 90% (T-90%).
- Oxygen Desaturation Index, defined as the average number of desaturation events per hour.

These variables were measured in all patients at baseline, and in the MAS treatment group at both follow-up visits. The CPAP treatment group had no information on sleep position nor SpO_2 during CPAP use. Hence, the direct comparison between the treatment groups at follow-up regarding HSAT variables was limited to the number of apneas and hypopneas.

Currently, no standardized success criteria for AHI improvements exist, but based on the definitions of OSA severity, OSA is "cured" if AHI is reduced to < 5 events per hour (American Academy of Sleep Medicine., 1999). In addition, several previous studies use AHI reduced ≥ 50% as satisfactory treatment effect in cases where AHI < 5 is not achieved (Aarab et al., 2011, Doff et al., 2013b, Petri et al., 2008). Successful AHI improvement in this RCT was defined as AHI < 10 or AHI reduced ≥ 50% from baseline since such AHI improvements from baseline are believed to be considerable beneficial in OSA treatment, and since only patients with AHI ≥ 10 were included at baseline in this RCT (Gjerde et al., 2016).

2.5.2 Friedman score

To evaluate relative size and position of the tongue, the Friedman score, also known as the Friedman palate position, Friedman tongue position, or modified Mallampati classification was used (Friedman et al., 2004, Friedman et al., 2008). The Friedman score was first described as a 4-stage-, and later as a 5-stage classification system categorizing the tongue position and size in a natural relaxed position in the mouth (Friedman et al., 1999, Friedman et al., 2008). The categories were defined as: I) the entire uvula and palatal tonsils visible; II) the complete soft palate and parts of the uvula visible; III) the uvula not visible, parts of the soft palate visible; and IV) only the hard palate visible (Friedman et al., 2004). The otorhinolaryngologist assessed the Friedman score by passive, visual inspection of the patient's oral cavity while positioned across from the patient.

The Friedman score should not be confused with Friedman stage since the latter represents a staging system where the Friedman score, tonsil size and BMI are combined in the prediction of treatment success following UPPP (Friedman et al., 2002).

2.6 Patient-reported outcomes

2.6.1 Baseline variables and compliance to treatment

A non-validated questionnaire mapping the patient's demographic and health characteristics was distributed to all patients found to have non-severe OSA at the day of the medical examination following the baseline HSAT. The questionnaire gathered data on age, sex, marital status, education level, smoking and drinking habits, allergic rhinitis, symptoms commonly associated with OSA, global questions regarding self-reported sleep quality, general and dental health status, and expectations to the treatment. In addition, the otorhinolaryngologist reported the height and weight of the patients and to which degree each patient was motivated for treatment (Appendix 2).

At both follow-up visits, patients also completed a non-validated questionnaire mapping self-reported compliance, benefits, and adverse effects related to their respective treatment. Patients were asked to estimate the percentage of nights using the treatment device through seven alternatives ranging from 0% to 100%, and then estimate the average number of hours they use their treatment device per night (Appendix 2). The chosen cut-off for adequate treatment compliance was in most analyses defined as 4 hours per night in more than 70% of nights on average (Paper II and III), which is commonly used in OSA literature (Kribbs et al., 1993, Madbouly et al., 2014). The cut-off was lowered to 4 hours per night in more than 50% of nights on average in Paper I to increase statistical power.

At the follow-up visits, 11 common benefits and 9 adverse effects found in CPAP and MAS treatment were listed in the questionnaire. The patients were asked to tick off the benefits and adverse effects applying to them and to describe experienced benefits or adverse effects other than those listed in the questionnaire.

The questionnaires used to gather baseline variables and compliance data were composed in a joint effort by the researchers involved in the planning of the trial. The questions were based on questionnaires presented in a study by Hoffstein et al. (1992).

2.6.2 Pittsburgh Sleep Quality Index

Self-reported sleep quality was measured at baseline and at both follow-up visits with the 19-item questionnaire "Pittsburgh Sleep Quality Index" (PSQI) (Appendix 2). Patients answered questions assessing seven aspects of sleep quality during the last month: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. Each domain gives a score ranging from 0 to 3 points with a lower score representing better sleep quality. The domain scores are added to form a global score ranging from 0 to 21 points. The developers of the PSQI questionnaire defined good sleep quality as ≤ 5 points on the global score and found a test-retest reliability of the global score at 0.85 (Buysse et al., 1989). The PSQI questionnaire is validated and translated to Norwegian (Pallesen et al., 2005, Shahid et al., 2012). Permission to use the PSQI was obtained from the University of Pittsburgh (Appendix 2).

2.6.3 Medical Outcomes Study Short-Form 36-Element Health Survey

Self-reported HRQoL was measured at baseline and both follow-up visits with the "Medical Outcomes Study Short-Form 36-Element Health Survey" (SF36) version 2 (Appendix 2). The HRQoL is presented in eight separate domains on a 0-100 score with a higher score representing better HRQoL: "Physical functioning", "role-physical", "bodily pain", "general health", "vitality", "social functioning", "role-emotional", and "mental health". The domain scores are created from 36 questions scored on Likert-scales with 3, 4, 5 or 6 alternatives. The absolute scores on the 0-100 scale are not comparable between the different domains (Ware and Sherbourne, 1992). However, the 0-100 score can be transformed into a norm-based score, where 50 points represent the mean score for each domain in the general population, thus enabling a direct comparison between the domains, as well as a direct comparison to the general population. In the norm-based scales, 50 ± 10 points represent 1 standard deviation from the general population's mean score. The upper and lower score limits vary across the domains in the norm-based scales (Ware et al., 2000). The SF36 produce no total, or global score (Lins and Carvalho,

2016). However, the eight norm-based domain scores are transformable into two aggregated scales: The "physical component score" and the "mental component score", presenting physical- and mental HRQoL respectively. The SF36 questionnaire is validated and translated to Norwegian (Loge et al., 1998). Norwegian reference values for the SF36 questionnaire used in the transformation into norm-based scales have been established on several occasions, most recently in 2018 (Jacobsen et al., 2018). Permission to use the SF36 version 2 was obtained from OptumInsight Life Sciences, Inc (Appendix 2).

2.6.4 Subjective daytime sleepiness

As one of the most important symptoms of OSA, daytime sleepiness was planned from the start to be assessed in all patients in this RCT using the Epworth's Sleepiness Scale. Unfortunately, a flawed version of the Epworth's Sleepiness Scale questionnaire, missing the question "How likely are you to doze off or fall asleep (…) when watching TV", was distributed to 46 patients at baseline. Missing 1 of 8 questions in the questionnaire made it impossible to accurately evaluate the total score without making extensive imputations. The daytime sleepiness was thus not separately assessed as intended with the Epworth's Sleepiness Scale in this thesis.

As a second-string solution, changes in the PSQI questions 5d, 5e and 8 respectively regarding ease of breathing during sleep, snoring and daytime sleepiness from baseline to the 12-month follow-up are presented in detail. PSQI question 5d, 5e and 8 are all presented as Likert scales where alternative 1 "Not during the last month" is the best and 4 "Three or more times a week" is the worst alternative. Reduced scores in these sub-scores are thus interpreted as improvements from baseline to follow-up. Although ordinal, the numeric scores are not continuous.

For reasons described above, the average sum of the Epworth's Sleepiness Scale in each treatment group could not be presented as a separate result, but the sum of the 7 questions included in the flawed version of the Epworth's Sleepiness Scale is discussed in section 4.2.3.1 in the light of the results from question 8 in the PSQI questionnaire.

2.6.5 Hospital anxiety and depression scale

The Hospital Anxiety and Depression Scale (HADS) is a 14-item validated questionnaire assessing symptoms of anxiety and depression in medical patients (Bjelland et al., 2002, Herrmann, 1997). The HADS questionnaire is divided into 2 domains, each comprising 7 items mapping symptoms of anxiety and depression respectively. Each item produces a score of 0-3, with a higher value representing more severe symptoms, providing a sum score range of 0-21 for each domain. A sum-score below 8 for either domain is considered normal levels of anxiety and depression symptoms. A sum score of 8-10 is considered borderline anxiety/depression, while a

sum score above 10 for either domain is considered as probable anxiety or depression (Herrmann, 1997, Zigmond and Snaith, 1983). The HADS questionnaire was completed by the patients at baseline and at both follow-up visits. The results from the HADS questionnaire are presented in detail in section 3.2.2, but were not presented in Papers I-III for reasons discussed in section 4.2.2. No information on licensing of the Norwegian version of the HADS questionnaire was found at the time of patient recruitment (Leiknes et al., 2016). A user license for the HADS questionnaire was thus obtained after the study period from GL Education Group Ltd. (Appendix 2).

2.7 Statistical analyses

Statistical analyses were performed using SPSS 26 statistical software package (IBM Corp, Armonk, NY, USA). A two-sided $p < 0.05$ was considered statistically significant in all analyses. An overview of the statistical methods and variables used in the analyses found in Paper I, II and III are presented in Table 5.

Table 5 Summary of study lengths, variables, and statistical methods used in Paper I, II and III.

	Paper I *(4-month follow-up)*	*Paper II* *(12-month follow-up)*	*Paper III* *(12-month follow-up)*
Outcome variables	PSQI global score Compliance to treatment AHI Improved sleep quality	Compliance to treatment Improved AHI	SF36 domain scores PSQI global score Compliance to treatment AHI Improved HRQoL Improved sleep quality
Independent variables and covariates	Treatment group Baseline PSQI global score Baseline AHI	Treatment group Friedman score Sex Age BMI Education level Smoking Tonsil size	Treatment group Baseline SF36 score Baseline PSQI global score Baseline AHI Age BMI Sex Smoking
Statistical analyses	Student's *t*-test Mann-Whitney U-test Pearson chi-square test Fisher's exact test Paired samples *t*-test Wilcoxon signed ranks test	Multivariable logistic regression Pearson chi-square test Fisher's exact test	Multivariable linear and logistic regression Paired samples *t*-test Wilcoxon signed ranks test Pearson correlation Pearson chi-square test Fisher's exact test

To avoid compromising the methodological strengths of randomized treatment allocation, an intention-to-treat (ITT) approach was used when comparing the treatment groups (Paper I and III). Along with the ITT analyses, per protocol (PP) analyses, which only included patients being

compliant to treatment, were performed to assess the compliance-dependent effects of the treatments.

2.7.1 Descriptive statistics (Paper I, II, & III)

All continuous variables are presented by mean (standard deviation) or median (inter-quartile range) for parametric and non-parametric data respectively. Categorical variables are presented as numbers (N), percentages, or both.

2.7.2 Reliable change index (Paper I & III)

To standardize changes from baseline to follow-up, the reliable change index (RCI) was calculated for each SF36 domain score and the PSQI global score. The RCI indicates whether each patient reports a change from baseline that is not likely to occur through test-retest variations, i.e., statistically significant change in the questionnaire variable of interest (Jacobson and Truax, 1991).

The RCI compares the individual patient's questionnaire score at baseline (x_1) and follow-up (x_2) and adjust for the standard deviation of the baseline score (SD) and the test-retest reliability of the questionnaire (r_{xx}). Provided this information, the RCI can be calculated using the following formula, as described by Currie et al. (2002):

$$\mathrm{RCI}=\frac{x_2-x_1}{\left\{2\left[\mathrm{SD}\left(1-r_{xx}\right)^{1/2}\right]^2\right\}^{1/2}}$$

In this RCT, the test-retest reliability for each SF36 domain (Paper III) was retrieved from Stavem et al. (2006) who tested and retested the SF36 questionnaire in a Norwegian standard population. For the PSQI global score (Paper I, and III), the test-retest reliability found by the PSQI developer when validating the questionnaire was used (Buysse et al., 1989).

The RCI values from different questionnaires are directly comparable since the standard deviation and test-retest reliability are taken into consideration. The RCI thus enables correlation analysis between changes in the SF36 domains and the PSQI global score to be performed (Paper III). For the same reason, a statistically significant RCI value is likely to also be clinically significant. In fact, a larger |RCI-value| indicates a greater clinical change (Jacobson and Truax, 1991). A two-sided statistically significant change in RCI at a 5% significance level is defined as a |RCI value| > 1.96, i.e., RCI values higher than 1.96 or lower than -1.96 represent significantly higher or lower score at follow-up compared with the baseline score, respectively.

2.7.3 Analyses between treatment groups (Paper I, II, & III)

Hypothesis testing between the CPAP and MAS treatment groups at follow-ups was performed using the Student's *t*-test for mean values in PSQI global score, and the Mann-Whitney U-test for median values in AHI and PSQI sub-scores. The Pearson chi-square or Fisher's exact tests were used when comparing the treatment groups regarding the number of patients with adequate compliance to treatment, AHI improvement, or improvements according to the RCI (SF36 domain scores and PSQI global score). The Fisher's exact test was used in categorical variables whenever the expected count in any 2 x 2 cross table cell was less than 5.

2.7.4 Analyses within treatment groups (Paper I & III)

Changes from baseline to follow-ups within each treatment group were tested with the Paired samples *t*-test for average SF36 domain scores and average PSQI global score and with the paired samples Wilcoxon signed ranks test for AHI and PSQI sub-scores.

2.7.5 Logistic regression (Paper II)

Logistic regression was used to assess the associations between Friedman score and AHI improvement and between Friedman score and compliance to treatment in Paper II. The regression models estimate odds ratio (OR) with 95% confidence intervals (95% CI) for adequately improved AHI and adequate compliance to treatment per 1-point increase in Friedman score. Two multivariable regression models were built on the crude model: Model 1 using age, sex, BMI, education level and smoking status as covariates, and model 2 using model 1 in addition to tonsil size according to Brodsky grade as covariates. Model 2 was regarded as the main model in Paper II.

2.7.6 Linear regression (Paper III)

Multivariable linear regression was used to assess the difference in mean SF36 domain scores and PSQI global score between treatment groups at the 12-month follow-up visit. The two main regression models presented in Paper III were adjusted for the baseline variables age, BMI, sex, smoking, AHI, and SF36 domain scores or PSQI global score respectively. The differences between the treatment groups were presented side-by-side by unadjusted mean values, and by the regression coefficient, representing the adjusted difference in mean values. The 95% CI and p-value were presented for the adjusted difference.

2.7.7 Correlation analyses (Paper III)

The correlation between SF36 domains and PSQI global score was explored using the Pearson correlation coefficient (Pearson's *r*). The analysis was performed using the RCI values from the

individual patients in each treatment group. Table 6 shows the chosen definitions of correlation strength between a given SF36 domain and PSQI global score using Pearson's *r*. The correlation was only explored for SF36 domains with a statistically significant change in mean score from baseline to follow-up.

Table 6 Correlation strength given by the absolute Pearson correlation coefficient (r).

Correlation	*None*	*Weak*	*Moderate*	*Strong*
r	0.0 – 0.09	0.1 – 0.29	0.3 – 0.49	0.5 – 1.00

2.7.8 Additional analyses not presented in Paper I-III

Some of the findings from this RCT are presented in this thesis but were not presented in Paper I, II and III. Direct comparison between the findings in Paper I and III is challenging since the cut-off for compliance to treatment chosen in Paper I was > 4 hours and > 50% of nights, not > 4 hours and > 70% of nights as used in Paper III. Moreover, the Student's *t*-test was used when comparing the treatment groups in Paper I while multivariable regression models were used in Paper III. The RCT study design minimizes the risk of confounding when comparing treatment groups, but the low number of compliant patients at follow-up advocate for the use of linear and logistic regression models instead of the Student's *t*-test. The sleep-quality data was therefore re-analyzed for both the 4- and 12-month follow-up visits using common regression models and using > 4 hours and > 70% of nights as the compliance cut-off.

To provide a broader approach to the research questions and aims of this thesis, supplementary analyses between and within the treatment groups are presented. The supplementary analyses include information regarding treatment compliance, daytime sleepiness, and results from the HADS questionnaire which was omitted from the Papers I and III. All statistical analyses not presented in Papers I-III are described in this section.

2.7.8.1 Logistic regression

Logistic regression was used to compare the number of patients in the CPAP and MAS treatment groups with significantly improved SF36 domain scores and PSQI global score after 12-month of treatment. However, these results were not presented in Paper III due to wide confidence intervals. In this thesis, the odds of having significantly improved scores when receiving MAS treatment compared to CPAP treatment is presented as OR with 95% CI in section 3.5. The RCI of each SF36 domain score and the PSQI global score were adjusted for the baseline variables age, BMI, sex, smoking, AHI, daytime sleepiness assessed by PSQI question 8, symptoms of anxiety and depression according to the HADS questionnaire, and the respective SF36 domain or PSQI global scores at baseline.

2.7.8.2 Linear regression

A comparison between the PSQI-results presented in paper I and III is presented in section 3.5.1. Multivariable linear regression analyses were used. The differences in PSQI global score between the CPAP and MAS treatment groups at the 4-month and 12-month follow-up visits were adjusted for age, BMI, sex, smoking, baseline AHI, baseline PSQI global score, baseline daytime sleepiness assessed by PSQI question 8 and baseline symptoms of anxiety and depression according to the HADS questionnaire.

2.7.8.3 Additional comparisons between and within treatment groups

Post hoc analyses regarding compliance to treatment, adverse effects from CPAP and MAS treatment, and reasons for non-compliance were performed using Pearson chi-square and Fisher's exact tests.

The differences in the PSQI sub-scores (question 5d, 5e and 8) presented in this thesis were analyzed using the Mann-Whitney U-test between the treatment groups. Changes from baseline to follow-up within the treatment groups were analyzed using the Wilcoxon signed ranks test.

Differences between the CPAP and MAS treatment groups were analyzed using the Student's *t*-test and changes in mean HADS scores within the treatment groups were analyzed using the paired samples *t*-test.

2.7.9 Sample size calculations

The overall sample size for the trial needed to reach a statistical power of 80% was based on expected differences between CPAP and MAS treatment groups at follow-up HRQoL (Paper III). The sample size calculation prior to the data collection found that 59 patients were needed in each treatment group at follow-up to show differences in HRQoL, presuming a 25 percentage-points difference in SF36 domain scores between CPAP and MAS treatment. Unfortunately, the presumed difference was not adequately evidence based. A new sample size calculation was therefore performed after trial initiation, based on the results from an RCT by Engleman et al. (2002) with 10% difference between CPAP and MAS treatment, and 20% standard deviation within the treatment groups. According to the new sample size calculation, 69 patients were needed to detect differences between the treatment groups in the HRQoL outcome using a Student's *t*-test. Since HRQoL was not reported in Paper I, a separate sample size calculation was performed based on self-reported sleep quality. Given a 15% difference in PSQI global score between CPAP and MAS treatment at follow-up and a 25% standard deviation within the treatment groups, 45 patients were needed in each treatment group at follow-up to detect differences in self-reported sleep quality.

2.8 Ethical considerations

The participation in clinical research as part of medical treatment raises several ethical issues, even though treatment in this RCT in principle was the standard treatment of non-severe OSA at the hospitals hosting the trial. By Norwegian law, all patients from the age of 16 have the right of co-determination when choosing a treatment recommended by health professionals (Syse, 2009). This right of co-determination also applies for treatment performed in a clinical research context, but the concept of randomization violates the possibility to influence the choice of treatment for both the health-care provider and the patient. Thus, an informed or valid consent from the patient to participate is essential for all clinical research to be ethical according to the Declaration of Helsinki (World Medical Association, 2013) and Norwegian law (Syse, 2000). All patients eligible for participation in this RCT were provided written information about the trial, randomization procedure, treatment modalities, prognosis and risks associated with the treatments, and their right to withdraw from the trial at any moment without stating any reason (Appendix 1). Based on this information, all patients gave a written consent to participate before they were enrolled in the trial.

When written information is provided for the patient, both clinicians and researchers designing clinical trials should acknowledge the risk of patients having poor or insufficient health literacy. A survey conducted in eight European countries estimated that about 12% of the adult population have insufficient health literacy, i.e., they have difficulties in assimilating and understanding health-related information (Sorensen et al., 2015). These patients are at risk of providing written consent to treatment or clinical trial participation, without fully comprehending the clinical and practical consequences associated with giving such consent. Moreover, patients having insufficient health literacy may not be aware of their reduced ability to assimilate the information they are given. This leaves more responsibility on the clinicians recruiting patients to the trial, to ensure that the written consent received from the patient is not solely an informed consent, but indeed a fully understood consent, i.e., a valid consent as described by Syse (2000). Not comprehending the implications of participating in the trial may be a reason for patients dropping out of the trial. Inclusion of patients not willing to participate in a clinical trial due to poor health literacy, may therefore potentially introduce bias and thus undermine the validity of the trial data.

All patients who withdrew from this RCT, or had unsatisfactory AHI reduction upon final follow-up, were offered a treatment other than the one they were allocated to in the trial. This practice is particularly important to pursue in all research using random allocation to treatment since patients and health-care providers are unable to influence the initial treatment choice. In this RCT, this implied that patients in the CPAP treatment group were offered treatment with MAS and vice

versa for patients in the MAS treatment group. It was particularly important to offer the CPAP treatment to patients experiencing unsuccessful MAS treatment since CPAP treatment is regarded the current gold standard of OSA treatment.

Unfortunately, the period before being offered an alternative treatment potentially increases the total treatment burden in cases where the patient is allocated to a suboptimal treatment. This may in turn increase the risk of the patient becoming sated from the given treatment (Sav et al., 2013). Some patients may therefore decline an effective and possibly necessary treatment, in part due to the participation in the RCT. There is no obvious way to prevent the potentially increased treatment burden from participating in a RCT. Ensuring that patients give a valid consent before participating in the RCT should reduce the risk of enrolling patients who do not cope with the potentially increased treatment burden. In this RCT, only patients with non-severe OSA were invited, thus minimizing the potential sequelae of untreated OSA in cases where the patient withdrew from the trial and refused further treatment (Marin et al., 2005, Marshall et al., 2008).

The RCT, including its expansion from a single- to a two-centered study, was approved by the Norwegian Regional Committee for Medical and Health Research Ethics, REC Central (registration #2014/956, Appendix 3) and was registered in ClinicalTrials.gov (registration #NCT02953028). The trial was initiated before July 2018 when the “General Data Protection Regulation” was introduced in Norway. Trial registration by the NSD - Norwegian Centre for Research Data was therefore not required (project #58775).

3 Results

3.1 Study population

The patients enrolled in the RCT had higher BMI and reported worse self-reported general health at baseline compared to the Norwegian general population (Krokstad et al., 2013, Statistisk sentralbyrå, 2018). Patients recruited in Tromsø had higher BMI ($p = 0.001$) and reported worse self-reported dental health ($p = 0.001$) than patients recruited in Trondheim but were otherwise similar, including all baseline questionnaire scores. Patient characteristics for study locations are presented in Table 7. Comparisons between the treatment groups at baseline are presented in Table 8. There were no statistically significant differences between the treatment groups at baseline in the characteristics reported.

The allocation and flow of patients in this RCT are presented in Figure 7. The median (inter-quartile range) time from treatment initiation to the follow-up visits, were 4 (4-6) months and 13 (12-15) months respectively. The most reported reasons for completely quitting treatment were noise and discomfort from the treatment device ($n = 8_{CPAP}/4_{MAS}$), the sensation of claustrophobia/suffocation ($n = 5_{CPAP}/1_{MAS}$), xerostomia ($n = 2_{CPAP}/2_{MAS}$) and insomnia ($n = 1_{CPAP}/0_{MAS}$). In the MAS treatment group, 1 patient was lost to follow-up although being compliant to treatment at the 4-month follow-up visit, and 2 patients refused to perform the HSAT at the 12-month follow-up visit due to the travel distance to the hospital. In total 8 patients failed to attend the 4-month follow-up visit but attended the 12-month follow-up visit. The number of patients presented in Figure 7 corresponds to the flow chart presented in Paper II but deviates from the flow chart presented in Paper III. The flow chart presented in Paper III showed the number of patients who completed the SF36 and PSQI questionnaires at follow-up.

Table 7 Patient characteristics at baseline, study site comparison, n (%).

Baseline variables	*Total (n=104)*	*Tromsø (n = 71)*	*Trondheim (n = 33)*
Age at inclusion, mean (sd)	51.7 (9.8)	51.5 (9.6)	51.6 (10.3)
BMI at inclusion, mean (sd)	31.5 (6.7)	32.8 (7.2)	28.8 (4.6)
Sex			
Female	37 (35.6)	25 (35.2)	12 (36.4)
Male	67 (64.4)	46 (64.8)	21 (63.6)
Marital status			
Cohabitating	81 (77.9)	54 (76.1)	27 (81.8)
Living alone	23 (22.1)	17 (23.9)	6 (18.2)
Allergic rhinitis			
Yes	17 (16.3)	11 (15.5)	6 (18.2)
No	87 (83.7)	60 (84.5)	27 (81.8)
Self-reported health			
Good-Excellent	29 (27.9)	16 (22.5)	13 (39.4)
Poor-Fair	75 (72.1)	55 (77.5)	20 (60.6)
Self-reported dental health			
Good-Excellent	31 (29.8)	14 (19.7)	17 (51.5)
Poor-Fair	73 (70.2)	57 (80.3)	16 (48.5)
Education level			
College or university	50 (48.1)	32 (45.1)	18 (54.5)
Other education	54 (51.9)	39 (54.9)	15 (45.5)
Alcohol consumption			
≤1 time/week	83 (79.8)	59 (83.1)	24 (72.7)
>1 time/week	21 (20.2)	12 (16.9)	9 (27.3)
Smoking status			
Non-smoking	83 (79.8)	58 (81.7)	25 (75.8)
Smoking	21 (20.2)	13 (18.3)	8 (24.2)

Table 8 Patient characteristics at baseline, treatment group comparison, n (%).

Baseline variables	*Total (n = 104)*	*CPAP (n = 55)*	*MAS (n = 49)*
Age at inclusion, mean (sd)	51.7 (9.8)	53.3 (10.2)	49.6 (9.0)
BMI at inclusion, mean (sd)	31.5 (6.7)	30.8 (6.2)	32.4 (7.2)
AHI at inclusion, median (inter-quartile range)	17.6 (13.2-23.5)	18.1 (15.3-24.6)	16.3 (12.4-23.0)
Sex			
Female	37 (35.6)	17 (30.9)	20 (40.8)
Male	67 (64.4)	38 (69.1)	29 (59.2)
Marital status			
Cohabitating	81 (77.9)	44 (80.0)	37 (75.5)
Living alone	23 (22.1)	11 (20.0)	12 (24.5)
Allergic rhinitis			
Yes	17 (16.3)	9 (16.4)	8 (16.3)
No	87 (83.7)	46 (83.6)	51 (83.7)
Self-reported health			
Good-Excellent	29 (27.9)	16 (29.1)	13 (26.5)
Poor-Fair	75 (72.1)	39 (70.9)	36 (73.5)
Self-reported dental health			
Good-Excellent	31 (29.8)	14 (25.5)	17 (28.8)
Poor-Fair	73 (70.2)	41 (74.5)	32 (71.2)
Education level			
College or university	50 (48.1)	23 (41.8)	27 (55.1)
Other education	54 (51.9)	32 (58.2)	22 (44.9)
Alcohol consumption			
≤1 time/week	83 (79.8)	43 (78.2)	40 (81.6)
>1 time/week	21 (20.2)	12 (21.8)	9 (18.4)
Smoking status			
Non-smoking	83 (79.8)	41 (74.5)	42 (85.7)
Smoking	21 (20.2)	14 (25.5)	7 (14.3)

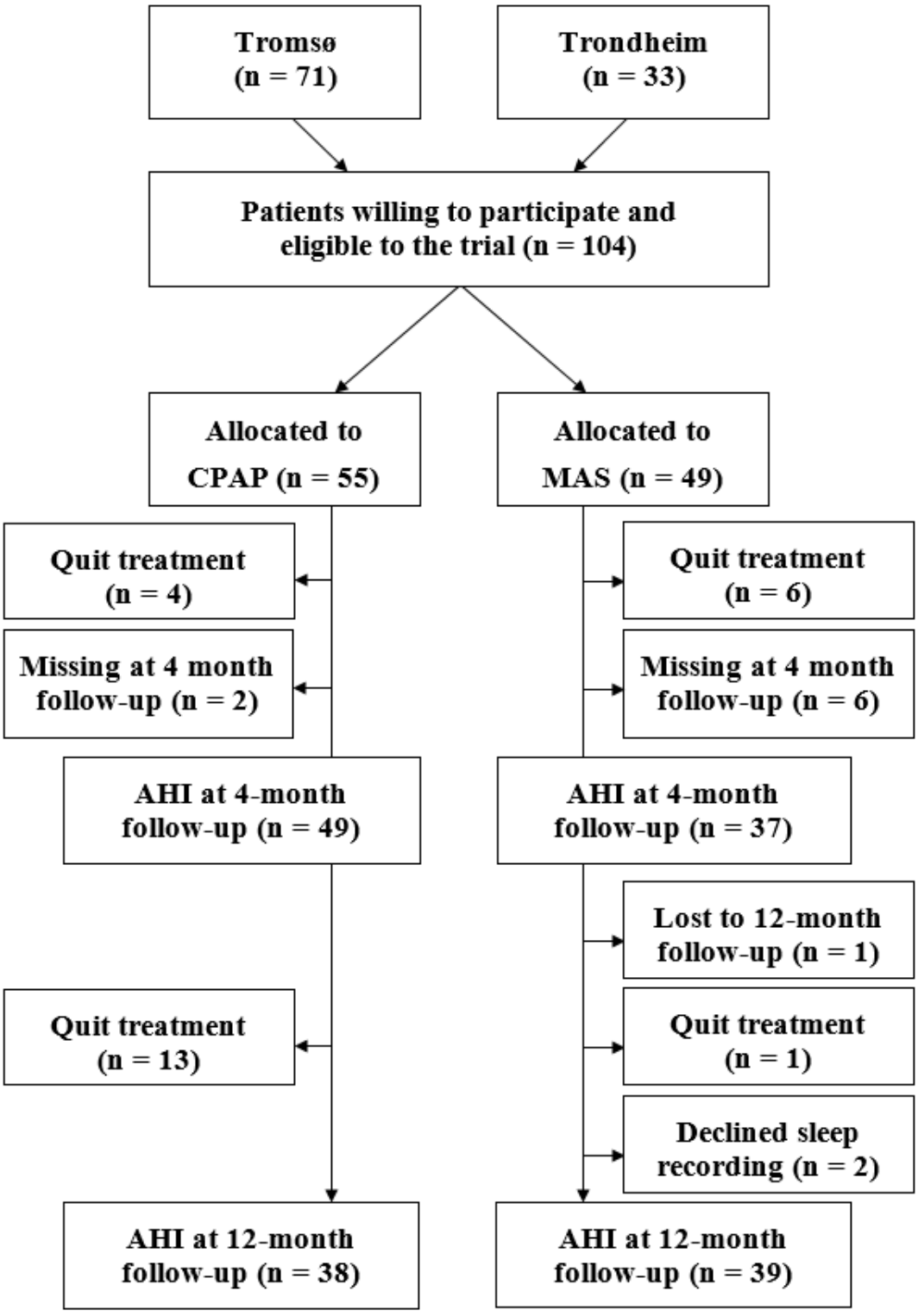

Figure 7 Patient allocation and flow throughout the trial.

3.2 Apnea-Hypopnea-Index and compliance to treatment

Although not the primary aim in any of the papers included in this thesis, the change in AHI and compliance to treatment was presented in all papers. The efficacy of CPAP and MAS treatment is commonly evaluated through the ability to reduce the number of apnea and hypopnea events during sleep. Yet, the change in AHI only applies for the time the treatment device is used, making compliance to treatment a key part of the overall treatment effectiveness. Therefore, the change in AHI and compliance to treatment lay the foundation for all interpretation of the main outcomes in Papers I-III. In Paper I, the AHI and compliance were assessed after 4 months of treatment, while Paper II and III reported AHI and compliance after 12 months of treatment. Patients being non-compliant and quitting treatment altogether before the follow-up visits were counted as non-compliant at follow-up. The results from the 4- and 12-month follow-up visits were similar in terms of CPAP being superior to MAS at reducing AHI, while compliance was significantly better in the MAS treatment group compared to the CPAP treatment group. The average AHI and compliance to treatment at follow-up visits are presented in Table 9. The change in AHI from baseline to both follow-up visits were significant ($p < 0.001$). Differences between the treatment groups in both AHI and compliance at both follow-ups were also statistically significant ($p < 0.001$).

Table 9 Median (inter-quartile range) AHI and percentage of patients compliant to treatment at follow-ups.

	AHI baseline	*AHI 4 months*	*AHI 12 months*	*Compliance 4 months*	*Compliance 12 months*
CPAP	18.1 (15.3-24.6)	1.1 (0.6-1.6) (49/55)	0.9 (0.7-1.4) (38/55)	31.5% (17/54)	32.7% (18/55)
MAS	16.3 (12.4-23.0)	7.9 (6.0-13.8) (37/49)	10.1 (6.1-16.5) (39/49)	75.0% (33/44)	75.0% (36/48)

The change in AHI from baseline to the 12-month follow-up visit for each patient in the CPAP ($n = 38$) and MAS ($n = 39$) treatment groups is illustrated in Figure 8. The illustration clearly shows the difference in AHI change with CPAP and MAS treatment but does not consider the compliance to treatment.

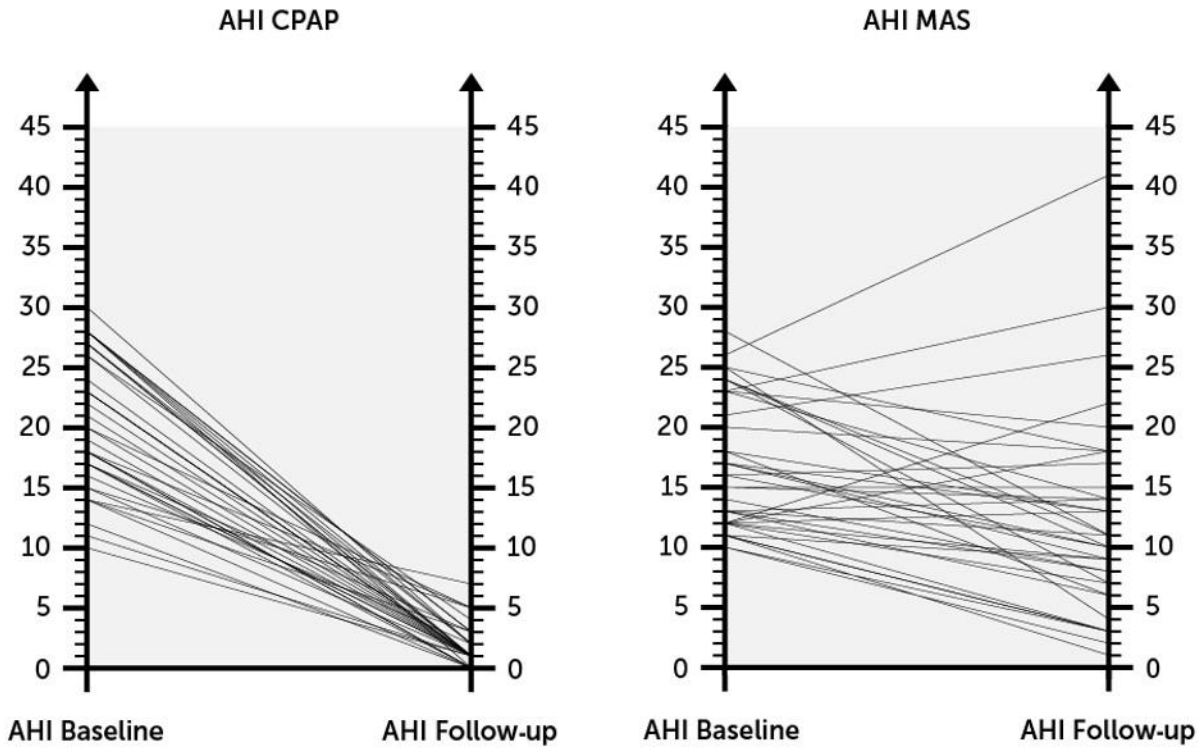

Figure 8 AHI at baseline and 12-month follow-up for individual patients in the CPAP and MAS treatment group. Illustration by Brett Guise, TkMidt.

The frequency of adverse effects reported by both compliant and non-compliant patients are presented in Table 10. A higher percentage of patients being compliant to treatment reported adverse effects compared to non-compliant patients in both treatment groups. In the CPAP treatment groups, 38% of the non-compliant patients reported no adverse effects, compared to 17% among patients being compliant to CPAP. Similarly, 31% of patients being non-compliant to MAS reported having experienced no adverse effects while 14% of patients compliant to MAS treatment reported having no adverse effects.

Table 10 Adverse effects reported by patients treated with CPAP (n = 55) and MAS (n = 49).

Adverse effect	*CPAP*	*MAS*
*Pain and discomfort associated with using the treatment device**	15 (27%)	34 (69%)
Xerostomia	18 (33%)	18 (37%)
Insomnia, claustrophobic or suffocating sensation	19 (35%)	3 (6%)
*Device being troublesome in bed***	26 (47%)	9 (18%)
Altered dental occlusion	0 (0%)	2 (4%)
No adverse effects reported	15 (27%)	12 (24%)

**Including skin-, muscular- and dental discomfort and pain, both short term and long term.*
***Including complains from bedpartners, excessive salivation, noise from the CPAP device and displacements of mask, hose, or MAS during sleep.*

The median (inter quartile range) use of CPAP or MAS for patients being non-compliant to treatment were 1.75 (0 – 3.5) or 4.75 (0 – 7.0) hours/night respectively. 91% of non-compliant patients estimated using the CPAP device ≤ 50% of nights, while 80% of non-compliant patients estimated using the MAS device ≤ 50% of nights. More men (90%) than women (50%) were compliant to MAS treatment (Chi square p = 0.003). Among patients being non-compliant to MAS treatment, only 1 (8%) reported having very good or excellent sleep quality compared to 12 (92%) reporting poor sleep quality at baseline (Chi square p = 0.008). No such differences were found in the CPAP treatment group (p = 0.53 and p = 0.24 respectively). There was no difference in mean age between patients being compliant to treatment (52.6 ± 9.5 years) and patients being non-compliant to treatment (50.5 ± 10.0 years) using the Student's *t*-test (p = 0.28).

Compared to patients being compliant to treatment, insignificantly more smokers and patients living alone were found among patients being non-compliant to treatment (chi-square p > 0.22). When only considering patients quitting treatment altogether, 10 (40%) were smokers, which was significantly more compared to the 11 (14%) smokers among compliant and non-compliant patients who had not given up on treatment at the 12-month follow-up visit (chi-square p = 0.005). On group level, patients being non-compliant to treatment improved both the PSQI global score and SF36 bodily pain-, vitality- and physical component score from baseline to the 12-month follow-up. The most prevalent reported reasons for non-compliance are listed in Table 11.

Table 11 Reported reasons for being non-compliant to treatment with CPAP (n = 37) and MAS (n = 13).

Reasons for not being compliant	*CPAP*	*MAS*
*Pain and discomfort associated with using the treatment device**	9 (24%)	6 (46%)
Xerostomia	5 (14%)	2 (15%)
Insomnia, claustrophobic or suffocating sensation	16 (43%)	2 (15%)
*Device being troublesome in bed***	11 (30%)	0 (0%)
Motivational issues	1 (3%)	1 (8%)
No adverse effects reported	9 (24%)	5 (38%)

**Including gagging, skin-, muscular-, nasal- and dental discomfort and pain.*
***Including complains from bedpartners, excessive salivation, noise from the CPAP device and displacements of mask, hose, or MAS during sleep.*

At baseline, the self-reported expectations and expressed motivation to treatment were medium to high in most patients and did not statistically differ between compliant and non-compliant patients (Fisher's exact test p > 0.19 and p > 0.66 respectively). No difference was found between patients

quitting treatment altogether and non-compliant patients who still wished to use their assigned device at the 12-month follow-up visit.

3.2.1 Symptoms of obstructive sleep apnea

The PSQI questions 5d, 5e and 8 assess the common symptoms of breathing difficulties during sleep, snoring and daytime sleepiness respectively. The percentage of patients reporting these symptoms as often, more often or less often after 12 months of treatment compared to baseline are presented in Table 12. Since the PSQI sub-scores are non-continuous scales, the numeric scores may be misleading and are thus not shown.

Table 12 Patients reporting changed symptom frequency after 12 months of treatment.

Changed symptom frequency (% of total group n)					
Symptom change Intention-to-treat	CPAP (n = 55)	MAS (n = 49)	**Symptom change** Per protocol	CPAP (n = 18)	MAS (n = 36)
Excessive daytime sleepiness			**Excessive daytime sleepiness**		
Less often	16.4%	30.6%	Less often	33.3%	25.0%
No change	78.2%	61.2%	No change	66.7%	66.7%
More often	5.5%	8.2%	More often	0.0%	8.3%
Difficulty breathing during sleep			**Difficulty breathing during sleep**		
Less often	25.5%	38.8%	Less often	27.8%	44.4%
No change	49.1%	59.2%	No change	44.4%	52.8%
More often	25.5%	2.0%	More often	27.8%	2.8%
Snoring or coughing during sleep			**Snoring or coughing during sleep**		
Less often	45.5%	59.2%	Less often	77.8%	66.7%
No change	43.6%	38.8%	No change	16.7%	30.6%
More often	10.9%	2.0%	More often	5.6%	2.8%

Per protocol: Compliance to treatment > 4 hours, > 70% of nights.

The ITT analyses (n = 104) using the Wilcoxon signed ranks test showed that subjective daytime sleepiness as measured by PSQI question 8 did not significantly improve statistically in the CPAP treatment group ($p = 0.08$) but did improve in the MAS treatment group ($p = 0.005$). No difference was found in daytime sleepiness between the CPAP and MAS treatment groups at the 12-month follow-up ($p = 0.55$) when using the Mann-Whitney U-test. Subjective breathing comfort during sleep did not improve in the CPAP treatment group ($p = 0.83$) but improved in the MAS treatment group ($p < 0.001$) and was significantly better than the CPAP treatment group at the 12-month follow-up visit ($p = 0.006$). Subjective snoring improved in both treatment groups from baseline to the 12-month follow-up (CPAP: $p = 0.001$, MAS: $p < 0.001$) and no difference between the treatment groups was found at the 12-month follow-up ($p = 0.35$).

In the PP analyses, only including patients reporting to use the CPAP (n = 18) or MAS (n = 36) device more than 4 hours, more than 70% of nights, the subjective daytime sleepiness significantly improved in the CPAP treatment group ($p = 0.03$) but not in the MAS treatment group ($p = 0.06$). Subjective breathing comfort during sleep did not improve in the CPAP treatment group ($p = 0.47$) but did improve in the MAS treatment group ($p = 0.001$). Subjective snoring improved in both treatment groups from baseline to the 12-month follow-up (CPAP: $p = 0.001$, MAS: $p < 0.001$). The differences between the treatment groups at the 12-month follow-up were not statistically significant (daytime sleepiness: $p = 0.34$, difficulties breathing during sleep: $p = 0.17$, snoring: $p = 0.65$).

Across both treatment groups, significantly more patients being compliant to treatment reported improved snoring (70.4%) compared to non-compliant patients (32.0%) using Fisher's exact test ($p < 0.001$). Although not statistically significant, a similar trend was observed with experienced difficulties breathing during sleep where 38.9% of compliant and 24.0% of non-compliant patients improved ($p = 0.24$) and excessive daytime sleepiness where 27.8% of compliant and 18.0% of non-compliant patients improved ($p = 0.51$) from baseline to the 12-month follow-up visit. Similar results were found when comparing patients quitting treatment altogether to both compliant and non-compliant patients still using their assigned device at the 12-month follow-up visit: Snoring improved among 21.6% of all patients quitting-, and 68.7% of all patients continuing treatment (Fisher's exact test $p < 0.001$). Difficulties breathing during sleep improved among 21.6% of all patients quitting-, and 37.3% of all patients continuing treatment (chi-square test $p = 0.26$). Excessive daytime sleepiness improved among 13.5% of all patients quitting and 28.4% of all patients continuing treatment (Fisher's exact test $p = 0.09$).

3.2.2 Symptoms of anxiety and depression

The HADS questionnaire was completed by 101 patients at baseline and by 88 and 78 patients at the 4- and 12-month follow-up visits respectively. The mean HADS scores at baseline and follow-ups were < 8 for both the anxiety- and depression scale, i.e., within the range commonly regarded as normal levels of anxiety and depression (Leiknes et al., 2016). No significant differences between the CPAP and MAS treatment groups were found at any visit in neither the ITT nor the PP analysis. The mean HADS scores and the percentage of patients with anxiety- or depression scale score ≥ 8 are presented in Table 13 (ITT) and Table 14 (PP). The mean HADS score was statistically significantly reduced from baseline to the 12-month follow-up visit in the ITT analysis (but not in the PP analysis) in the CPAP treatment group (anxiety $p_{ITT} = 0.04$, $p_{PP} = 0.18$/depression $p_{ITT} = 0.01$, $p_{PP} = 0.08$). Correspondingly, the HADS scores were significantly reduced from baseline to the 12-month follow-up visit in both the ITT and PP

analyses in the MAS treatment group (anxiety $p_{ITT} = 0.004$, $p_{PP} < 0.001$/depression $p_{ITT} < 0.001$, $p_{PP} < 0.001$).

Table 13 Intention-to-treat mean HADS scores and n anxiety-/depression score ≥ 8 at baseline and follow-ups

HADS Score	*Anxiety Baseline*	*Anxiety 4 months*	*Anxiety 12 months*	*Depression Baseline*	*Depression 4 months*	*Depression 12 months*
CPAP mean (sd)	5.0 (3.1)	4.4* (3.1)	4.2* (3.0)	3.9 (3.3)	3.2* (3.0)	3.0* (3.1)
MAS mean (sd)	4.8 (3.1)	4.2 (3.0)	3.7* (2.8)	4.8 (3.4)	3.7* (3.1)	3.0* (2.2)
CPAP n score ≥ 8	11/54	8/54	8/54	8/54	6/54	7/54
(% score ≥ 8)	(20.4%)	(14.8%)	(14.8%)	(14.8%)	(11.1%)	(13.0%)
MAS n score ≥ 8	11/47	8/47	6/48	10/47	7/47	3/48
(% score ≥ 8)	(23.4%)	(17.0%)	(12.5%)	(21.3%)	(14.9%)	(6.3%)

**Statistically significant change from baseline to follow-up within treatment group, paired samples t-test (P < 0.05).*

Table 14 Per protocol mean HADS scores and n anxiety-/depression score ≥ 8 at baseline and follow-ups

HADS Score	*Anxiety Baseline*	*Anxiety 4 months*	*Anxiety 12 months*	*Depression Baseline*	*Depression 4 months*	*Depression 12 months*
CPAP mean (sd)	5.0 (3.1)	4.0* (2.8)	4.4 (2.9)	3.9 (3.3)	3.0* (3.0)	3.1 (3.2)
MAS mean (sd)	4.8 (3.1)	4.2 (3.1)	3.4* (2.7)	4.8 (3.4)	3.2* (3.0)	2.9* (2.3)
CPAP n score ≥ 8	11/54	6/49	6/37	8/54	5/49	5/37
(% score ≥ 8)	(20.4%)	(12.2%)	(16.2%)	(14.8%)	(10.2%)	(13.5%)
MAS n score ≥ 8	11/47	7/39	4/41	10/47	5/39	3/41
(% score ≥ 8)	(23.4%)	(17.9%)	(10.3%)	(21.3%)	(12.8%)	(7.3%)

**Statistically significant change from baseline to follow-up within treatment group, paired samples t-test (P < 0.05).*

3.3 Paper I

Self-reported sleep quality with mandibular advancement device or continuous positive airway pressure: A randomized clinical trial on patients with mild and moderate obstructive sleep apnea.

The main aim of Paper I was to compare self-reported sleep quality after the initial phase (4 months) of CPAP or MAS treatment in non-severe OSA.

At the 4-month follow-up visit 17 (31.5%) and 33 (75.0%) of the patients in the CPAP and MAS treatment group respectively used their assigned treatment device > 4 hours and > 70% of nights. Due to the poor compliance to treatment, particularly in the CPAP treatment group, an alternative cut-off for defining compliance to treatment was used in Paper I: > 4 hours and > 50% of nights. Using this cut-off, the number of patients included in the PP analysis at follow-up were 21 (38.9%) in the CPAP treatment group and 35 (79.5%) in the MAS treatment group. The difference in compliance between treatment groups using any of these cut-off definitions were statistically significant ($p < 0.001$).

Both the CPAP and the MAS treatment group improved the PSQI global score (ITT: $p = 0.01$, and $p < 0.001$, respectively. PP: $p = 0.02$, and $p < 0.001$, respectively). As presented in Paper I, statistically significant differences were not found between the treatment groups in neither the ITT nor the PP analyses ($p = 0.11$ and $p = 0.55$ respectively) at the 4-month follow-up visit using the Student's *t*-tests. When adjusting for baseline variables through linear regression analyses the PSQI global score after 4 months of treatment was higher in the CPAP treatment group compared to the MAS treatment group ($p = 0.02$) in both the ITT and PP analyses (Table 15).

Table 15 PSQI global score at baseline and at the 4-month follow-up visit.

	Baseline		*4-month follow-up*			
	CPAP $n^{ITT} = 55$ $n^{PP} = 21$	MAS $n^{ITT} = 49$ $n^{PP} = 35$	CPAP $n^{ITT} = 54$ $n^{PP} = 21$	MAS $n^{ITT} = 44$ $n^{PP} = 35$	Adj. difference MAS – CPAP (95% CI)§	P Δ MAS – CPAP at follow-up
PSQI ITT	7.7 (3.5)	8.0 (3.1)	6.7 (3.4)	5.7 (2.5)	-1.3 (-2.3 – -0.2)	.02
PSQI PP	7.1 (3.5)	8.1 (3.1)	5.8 (3.3)	5.3 (2.5)	-1.4 (-2.5 – -0.2)	.02

P < 0.05 – Significant difference between MAS and CPAP treatment groups, based on linear regression analysis adjusted for baseline variables (Age, BMI, sex, smoking, baseline AHI / PSQI global score / PSQI question 8 sleepiness and symptoms of anxiety and depression according to HADS).

The RCI in the ITT population showed that more patients in the MAS treatment group (38.6%) compared to the CPAP treatment group (16.7%) had an improved PSQI global score after 4 months of treatment ($p = 0.01$). In the PP population, a similar result was found; more patients

in the MAS treatment group (45.7%) than the CPAP treatment group (19.0%) improved the PSQI global score according to the RCI (p = 0.04). When adjusting for baseline variables using multivariable logistic regression as described in section 2.7.8.1, the patients were less likely to have significantly improved PSQI global score in the CPAP treatment group than in the MAS treatment group in both the ITT (p = 0.003) and PP analyses (p = 0.04) (Table 16).

Table 16 The number of patients with improved PSQI global score after 4 months of treatment (RCI < -1.96).

	CPAP n=54	**MAS n=44**	**OR (95% CI)**	**P**
Improved PSQI (ITT)	16.7 % (9/54)	38.6 % (17/44)	12.1 (2.4 – 61.3)	.003
Improved PSQI (PP)	19.0 % (4/21)	45.7 % (16/35)	7.8 (1.1 – 57.7)	.04

OR: Odds ratio (95% confidence interval), reference category: CPAP.
P < 0.05 – Significant difference between MAS and CPAP treatment groups, based on logistic regression analysis adjusted for baseline variables (Age, BMI, sex, smoking, baseline AHI / PSQI global score / PSQI question 8 sleepiness and symptoms of anxiety and depression according to HADS).

To facilitate the comparison between the results from the 4- and 12-month follow-up visits, the results from the 4-month follow-up visit using compliance cut-off > 4 hours and > 70% of nights in the PP analyses are presented in section 3.5.1 (Table 19 and Table 20).

3.4 Paper II

Friedman score in relation to compliance and treatment response in non-severe obstructive sleep apnea

The main aim of Paper II was to investigate the association between Friedman score and compliance to treatment and between Friedman score and AHI improvement in patients with non-severe OSA receiving CPAP or MAS treatment.

The patients in the RCT were reasonably distributed between the various Friedman scores: 22 had score I, 23 had score II, 32 had score III, and 27 had score IV. Baseline characteristics except for smoking and tonsil size were similar across Friedman scores: Fewer patients with grade III were smokers, and more patients with grade II had tonsil size > 1 compared to patients with other Friedman scores. Since 98.1% of the patients had tonsil size < Brodsky grade 3, it was not feasible to combine Friedman score, BMI and tonsil size into the Friedman staging system.

The main logistic regression model was adjusted for age, sex, BMI, education level, smoking and tonsil size. In neither the crude logistic regression model, nor the main model, was an increased Friedman score associated with changed odds of being compliant to treatment (main model OR: 0.85, 95% CI: 0.59-1.23) or having adequate AHI reduction (main model OR: 1.05, 95% CI: 0.62-1.76) at the 12-month follow-up visit. This was the case for each treatment group and the overall

RCT population. The distributions of patients compliant to treatment (n = 54/103) and patients with adequate AHI improvement (n = 59/77) across Friedman score at follow-up are illustrated in Figure 9 and Figure 10 respectively.

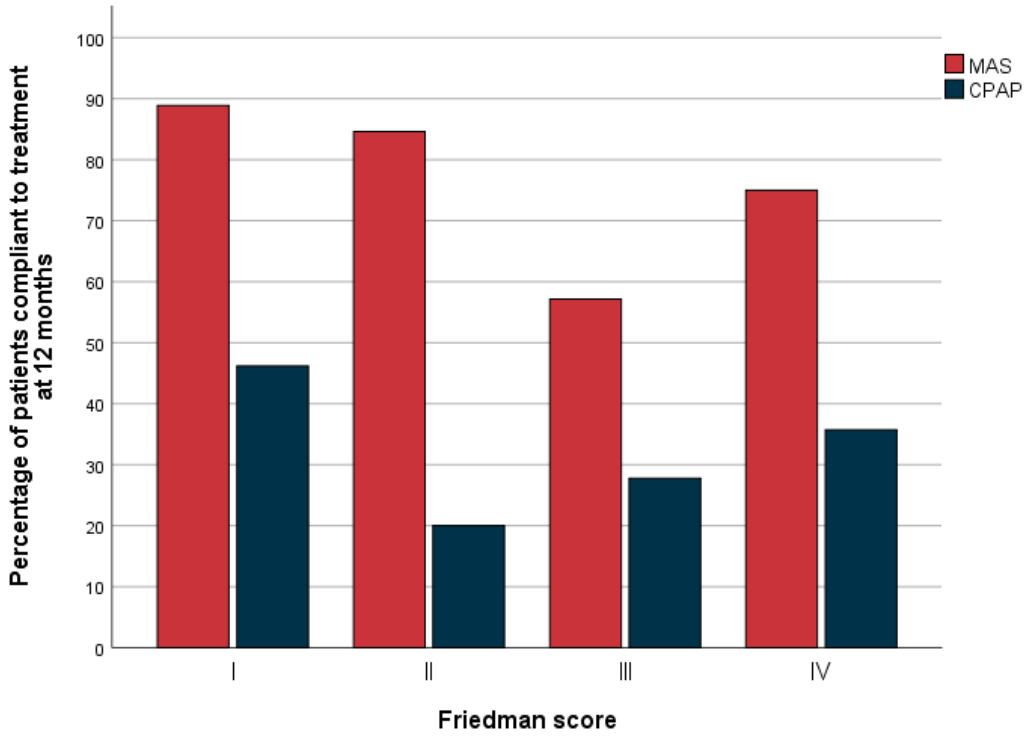

Figure 9 Patients compliant to CPAP (n = 18/55) and MAS (n = 36/48) at 12-month follow-up per Friedman score.

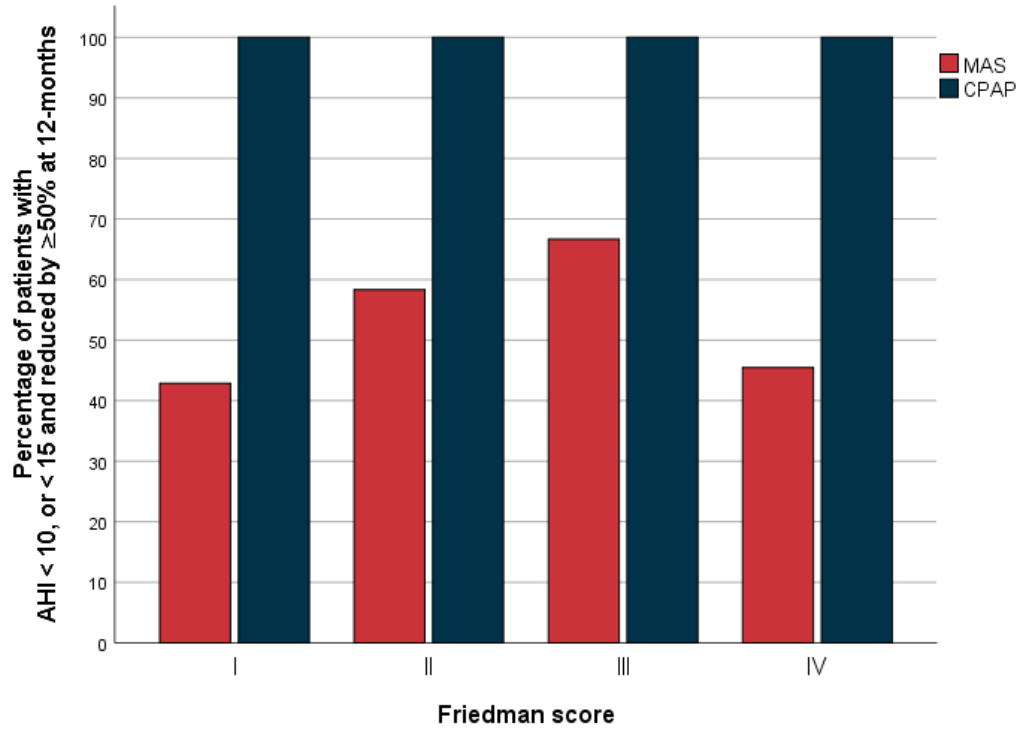

Figure 10 Patients with adequate AHI-improvement with CPAP (n = 38/38) and MAS (n = 21/39) at 12-month follow-up per Friedman score.

3.5 Paper III

Health-related quality of life and sleep quality after 12 months of treatment in non-severe obstructive sleep apnea: A randomized clinical trial with Continuous Positive Airway Pressure and Mandibular Advancement Splints

The main aim of Paper III was to compare CPAP and MAS treatment in non-severe OSA in respect to the HRQoL and self-reported sleep quality after 12 months of treatment. Correlation between HRQoL and sleep quality was also assessed.

The participants in the trial had mean SF36 domain scores at baseline below, but within 1 standard deviation from the general Norwegian population mean scores. The individual domains and component scores were mostly normally distributed. However, the distributions in the domains Physical Functioning, Role Physical, Bodily Pain, Social Functioning, and Role Emotional were to some extent skewed towards the higher scores. The ITT analyses showed improvements in the SF36 physical component score (from 48.8 ± 7.6 to 50.5 ± 8.0, $p = 0.03$) in the CPAP treatment group and in the mental component score (from 44.9 ± 12.1 to 49.3 ± 9.2, $p = 0.009$) in the MAS treatment group. In the PP analyses the mental component score were improved in the CPAP treatment group (from 47.6 ± 9.6 to 53.2 ± 4.9, $p = 0.003$) and in the MAS treatment group (from 44.1 ± 12.5 to 50.5 ± 8.0, $p = 0.003$). In both treatment groups, and both ITT and PP analyses, the SF36 vitality domain showed the biggest improvement from baseline to follow-up. Minor improvements were found in other individual domains, which are reflected in the component score improvements. Changes in each SF36 domain from baseline to follow-up in the CPAP and MAS treatment group found in the ITT analyses are presented in Figure 11. Corresponding changes found in PP analyses are presented in Figure 12.

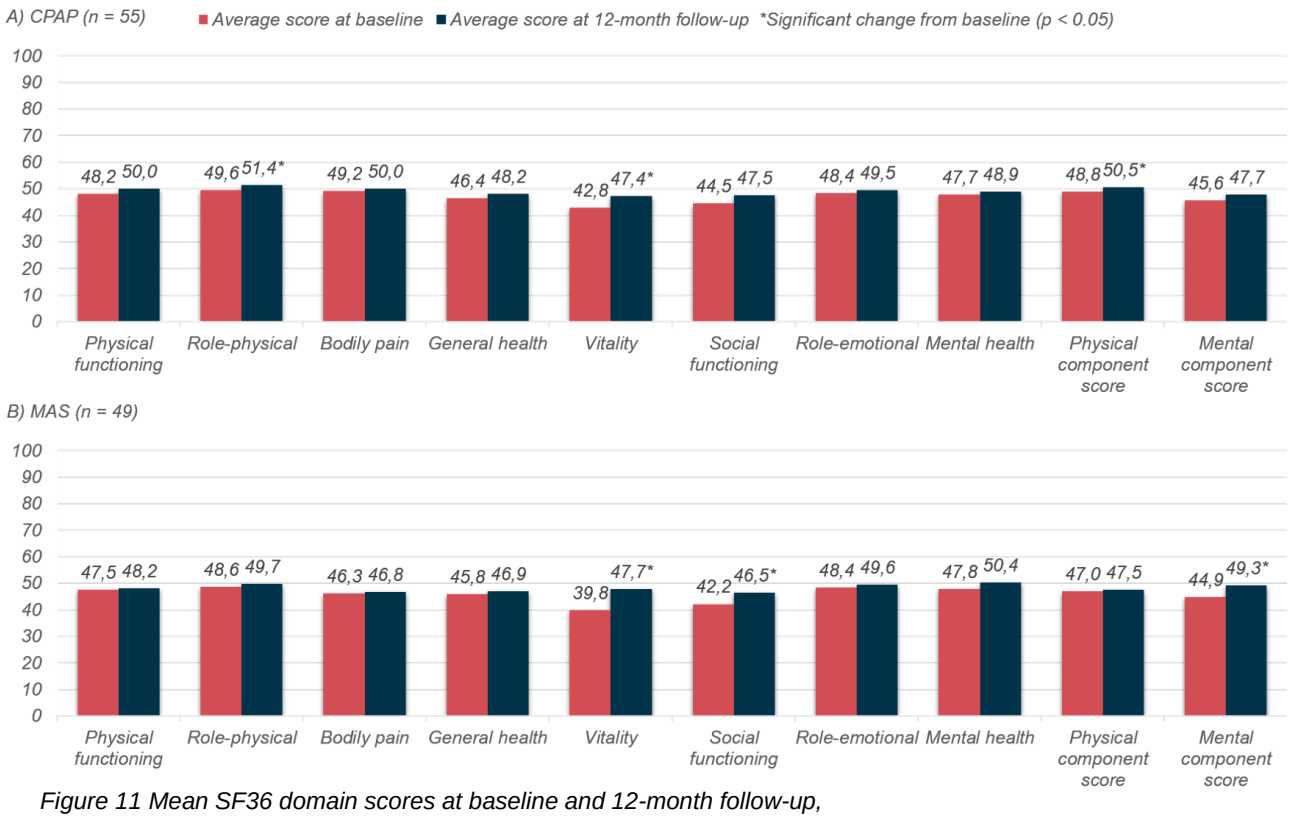

Figure 11 Mean SF36 domain scores at baseline and 12-month follow-up, intention-to-treat analysis. A) CPAP treatment group, B) MAS treatment group.

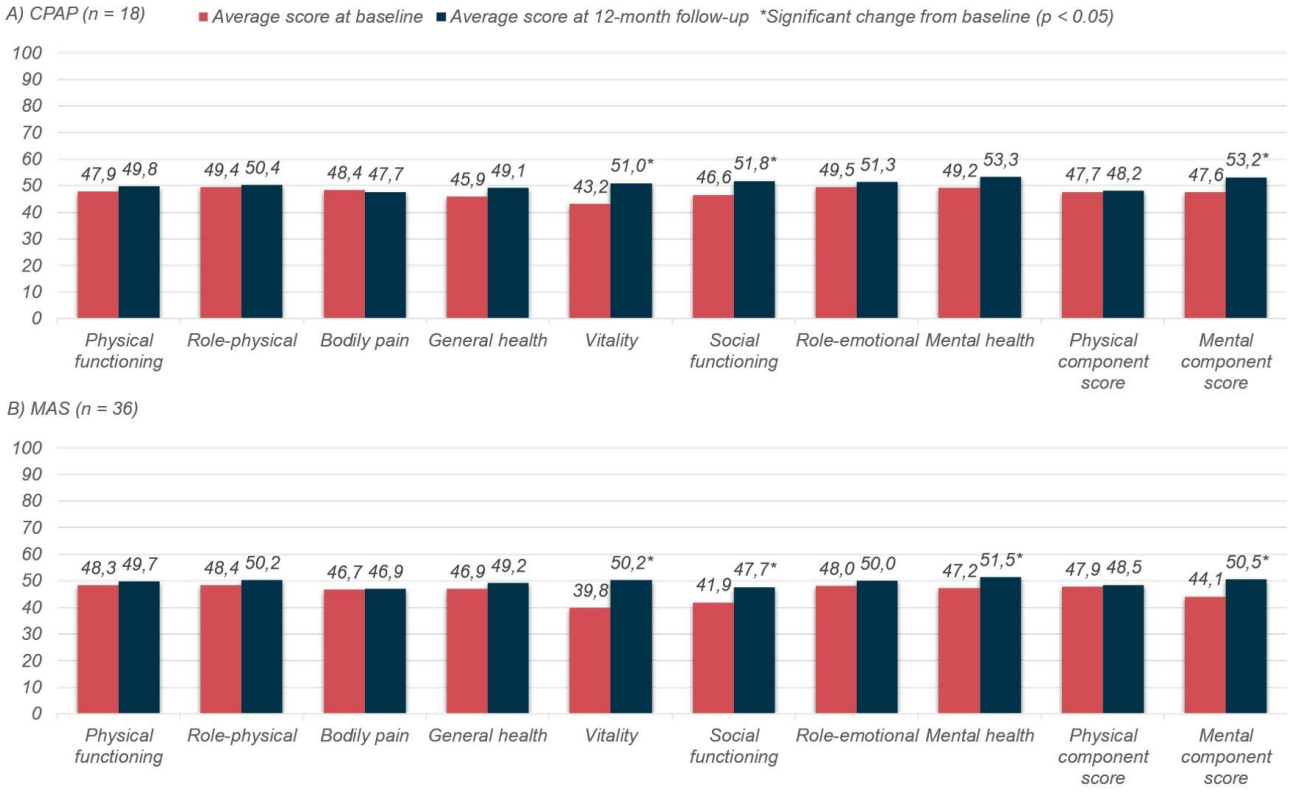

Figure 12 Mean SF36 domain scores at baseline and 12-month follow-up, per protocol analysis. A) CPAP treatment group, B) MAS treatment group.

In the ITT analysis, the PSQI global score was improved from baseline to the 12-month follow-up by both CPAP (from 7.7 ± 3.5 to 6.6 ± 2.9, $p = 0.006$) and MAS (8.0 ± 3.1 to 6.1 ± 2.6, $p < 0.001$) treatment. Similarly, the PP analysis showed improvement in PSQI global score in both the CPAP (from 7.1 ± 3.4 to 5.7 ± 2.3, $p = 0.03$) and MAS treatment group (from 7.7 ± 3.3 to 5.4 ± 2.5, $p < 0.001$).

Neither the ITT nor PP analyses found any statistically significant differences between the CPAP and MAS treatment group in any of the SF36 domain scores, component scores, or PSQI global score at the 12-month follow-up visit.

This was also true for the number of patients with significant improvement in SF36 domain scores and PSQI global score from baseline to the 12-month follow-up visit, but the chi-square and Fisher's exact tests presented in Paper III were not adjusted for baseline variables. Table 17 and Table 18 show the adjusted odds ratio for having improved SF36 domain scores according to the RCI in the MAS treatment group compared to the CPAP treatment. In the PP analysis, odds ratio could not be presented due to wide confidence intervals in 7 of the 10 SF36 domain/component scores.

Table 17 The number of patients with significantly improved SF36 domain scores from baseline to follow-up (RCI > 1.96), intention-to-treat.

	Significantly improved HRQoL			
SF36 domains	CPAP n=55	MAS n=49	OR (95% CI)	P
Physical functioning	16.4% (9/55)	12.2% (6/49)	1.2 (0.2 – 6.2)	.82
Role-physical	12.7% (7/55)	12.2% (6/49)	0.2 (0.0 – 2.1)	.18
Bodily pain	7.3% (4/55)	10.2% (5/49)	1.3 (0.2 – 8.8)	.76
General health	21.8% (12/55)	28.6% (14/49)	2.2 (0.7 – 7.2)	.20
Vitality	36.4%* (20/55)	44.9%* (22/49)	1.7 (0.6 – 5.0)	.34
Social functioning	12.7% (7/55)	18.4% (9/49)	3.6 (0.6 – 22.2)	.17
Role-emotional	9.1% (5/55)	12.2% (6/49)	8.8 (0.3 – 230.3)	.19
Mental health	14.5% (8/55)	22.4% (11/49)	2.7 (0.7 – 11.0)	.17
Physical component	10.9% (6/55)	8.2% (4/49)	0.6 (0.1 – 2.8)	.49
Mental component	18.2% (10/55)	20.4%* (10/49)	3.4 (0.5 – 24.7)	.22

**Significant correlation to the PSQI global score.*
OR: Odds ratio (95% confidence interval), reference category: CPAP.
P > 0.05 – No significant difference between MAS and CPAP treatment groups, based on logistic regression analysis adjusted for baseline variables (Age, BMI, sex, smoking, baseline AHI / respective SF36 domain score / PSQI question 8 sleepiness and symptoms of anxiety and depression according to HADS).

Table 18 The number of patients with significantly improved SF36 domain scores from baseline to follow-up (RCI > 1.96), compliant patients only.

	Significantly improved HRQoL			
SF36 domains	CPAP n=18	MAS n=36	OR (95% CI)	P
Physical functioning	11.1% (2/18)	11.1% (4/36)	N.A.	1.0
Role-physical	5.6% (1/18)	13.9% (5/36)	N.A.	1.0
Bodily pain	5.6% (1/18)	11.1% (4/36)	N.A.	.30
General health	27.8% (5/18)	36.1% (13/36)	2.6 (0.4 – 17.6)	.33
Vitality	38.9%* (7/18)	50.0% (18/36)	0.7 (0.1 – 4.8)	.67
Social functioning	5.6% (1/18)	19.4% (7/36)	N.A.	1.0
Role-emotional	11.1% (2/18)	13.9% (5/36)	N.A.	1.0
Mental health	16.7% (3/18)	25.0% (9/36)	3.1 (0.2 – 44.0)	.40
Physical component	5.6% (1/18)	11.1% (4/36)	N.A.	.98
Mental component	22.2% (4/18)	22.2% (8/36)	N.A.	1.0

**Significant correlation to the PSQI global score.*
OR: Odds ratio (95% confidence interval), reference category: CPAP.
P > 0.05 – No significant difference between MAS and CPAP treatment groups, based on logistic regression analysis adjusted for baseline variables (Age, BMI, sex, smoking, baseline AHI / respective SF36 domain score / PSQI question 8 sleepiness and symptoms of anxiety and depression according to HADS).
N.A.= Not Applicable – Confidence interval range from zero to infinity.

In the ITT analysis, the individual patients' improvement in the SF36 vitality domain score moderately correlated to the improvement in the PSQI global score in both treatment groups (CPAP: $|r| = 0.47$, $p < 0.001$; MAS: $|r| = 0.36$, $p = 0.01$). In the MAS treatment group, there was also a weak correlation between improvements in the SF36 mental component score and PSQI global score ($|r| = 0.28$, $p = 0.05$). In the PP analysis, the improvement in the SF36 vitality domain was strongly correlated with that of the PSQI global score in the CPAP treatment group ($|r| = 0.51$, $p = 0.03$). No other SF36 domain scores or component scores with significant improvement were correlated to improvements in the PSQI global score.

3.5.1 PSQI comparisons between Paper I and Paper III

The mean PSQI global score at the 4- and 12-month follow-up visit and the adjusted difference between the CPAP and MAS treatment group are shown side by side in Table 19. At the 4-month follow-up visit the CPAP treatment group had a statistically significantly higher PSQI global score compared to the MAS treatment group ($p = 0.02$) in the ITT analysis. A similar trend was

found at the 12-month follow-up visit but the difference was not statistically significant (p = 0.06). No statistically significant difference between the CPAP and MAS treatment groups was found in the PP analysis at neither follow-up visits.

Table 19 Differences in mean PSQI global score between the CPAP and MAS treatment groups at baseline and after 4 and 12 months.

	Baseline		*4-month follow-up*			*12-month follow-up*		
n^{ITT} n^{pp}	CPAP n=55 n=18	MAS n=49 n=36	CPAP n=54 n=17	MAS n=44 n=33	Adj. difference MAS – CPAP (95% CI), P value	CPAP n=55 n=18	MAS n=49 n=36	Adj. difference MAS – CPAP (95% CI), P value
PSQI ITT	7.7 (3.5)	8.0 (3.1)	6.7 (3.4)	5.7 (2.5)	-1.3 (-2.3 – -0.2), .02	6.6 (2.9)	6.0 (2.6)	-0.9 (-1.9 – 0.1), .06
PSQI PP	7.1 (3.8)	7.7 (3.3)	5.8 (3.3)	5.3 (2.5)	-1.1 (-2.4 – 0.2), .10	5.7 (2.3)	5.4 (2.5)	-0.8 (-2.1 – 0.4), .18

P < 0.05 – Significant difference between MAS and CPAP treatment groups, based on linear regression analysis adjusted for baseline variables (age, BMI, sex, smoking, baseline AHI / PSQI global score / PSQI question 8 sleepiness and symptoms of anxiety and depression according to HADS).

A similar pattern was found when comparing the number of patients having significantly improved PSQI global score from baseline to the 4- and 12-month follow-up visits respectively (Table 20). The patients in the MAS treatment group had higher odds of having significantly improved PSQI global score after 4 months of treatment (p = 0.003) in the ITT analysis. Note that the 95% confidence interval for the OR was 2.4 – 61.3, indicating that this finding is dubious. No statistically significant odds ratio between the CPAP and the MAS treatment groups was found for the number of patients with improved PSQI global score at the 12-month follow-up visit. Neither was there any statistically significant difference in the PP analysis at the 4-month follow-up. All differences between the CPAP and MAS treatment groups shown in Table 19 and Table 20 were adjusted for baseline variables as described in section 2.7.8.2.

Table 20 The number of patients with improved PSQI global score after 4 and 12 months of treatment (RCI < 1.96).

	4-month follow-up				**12-month follow-up**			
	CPAP n=54	MAS n=44	OR (95% CI)	P	CPAP n=55	MAS n=49	OR (95% CI)	P
Improved PSQI (ITT)	16.7% (9/54)	38.6% (17/44)	12.1 (2.4 – 61.3)	.003	18.2% (10/55)	32.7% (16/49)	2.5 (0.7 – 9.0)	.15
Improved PSQI (PP)	11.8% (2/17)	45.5% (15/33)	4.9 (0.5 – 45.7)	.16	16.7% (3/18)	33.3% (12/36)	3.6 (0.3 – 41.0)	.30

OR: Odds ratio (95% confidence interval), reference category: CPAP.
P < 0.05 – Significant difference between MAS and CPAP treatment groups, based on logistic regression analysis adjusted for baseline variables (Age, BMI, sex, smoking, baseline AHI / PSQI global score / PSQI question 8 sleepiness and symptoms of anxiety and depression according to HADS).

4 Discussion

The interpretation of the results presented in this thesis follows a discussion regarding methodological issues that should be acknowledged when interpreting the results.

4.1 Methodological issues

4.1.1 Study design

Given ideal conditions, properly planned and executed random allocation to treatment ensures identical treatment groups. This prevents bias from patient selection and confounding variables, leaving the allocated intervention as the primary explanation of any differences in outcome between the treatment groups. Thus, a RCT may expose causal associations between intervention and outcome and is regarded the "gold standard" study design in clinical research. Unfortunately, the ideal conditions necessary to ensure that the allocation to treatment is the only factor influencing the outcome hardly exists in reality (Moher et al., 2010, Schulz, 1997, Schulz, 1998). In the RCT upon this thesis is based, several factors potentially undermined the benefits associated with the RCT study design. Most importantly, blinding of the health-care providers and patients was impossible, possibly introducing performance bias and attrition bias. This RCT was also to some degree susceptible to selection bias since an unknown fraction of the regional total OSA population might not have been referred to the hospitals recruiting patients to the RCT. Moreover, some patients did not show at the follow-up visits, possibly introducing bias and confounding in the analyses. Yet, the nature of random allocation to treatment should still limit most of the potential biasing and cofounding variables in this RCT, compared to e.g., case-control studies, cohort studies and other observational study designs. Indeed, it should be expected that most of the confounders and biases in this RCT are feasible to identify. The identification and handling of potential confounders are discussed in section 4.1.3 (Handling of confounders).

Another limitation in this RCT is the lack of a placebo treatment group. The data gathered prior to treatment were all from untreated OSA patients that show the situation for untreated patients. However, without a placebo group it is impossible to known to which extent changes from baseline to follow-ups could be attributed to placebo effects such as patients becoming aware of the mechanisms and severity of OSA and having their symptoms acknowledged by health-care professionals (Isidoro et al., 2015). Similarly, without a placebo group it is impossible to adjust for placebo effects in any outcomes of the RCT. Even though changes from baseline to follow-ups are associated with uncertainties related to placebo effects, comparisons between treatment groups are still valid without comparing changes to a placebo group. The effects observed in the treatment groups of a well conducted RCT are likely representative of the effects found in

ordinary clinical practice, but conclusions regarding causal effects from treatment cannot be made without adjusting for placebo effects.

Since this RCT compared two active treatment alternatives, the trial should be classified as a "non-inferiority trial" or an "equivalence trial". In contrast, a "superiority trial" usually compare an active treatment to a placebo treatment or passive control group. Since identifying lack of difference between active treatment groups are as important as finding differences between them, an optimal non-inferiority trial should reach a statistical power of 95%. As discussed in section 4.1.2 (Sample size) this was not feasible in this RCT, thus the risk of statistical type II errors should be considered when interpreting lacking differences between the treatment groups.

4.1.1.1 Randomization process

The patients were randomized to either CPAP or MAS treatment after consenting on participation in the trial. The randomization procedure was included as the last step of the physical examination by otorhinolaryngologists at the University Hospital in Northern Norway and St. Olavs Hospital. The randomization procedure in this trial was analogue, using a masked envelope at each study site containing 30 lots from the start, which were refilled prior to the allocation of the 31st patient at each study site. In the end, 3 more patients were allocated to the CPAP treatment group than to the MAS treatment group at each study site, but this unequal allocation was very likely to arise at random. During the recruitment period, no events compromising the random allocation of patients were reported, suggesting that all steps of the randomization procedure worked adequately. Any differences between the treatment groups at baseline should thus occur at random (Altman and Doré, 1990). Although presented in this thesis, significance testing at baseline could thus be regarded superfluous according to the CONSORT 2010 statement (Altman, 1985).

Sleep-quality and HRQoL are associated with seasonal variation, which is particularly profound in the northern parts of Norway, where the winter is characterized by the polar night and the midnight sun provides daylight throughout the night during the summer. Due to the large variations in daylight between seasons, an unequal distribution of patients to treatment groups throughout the seasons is a potential source of bias, even though occurring at random. Hence, block randomization was chosen in this RCT, although this hypothetically increased the risk of the otorhinolaryngologists, responsible for the randomization, to be able to predict the next allocation at the end of each block. This risk was deemed less severe than the risk of creating season-related bias by not using block randomization. By using block randomization at each study site, the risk of unequal allocation to the treatment groups across study sites was also reduced.

4.1.1.2 Study centers

The RCT was performed in the cities of Tromsø and Trondheim, separated by more than 1 100 kilometers. Patients in Trondheim were recruited at both a public and a private hospital, whereas patients referred to the private ENT clinic in Tromsø were not considered for participation in the trial. The geographical differences, and possible different characteristics between patients referred to public vs. private hospitals, may contribute to differences between the two study sites regarding the study populations. Indeed, patients enrolled in Tromsø reported on average worse subjective dental health and had higher BMI than patients recruited in Trondheim. This corresponds with studies and official statistical information that indicate similar patterns in the use of dental services and BMI between the counties of Trøndelag and Troms and Finnmark (Adekoya and Brustad, 2012, Folkehelseinstituttet, 2020). In addition, patients referred for OSA treatment in Trondheim had on average longer hypopnea duration compared to Tromsø ($p < 0.001$). The reason for this difference is unknown, but it could be hypothesized that this is related to the difference in BMI between the study sites. By recruiting patients from both private and public hospitals, potential differences between referral patterns between private and public healthcare should be counterbalanced, increasing the external validity of the trial population. Interestingly, no differences were found between patients referred to the private and public hospitals, although undetected differences in patient characteristics cannot be ruled out.

4.1.1.3 Calibration process

The adherence to the study protocol by the health-care personnel in this RCT was monitored by the researchers TKSA and LMB throughout the study period. However, no kappa values for inter- and intra-observer reliability were calculated. Kappa values expose subtle variations between observers that otherwise may remain unnoticed and possibly introduce performance- and attrition bias through the health-care personnel's handling of the enrolled patients. Hence, the kappa values should ideally have been calculated after the calibration of health-care personnel in this RCT. On the other hand, all observed health-care personnel showed excellent adherence to the study protocol when treating patients enrolled in this RCT.

The good and consistent adherence to the study protocol observed throughout this RCT may be attributed to the checklists integrated in the questionnaires and forms completed by the otolaryngologists, sleep technicians and dentists at the baseline examination, at the time of adaptation of the allocated treatment device and at both follow-up sessions. Adherence to the study protocol and standardized handling of the patients in this RCT was also ensured through hand-picking and frequent monitoring the personnel involved in the RCT. No health-care personnel were to be involved in this RCT if they expressed any nonchalant attitudes towards the

adherence to and execution of the study protocol and checklists. Besides, training and calibration were performed until there were no doubt that the treatment of patients were performed in a standardized manner by all involved personnel.

The calibration sessions and monitoring of the personnel involved in the RCT was performed prior to the inclusion of the first patients, but no fixed interval between the following calibration sessions was set. This practice may have resulted in inadvertently large intervals between calibration sessions. Ideally, the calibration process and monitoring of personnel should therefore have been carefully planned prior to the study start. The lack of predetermined calibration intervals and kappa values is unarguable a limitation in this thesis but considering the observed adherence to the study protocol it is unlikely that differences between health-care personnel significantly impact the results presented in this thesis.

4.1.1.4 Eligibility criteria

Since the overall aim of the RCT was to compare primary CPAP and MAS treatment, the eligibility criteria were chosen to ensure that CPAP was the primary treatment alternative for all patients according to existing guidelines for non-severe OSA treatment (Skår et al., 2015). The hospitals hosting this study do not offer CPAP treatment to patients with baseline AHI < 10, thus the lower AHI limit for participating in this trial was set accordingly. All patients had to be eligible for both CPAP and MAS treatment due to the random allocation to treatment. This required all patients to have adequate dental support and absence of considerable temporomandibular dysfunction or other anatomical abnormalities disqualifying for either CPAP or MAS treatment. Since HRQoL and compliance to treatment were studied, patients had to be CPAP and MAS naïve, resulting in the exclusion of all patients with previous CPAP or MAS experience. Drug abuse, daily use of sedative medication and severe psychiatric disorders were exclusion criteria for the same reason.

The available literature at the time when the trial was planned, suggested that MAS treatment was reserved for treating mild and moderate OSA and CPAP intolerant patients with any OSA severity (Marklund et al., 2012). Enrolling treatment naïve patients with severe OSA patients was thus considered ethically dubious at the time. However, more recent literature does question the use of AHI as the sole measure of OSA severity, indicating that MAS treatment may after all be a more relevant treatment option for selected patients with severe OSA as well (Patel and Mehra, 2015, Sutherland et al., 2018).

4.1.2 Sample size

All clinical trials should enroll enough patients to provide a high probability of detecting differences between treatment groups in the main outcomes. To properly plan a clinical trial, the estimated number of patients needed to show statistically significant differences is calculated based on the expected effect size, i.e., the expected difference between the treatment groups (Moher et al., 2010). In this RCT, the sample size was calculated to meet the requirements of $\alpha = 0.05$ and $1-\beta = 0.80$. That is, having an 80% chance of detecting true differences between treatment groups, and a 95% chance of correctly falsifying the null hypothesis whenever differences between treatment groups are found. In other words, assuming that the required sample size was reached, the trial should have a statistical power of 80%. Analyses performed on too small sample sizes are prone to type II errors, i.e., not detecting real differences between study groups. However, the calculated sample size is merely a guide in the planning phase of the study. As soon as the data are analyzed, the size of the confidence intervals are indicative of the actual risk of type II errors in the results from the RCT (Levine and Ensom, 2001, Moher et al., 2010).

Proper estimation of sample size is important for both scientific and ethical reasons (Moher et al., 2010): Carrying out a clinical trial where the null hypothesis demand an unrealistic number of patients to be falsified are scientifically unfeasible and unethical since patients then are enrolled in a trial for no scientific reason. On the other hand, recruiting surplus patients to a clinical trial with respect to the number needed to falsify a null hypothesis is regarded abuse of resources and unethical as well. On the other hand, it is also regarded unethical not to publish trials that for some reason fail to reach the planned sample size (Moher et al., 2010, Schulz and Grimes, 2005). Although such research results should be published, the actual power of the trial may be lower than calculated, resulting in an increased risk of type II errors in the findings.

The calculated sample size in this RCT was based on differences in HRQoL, the outcome variable anticipated to produce the smallest effect size. Unfortunately, the calculated sample size ($n = 138$) was greater than the actual sample size reached in the trial ($n = 104$). This RCT was thus arguable "underpowered" for detecting the calculated effect size in HRQoL. However, the sample size was sufficient according to power calculations based on differences in self-reported sleep quality ($n = 90$). Regardless of the calculated power, the confidence intervals should be assessed for the best indication for whether the findings are likely to be true (Levine and Ensom, 2001, Schulz and Grimes, 2005). Although a considerable portion of patients did quit treatment prior to the 12-month follow-up visit, thus not providing viable AHI measurements, information on compliance to treatment were available for 103 patients. Hence only 1 patient were regarded truly lost to follow-up at the 12-month follow-up. The patient lost to follow-up used MAS until the

4-month follow-up visit, but the patient did not show at the 12-month visit and whether this patient was compliant to treatment after the 4-month follow-up is thus unknown.

4.1.3 Handling of confounders

As discussed in 4.1.1 (Study design), confounders are likely to be present in the data analyses. Confounders are variables that influence both the exposure and outcome variables, e.g., increasing BMI do probably increase Friedman score and reduce the likelihood of treatment success in OSA patients, as illustrated in Figure 13. The random allocation of patients minimizes the number of potential confounders, making identification and handling of the remaining confounders easier. This is particularly important in the non-ITT analyses since some of the patients enrolled in the trial are excluded from those analyses. The exclusions of patients in the PP analysis are probably not at random, thus violating the benefits provided by the randomization at baseline and increasing the number and severity of confounders in the data (DeMets and Cook, 2019). Besides, analyses of data from observational studies, such as in Paper II, should always be adjusted for confounding variables since they do not benefit from the randomization of patients at all, even though performed in an RCT setting.

Identifying and selecting confounders should be performed in accordance with the aim of the study and based on existing literature describing variables associated with the outcome variable of interest. This process should include the use of directed acyclic graphs, facilitating the identification of both confounding, modifying and colliding variables (Shrier and Platt, 2008). The direct acyclic graphs and statistical models should be kept as simple as possible. Hence, variables being correlated or similar to each other should be reduced to one variable e.g., by removing the variable that affects the statistical model the least (Chowdhury and Turin, 2020). Figure 13 shows an example of a directed acyclic graph (Textor et al., 2017) used to identify variables confounding the association between Friedman score and adequate AHI improvement.

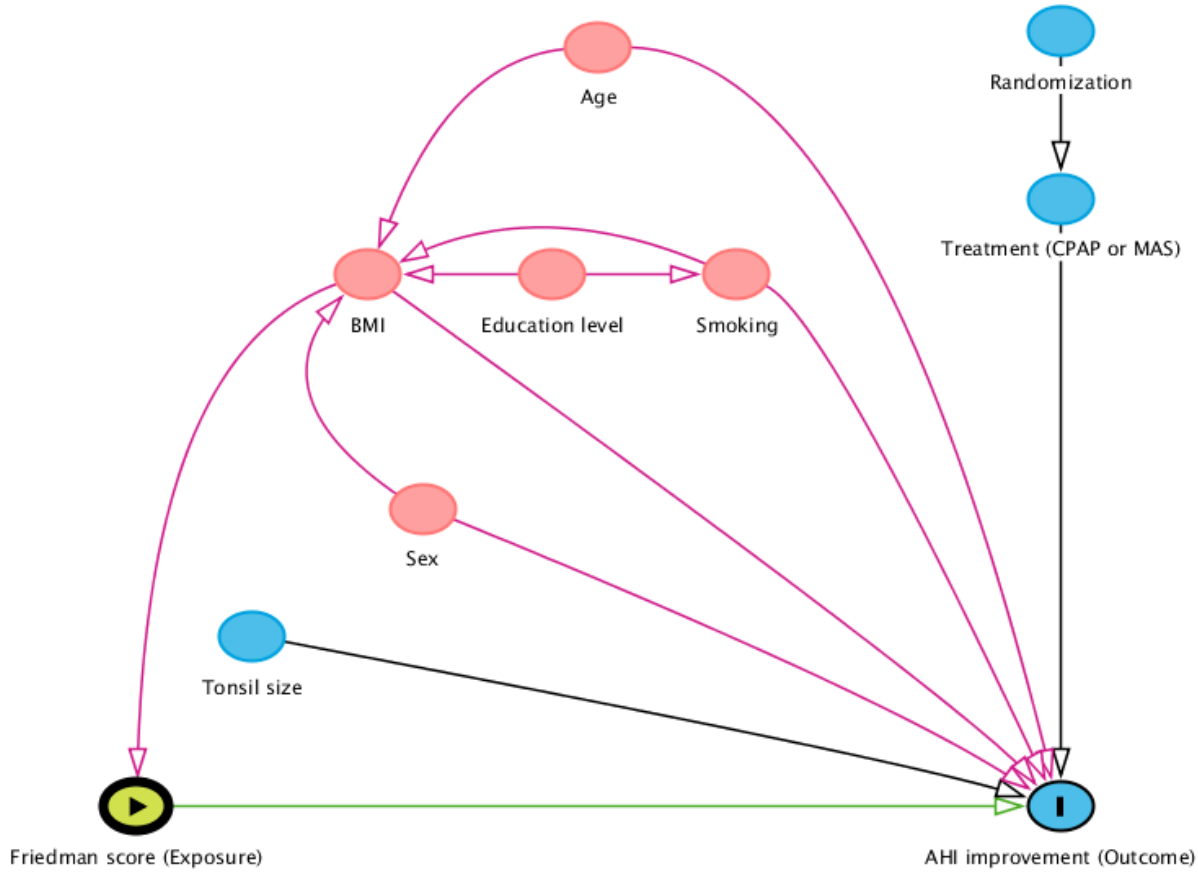

Figure 13 Example of a directed acyclic graph used for identification of potential confounders in one of the analyses presented in Paper II. The arrows show the direction of effects, variables colored red are potential confounders that directly or indirectly affect both the Friedman score and AHI improvement, variables colored blue are not affecting the Friedman score and are not regarded as confounders in this analysis.

4.1.4 Intention-to-treat vs. per protocol analyses

The results from a RCT should always be analyzed according to the ITT principle (DeMets and Cook, 2019). In short, the ITT principle implies that all patients enrolled in the trial are included in the final analyses, regardless if they dropped out from the trial, had missing questionnaire entries, or were non-compliant to treatment (Hollis and Campbell, 1999). ITT analyses thus require all missing data on follow-up to be replaced, possibly creating bias in the process (Altman, 2009, Herman et al., 2009). Nevertheless, analyzing the data according to the ITT principle is the only way to maintain the methodological strengths of randomization, which ensures that treatment groups are in every way identical at baseline (DeMets and Cook, 2019). Theoretically, the random allocation to intervention means that the only variables causing differences between treatment groups at follow-up are associated with the respective intervention. Moreover, the ITT analyses include patients who are non-compliant or dropped out of the trial, providing the results most representative to clinical practice, and should be presented as the main result in any RCT (Hollis and Campbell, 1999, Sedgwick, 2015). Although the random allocation to intervention minimizes

the risk of having confounding variables at baseline, differences can arise at random between treatment groups. The ITT analyses should thus be adjusted for baseline variables in the statistical analyses. This is particularly important in trials with few participants due to the increased risk of random differences arising when statistical power diminish.

Alongside the ITT analysis, a PP analysis should follow, exploring the impact of e.g., non-compliant patients in the ITT analysis. The PP analyses may also assess the ideal efficacy of interventions in the trial since patients non-compliant to treatment are excluded from these analyses. However, PP analyses are inherently prone to bias and confounding (DeMets and Cook, 2019) and should be adjusted for baseline variables and variables associated with dropout or non-compliance in the trial (Sedgwick, 2015). Since 1 patient in the CPAP and 5 patients in the MAS treatment group had no available information on compliance status at the 4-month follow-up visit, they had to be excluded from all analyses in Paper I. The primary analysis at the 4-month follow-up is thus arguably not a strict ITT analysis.

4.1.5 Handling of missing data

All methods for replacing missing data in a RCT are associated with the risk of introducing bias to the data. To limit such bias, the clinical and research setting should be considered when choosing the method for replacing missing data (Herman et al., 2009, Hollis and Campbell, 1999). In this thesis, any missing entries in the SF36 questionnaire (n = 7) were replaced according to the methods described by Ware et al. (2000). Missing entries in the PSQI questionnaire (n = 9) and the baseline HADS questionnaire (n = 3) were replaced through multiple imputations, as recommended by the CONSORT 2010 statement (Altman, 2009, Moher et al., 2010). The imputations were calculated from average values and adjusted for demographic variables, OSA severity, and similar questions and questionnaires used in the patient anamnesis (Kneipp and McIntosh, 2001).

In cases where the patient had not used the treatment device at all or next to nothing, the reversible nature of CPAP and MAS treatment allows for the use of the last observation carried forward (LOCF) method when replacing missing data at the 12-month follow-up (Herman et al., 2009, Hollis and Campbell, 1999). Patients being completely non-compliant to treatment do not change their AHI, SF36 domain scores, or PSQI global score from baseline due to the allocated treatment device (Mehta et al., 2001, Young et al., 2013, Kohler et al., 2011). Data from baseline or data from the 4-month follow-up visit was thus used to replace missing data at the 12-month follow-up, mainly in patients dropping out from both the trial and treatment (n = 27). The patients dropping out of the trial were all non-compliant. Indiscrete use of the LOCF method to replace

missing data at the final follow-up entail a considerable risk of introducing bias and masking effects from the treatment (Altman, 2009, Lane, 2008, Moher et al., 2010, Molnar et al., 2008). The use of LOCF was thus limited and approached with outmost care in this RCT. The seasonal changes in daylight duration from baseline to the 4-month follow-up visit, and from the 4- to the 12-month follow-up visit may bias the patient-reported outcomes. However, using patient-reported data from baseline at the 12-month follow-up in completely non-compliant patients should not be biased by seasonal changes. On the other hand, data at the 4-month follow-up are inherently more representative than baseline data in patients who have tried to comply with CPAP or MAS treatment regimes. Besides, dropouts between the 4- and 12-month follow-up visits may occur all year round, possibly counterbalancing the bias from seasonal variations.

4.1.6 Delayed response in patient-reported outcomes

The patient-reported outcomes included in this thesis were measured by questionnaires asking the patient to report on the situation for the weeks leading up to the follow-up visits. The retrospective nature of the questionnaires causes a potential discrepancy between self-reported data and the data gathered from the HSAT and CPAP devices. For the MAS treatment group, the measured efficacy of the MAS device represents only the night of the HSAT, while the patient-reported outcomes may in part represent a situation prior to the HSAT, which may be somewhat outdated at the time of the follow-up visit. Similarly, the efficacy of the CPAP device is reported as average values from the last 90 days leading up to the follow-up, thus potentially representing a clinical situation prior to the time-period reflected in the patient-reported outcomes. The potential inertia found in the response from CPAP and possibly MAS treatment may to some degree further aggravate a delayed response in the patient-reported outcomes (Phillips et al., 2007, Young et al., 2013). In most cases, the delayed response in patient-reported outcomes is insignificant and the problem is merely hypothetical. However, the possible time discrepancy between objectively measured data and data reported by questionnaires should be kept in mind when interpreting the patient-reported outcomes.

4.1.7 Subjective vs. objective compliance to treatment

The use of self-reported compliance to treatment is an undisputable limitation in this thesis. During the planning stage of the RCT, objective measurement of compliance in the MAS treatment group was considered, but regulations at the time enforced by The Norwegian Data Protection Authority made such data collection impractical. Hence, objective data on compliance was accessible in the CPAP treatment group only. To ensure comparability between the treatment groups, self-reported compliance was assessed in both groups, assuming that patients were equally sincere when reporting their compliance to treatment. This assumption may be criticized

since the patients receiving CPAP treatment had to sooner or later become aware that the use and efficacy of the treatment were logged by the CPAP device. Patients in the MAS treatment group, on the other hand, had no reason to believe that a dishonest report on compliance to treatment could be revealed in any way. However, patients in none of the treatment groups had anything to gain on being dishonest about their compliance to treatment. On the contrary, patients were likely to estimate their compliance to treatment as accurate as possible to ensure optimal healthcare. When comparing objective and subjective compliance in the CPAP treatment groups, 6/54 patients at the 4-month follow-up and 4/55 at the 12-month follow-up misreported their compliance compared to objectively measured compliance to treatment. Most of them overestimated their use but were close to correctly estimating their compliance in general. Previous studies have shown that objective compliance after 12 months of MAS treatment is on average only slightly overestimated using questionnaires (Dieltjens et al., 2013). Although the compliance study by Dieltjens et al. (2013) was performed in the Netherlands, there is no reason to believe that patients in this RCT were significantly more or less precise in their reporting of the compliance to treatment. A key reason for this is that patients using the MAS typically wear the MAS throughout the whole night, thus it is difficult to overestimate the number of hours using the MAS device during a typical night. Those who overestimate compliance in the MAS treatment group are therefore most likely overestimating the number of nights using the MAS throughout the week.

Although the common cut-off for adequate compliance in OSA treatment is defined by using the treatment device more than 70% or 5 days per week, the questionnaire used in this trial did not provide “70% of nights” as an option. The lowest possible estimate of adequate use of the treatment device was “75% of nights”. This could have contributed to underestimating the number of compliant patients in the trial. However, no patients with objectively measured compliance > 70% of nights reported using the CPAP device < 75% of nights. Thus, the discrepancy between the reported cut-off for adequate compliance to treatment, and the possible answers given in the questionnaire concerning compliance are an unlikely source of bias. In fact, the discrepancy would rather contribute to reducing the risk of overestimating the compliance to treatment in both treatment groups. Overall, the risk of bias associated with the self-reported compliance to treatment in this RCT is likely to be minor.

4.1.8 Internal and external validity

The findings in a RCT should have both internal and external validity, i.e., showing the true results from the studied interventions, and being valid outside the research setting respectively (Akobeng, 2008). The internal validity depends on the number and severity of bias in the trial,

i.e., systematic errors in the recruitment and treatment of patients, and data analyses in the RCT. If the internal validity is poor, the external validity is irrelevant. However, many of the measures ensuring good internal validity such as eligibility criteria, random allocation to treatment, minimizing personalized information and treatment, do reduce the external validity of the findings. External validity is therefore often limited to the trial population and patients most alike those enrolled in the trial (Akobeng, 2008). In this RCT, several potential sources of bias were identified. These are categorized by selection bias, performance bias and attrition bias, and are discussed next.

4.1.8.1 Selection bias

The block randomization process in the RCT ensured that confounding baseline variables and differences between study sites were equally distributed between the treatment groups. It was also important to achieve an even distribution of patients throughout the year in both treatment groups since some variables such as self-reported sleep quality and HRQoL are vulnerable to changing seasons. However, the risk of bias associated with the recruitment of patients to the trial was not eliminated.

All patients receiving screening and treatment for primary OSA in Norway are referred from primary health care to either public or private hospitals. In any case, OSA treatment is associated with only a small co-payment for all patients with AHI > 10, thus, bias related to the monetary cost of CPAP and MAS treatment is negligible. Yet, current guidelines imply that only patients who fail CPAP treatment are offered MAS treatment in Norwegian hospitals. Hence, there is a possibility that some patients consented to participate in the trial, hoping that they were offered MAS treatment without having to try using a CPAP device first, potentially affecting compliance to treatment. Since all patients in this trial were CPAP and MAS naïve, this scenario is implausible, but we noticed that a small number of patients ($n < 5$) did withdraw from the trial prior to treatment initiation after initially consenting to participate in the trial. The reason for withdrawal could possibly be dissatisfaction with their allocated treatment alternative, but this remains unknown. These patients were excluded from all analyses since they never initiated treatment, and the allocation lot they drew at randomization was replaced in the concealed envelope. Unfortunately, the exact total number of patients referred and screened for OSA at the hospitals recruiting patients to the trial during the recruitment period is unknown, but it was noted that only a small fraction of the patients fulfilling the inclusion criteria declined participation in the RCT. The missing information about the total number of referred patients and about eligible patients not participating in the trial is a potential source of selection bias. At some level, this bias does impair the external validity of the results, thus the total number of screened patients should

have been carefully and systematically recorded throughout the complete recruitment period of the RCT.

4.1.8.2 Performance bias

Since no blinding of patients and health-care personnel was possible, this RCT is particularly susceptible to performance bias, which is systematic differences in the care given to the treatment groups. Indeed, the CPAP and MAS are two technically very different treatments, each requiring specialized health-care professionals to perform and monitor treatment. This is itself a source of performance bias, in addition to patients behaving differently in the interaction with their allocated treatment. However, when comparing different treatments alternatives, and not variants within the same type of treatment, this is not necessarily compromising the internal validity. To ensure good internal validity in an RCT comparing two different treatments without blinding, the study protocols in both treatment groups need to be coordinated and complied with by all clinical personnel. Particularly in respect to variables common between the treatment groups. To minimize the risk of performance bias, all clinical personnel in this RCT were instructed to standardize their interaction with the patients and avoid commending any of the treatment options in OSA treatment.

Although blinding the patients and clinical personnel was not feasible in this RCT, blinding the statistical analyses could have been performed. This would have ensured that data were not overanalyzed in the search for findings supporting one of the treatments (Akobeng, 2008). Such blinding requires the engagement of researchers not involved in the data collection to perform the data analysis. Unfortunately, limited funding made blinding the researchers analyzing the data unfeasible in this trial. Hence, the researchers analyzing the data paid particular attention to- and were cautious of the risk of detection bias when analyzing the data.

4.1.8.3 Attrition bias

The systematic differences between treatment groups in trial dropouts are most often referred to as attrition bias (Akobeng, 2008). Due to expected differences in dropouts between treatment groups, the preferred way to analyze RCT data is by the ITT approach. Analyses performed without including all patients enrolled in the trial do undermine the strengths of randomization and will introduce confounders and bias in the data. However, PP analyses are also useful e.g., when investigating the effect of compliance to treatment on the outcome of interest. Yet, results from PP analyses need to be interpreted with caution due to lower sample sizes and the unavoidable disadvantage of attrition bias. Adjusting for potential confounders and variables

leading to bias becomes increasingly important in smaller sample sizes since they inherently produce less precise result than larger sample sizes.

In this RCT, sleep recording data from patients who did not show at any of the follow-up visits or did not use the CPAP device at all were not accessible, thus strict ITT analyses of the AHI could not be performed. On the other hand, the AHI when using the treatment device is of less interest if the patient is non-compliant to treatment, making PP analysis of AHI more clinically relevant, despite the risk of attrition bias. In the remaining outcomes in this RCT, very few patients had missing data that were not replaceable through multiple imputations as recommended by CONSORT 2010 (Altman, 2009, Moher et al., 2010).

4.1.8.4 Dropout analyses

Dropout analyses are required to assess the risk of attrition bias in the results. In this thesis, two main analyses were performed to assess the impact from dropouts on the internal and external validity: 1) Comparison of baseline variables between patients dropping out, and patients not dropping out from the trial, and 2) Comparison of results with and without imputed data in at follow-up. The follow-up data had missing entries for two reasons: Random missing entries in questionnaires, which were successfully replaced using multiple imputations (Moher et al., 2010), and completely missing individual datasets due to withdrawal from the trial altogether. The latter data were replaced by LOCF in cases where this technique was considered viable (see section 4.1.5 [Handling of missing data]).

In total, 27 patients (26.0%) dropped out prior to the 12-month follow-up visit (Figure 7). From these, 10 (9.6%) dropped out before the 4-month follow-up visit. The same proportion of patients dropping out was found in Tromsø and Trondheim. No differences were found between the 27 patients dropping out and the remaining patients at baseline. However, prior to the 4-month follow-up more women (18.9% vs. 4.5%) and smokers (23.8% vs. 6.0%) dropped out of the trial. The 6 patients labelled as missing at the 4-month follow-up visit, did not receive the postal invitation to the follow-up and were thus regarded as missing at random. These patients were not regarded as dropouts at the 4-month follow-up visit since they showed up at the 12-month follow-up visit.

Analyses only involving patients with complete data at baseline and follow-up (complete case analyses) were performed for every outcome presented in this thesis. Compared to the ITT results at the 4-month follow-up, the complete case analyses found that the CPAP treatment group had worse PSQI global score than the MAS treatment group ($p = 0.03$), although scores in either treatment group were rather similar to the ITT analysis. The number of patients reporting

significant improvement in PSQI global score in the PP analysis was no longer different between the treatment groups when only including complete cases in the analysis at the 4-month follow-up. At the 12-month follow-up, the results from the complete case analyses did not differ from the corresponding ITT analyses in either treatment group.

Although imputed data presuppose assumptions about the data material, complete case analyses are more prone to bias than ITT analyses due to the missing patients and reduced statistical power. Nevertheless, the complete case analyses, and assessment of patients dropping out from the trial show that the overall internal and external validity seems conserved despite 27 patients dropping out from the trial between baseline and the 12-month follow-up visit.

4.1.8.5 External validity

Apart from the randomization procedure and the questionnaires, the study protocols for both treatment groups were very similar to the usual way patients with non-severe OSA are treated at the hospitals hosting the trial. Whether the patients in this trial were representative for all Norwegian OSA patients is not known, but by recruiting patients from two cities, and from both public and private hospitals, the external validity should be satisfactory. Hence, the results in this trial are probably representative for primary OSA patients referred to Norwegian public and private hospitals with baseline AHI between 10 and 30, without nasal obstructions or tonsillar hypertrophy. However, the results may not be representative for patients with social snoring, upper airway resistance syndrome, severe OSA or obesity hypoventilation syndrome, although these conditions could be considered different severities of the same respiratory disorder (American Academy of Sleep Medicine, 2014, Lavigne et al., 2009).

4.1.8.6 Restrictions related to journal policies

Preferences regarding content, terminology and level of details described in the various sections of paper manuscripts inevitable vary amongst academic journals, mostly due to differences in target audiences. The journals who published Paper I, II and III are mainly oriented towards practicing clinicians, thus some of the details and literature references regarding research methodology were omitted from the published papers and described in this thesis only. Furthermore, the terminology policy deviated between the journals: The terms “respiratory event index” and “mandibular advancement device” (MAD) were respectively preferred over “apnea hypopnea index” and mandibular advancement splint” by the Journal of Dental Sleep Medicine. The difference in established terminology policies of the journals is the reason why both terms are mentioned between Paper I, II and III, and this thesis.

4.1.9 Assessment of treatment device efficacy

At the follow-up visits, the methods used to evaluate treatment efficacy differed between the CPAP and MAS treatment groups. Ideally, the efficacy of both the CPAP and MAS treatment device should have been evaluated in identical manners using HSAT at baseline and both follow-up visits, providing a direct comparison between the treatment groups without reservations. Unfortunately, the funding of this RCT did not cover HSAT at follow-up in the CPAP treatment group, hence the CPAP efficacy in this RCT was only available through the recordings and calculations made the CPAP device software.

The CPAP treatment group had their efficacy data continuously logged and calculated by the CPAP device. A mean AHI score was composed from observations from the last 90 days prior to the follow-up visit. In contrast, the MAS patients were assessed through a one-night HSAT while wearing the MAS at the follow-up visit. This difference makes the findings in the MAS treatment group more susceptible to night-to-night variations affecting the HSAT variables at follow-up than the CPAP treatment group. Variables such as temporary rhinitis and the amount of supine sleep are known to influence the efficacy of MAS treatment, which imply that the night of HSAT at follow-up may not accurately estimate the true efficacy of the MAS in each individual patient (Alshaer et al., 2018, Marklund et al., 2004, Marklund et al., 2015). Indeed, 5 of the 8 MAS patients having higher AHI at the 12-month follow-up visit had increased the proportion of supine sleep by > 20%-points from baseline to follow-up. However, at group level, this effect should cancel out between patients, resulting in a representative median AHI for the complete treatment group.

In contrast to the variables measured during the HSAT, the data retrieved from the CPAP device does not include information on SpO_2. This prevents comparisons of hypoxia, e.g., oxygen desaturation index and T-90% between the CPAP and MAS treatment group at follow-ups. However, it is likely that the SpO_2 was restored to non-OSA levels in most patients whenever the CPAP device was used, since all CPAP patients in this RCT achieved AHI < 5 at the 12-month follow-up visit (Fabius et al., 2018, Koivumaki et al., 2018, Young et al., 2013).

Nevertheless, using different methods between the treatment groups for evaluating the treatment efficacy may introduce systematic bias in the treatment evaluation, potentially compromising the internal validity of the results. Most importantly, the AHI at follow-ups in the CPAP treatment group may be underestimated due to the AHI being automatically calculated without using desaturation events when calculating hypopnea events (Fanfulla et al., 2021, Schwab et al., 2013). Thereby systematically and erroneously increasing the difference in AHI between the treatment

groups at follow-ups. On the other hand, the accuracy of the AHI found in the CPAP treatment group at follow-ups, being an average AHI from several nights, may be better than the AHI found by the one-night HSAT recording. Moreover, no patients in this RCT had AHI > 30 at baseline, probably increasing the accuracy of the estimated residual AHI in the CPAP treatment group (Ueno et al., 2010).

Despite the limitations associated with using dissimilar methods for assessing treatment efficacy, the methods used in this RCT should each provide sufficiently precise AHI estimates to provide valid comparisons between the treatment groups at group level. This is supported by the difference in AHI at follow-ups in this RCT being comparable to the difference between CPAP and MAS treatment in previous RCTs (Liu et al., 2017, Schwartz et al., 2018, Sharples et al., 2016). Moreover, the methods for evaluating the treatment efficacy in this RCT mirrors the current evaluation routines used at the hospitals hosting this RCT, thereby maintaining the external validity of the results.

4.1.10 Polysomnography vs. Home sleep apnea testing

The type 3 polygraphic sleep monitoring used in a HSAT setting is the standard screening procedure for patients with suspected primary OSA in most Norwegian hospitals (Skår et al., 2015). Thus, HSAT was used in this RCT, despite most international OSA literature basing the OSA diagnosis on PSG. PSG was for a long time regarded as the only reliable method of diagnosing OSA (American Academy of Sleep Medicine, 2005), but the ICSD-3 introduced HSAT as a valid method for diagnosing OSA (Sateia, 2014). Kapur et al. (2017) stated that > 4 hours of good quality HSAT is adequate to diagnose OSA, presupposing a PSG is performed when HSAT provides a negative result in patients with obvious symptoms of OSA. Nevertheless, the differences between PSG and HSAT scores needs to be acknowledged when comparing results in clinical OSA research.

Compared to polysomnography, the type 3 polygraphic sleep monitor is a less advanced method for diagnosing OSA. HSAT using the type 3 polygraphic sleep monitor is not able to identify when the patient is asleep with the same accuracy as PSG, which monitor brain activity to identify when the patient is asleep. Hence, it is unlikely that the patient is asleep during the complete time included in the HSAT records. Being incorrectly registered as sleeping for just a minor portion of the night will contribute to underestimation of the AHI compared to PSG, (Berry et al., 2012). For the same reason, HSAT cannot precisely identify all arousals occurring due to OSA while the PSG make precise observation of changes in sleep stages. This too contribute to a lower AHI score with HSAT compared to PSG, i.e., when compared to recordings made using PSG, HSAT

may underdiagnose OSA (Kapur et al., 2017, Nerfeldt et al., 2014). On the other hand, modern PSG may be too sensitive to hypopneas and thereby over-diagnose OSA, at least in respect to clinically relevant hypopneas (Heinzer et al., 2015). In that sense, in patients not having severe comorbid conditions, HSAT may have better sensitivity for OSA than full PSG.

Since the AHI is supposed to be estimated from the total time the patient is asleep, the American Academy of Sleep Medicine (2016) recommend that the term AHI is reserved to findings made by PSG. If so, the number of apnea- and hypopnea events during HSAT should be referred to as respiratory events and not apnea and hypopnea events. Whenever the total number of apnea and hypopnea events are divided on the time spent in bed, as in HSAT scoring, it should be referred to as the respiratory event index (REI). In other words, OSA severity should be graded by AHI only when diagnosed with PSG, and by REI when diagnosed with HSAT. However, the term "respiratory event" is yet to be implemented as the day-to-day terminology used among clinical personnel and researchers at Norwegian hospitals. AHI is therefore still commonly used to describe the number of apnea and hypopnea events found in both PSG and HSAT. Hence, the term AHI is used throughout this thesis, despite the number of apnea and hypopnea events being determined by HSAT in the RCT upon which this thesis is based.

In the Papers I, II and III, the nasal- or RIP-flow decrease in the hypopnea events was erroneously defined as ≥ 50%. However, the true threshold used in the RCT was ≥ 30% as described in section 2.3.1, which concur with the scoring guidelines cited in all papers (Berry et al., 2012). The falsely reported threshold for nasal- or RIP-flow decrease arose from a typing error that, despite careful proofreading, managed to slip through to publication. Corrigenda have thus been issued for two the three papers (Berg et al., 2020, Berg et al., 2021), and a corrigendum for Paper II has been submitted to the International Journal of Otolaryngology. It should be recognized that this typing error does not in any way affect the results presented in any of the papers, nor this thesis.

4.2 Interpretation of results

4.2.1 Apnea-Hypopnea-Index and compliance to treatment (Paper I, II, & III)

A comparison between treatment groups in respect to AHI at follow-up provided necessary context for interpretation of the primary aims in Papers I-III and should have been presented as a secondary aim in Paper III as it was in Paper I and II. At the 4- and 12-month follow-up visits, both treatment groups had significantly reduced the AHI from baseline. CPAP reduced AHI more than MAS treatment, but the best compliance to treatment was found in the MAS treatment group. These findings were in line with the current evidence (Doff et al., 2013b, Phillips et al., 2013,

Schwartz et al., 2018, Sharples et al., 2016). Figure 8 in section 3.2 illustrates the CPAP treatment's outstanding ability to improve the AHI and the less predictable efficacy of the MAS treatment. However, the ability to improve the AHI is irrelevant if the treatment device is not used. Weaver et al. (2007) argue that the CPAP's ability to restore daytime function is positively correlated with the compliance to CPAP treatment, suggesting at least 4 hours, and preferably 6-7.5 hours use per night for optimal treatment effect. McEvoy et al. (2016) found that the average use of CPAP less than 4 hours per night did not significantly prevent adverse cardiovascular events in patients with moderate and severe OSA. Hence, it seems reasonable to use the arbitrary cut-off for adequate compliance commonly defined as CPAP use more than 4 hours per night, more than 70% of nights or 5 nights a week (Gottlieb and Punjabi, 2020, Kribbs et al., 1993). In the absence of better recommendations, this cut-off is also used for the compliance to MAS treatment, although using the treatment device throughout the whole night, every night should be regarded the optimal and preferred compliance to treatment (Askland et al., 2020). Correspondingly, the decision to deviate from the common definition of treatment compliance in Paper I is problematic in respect to the reasoning behind the "70% of nights or 5 nights a week" cut-off. Deviating from the most common cut-off also complicates comparisons between the results reported in Paper I and other studies. The low number of patients compliant to CPAP treatment at the 4-month follow-up visit did nevertheless compel the need for an alternative definition of compliance when analyzing the differences between treatment groups. Hence, using "50% of nights" as the cut-off was a compromise between the risk of type II error and the disadvantages of using an unstandardized cut-off for treatment compliance. After all, these results did not significantly differ from the results found when using "70% of nights" as the treatment compliance cut-off, as discussed in Paper I.

Since the AHI improvement is only valid for the time the respective treatment device is actively used, compliance to treatment must be considered when discussing the effectiveness of CPAP and MAS in OSA treatment (Kohler et al., 2011, Mehta et al., 2001). The treatment effectiveness, i.e., AHI improvement adjusted for compliance to treatment, can be assessed by calculating the sleep adjusted residual AHI (Sutherland et al., 2015):

$$\text{Sleep Adjusted Residual AHI} = \frac{\left(\text{AHI}_{\text{Treatment}} \times \text{Hours}_{\text{Treatment}}\right) + \left(\text{AHI}_{\text{Untreated}} \times \text{Hours}_{\text{Untreated}}\right)}{\text{Hours}_{\text{Total Sleep Time}}}$$

Performing this calculation in this RCT by using the last registered compliance data (4-month: n = 23, 12-month: n = 81), the CPAP treatment group scored 13.0 ± 8.2, while the MAS treatment group scored 13.8 ± 7.5, which represents an insignificant difference between the two treatment

groups (Student's *t*-test, p = 0.59). This suggests a similar overall effectiveness of CPAP and MAS treatment in this RCT at group level. However, this result presupposes that the AHI returns to baseline values immediately after cessation of CPAP or MAS treatment, which is not necessarily the case in CPAP treatment (Phillips et al., 2007). Moreover, this result presupposes an equally sincere reporting of compliance in both treatment groups. The sleep adjusted residual AHI approximates the relative treatment efficacy measured with AHI in respect to treatment compliance. However, the severity of individual apnea- and hypopnea events, and the degree of nocturnal hypoxia are not considered (Sutherland et al., 2015, Veasey and Rosen, 2019).

Insufficient AHI improvement in MAS treatment may be related to supine dependent OSA, in which MAS treatment is expected to be less effective (Omobomi and Quan, 2018). In this RCT, no significant association was found between the proportion supine sleep and AHI, but patients who had > 20% less supine sleep at the 12-month follow-up HSAT compared to baseline, tended to experience a greater AHI improvement than the remaining MAS treatment group. This supports that positional therapy may be a supplement that enhances the efficacy of MAS treatment, although the evidence for such combined treatment is weak (Ravesloot et al., 2017). Changes in BMI from baseline to follow-up may also affect changes in AHI, especially in the MAS treatment group (Holley et al., 2011, Marklund, 2017). However, no change in mean BMI from baseline to the 4- and 12-month follow-up visits was found in any of the treatment groups.

The main short-time objective in OSA treatment is obviously to relieve the acute symptoms of poor sleep quality, such as fatigue and daytime sleepiness, but the long-term advantages of treating OSA may be even more important. There is no consensus on how to define whether a long-term successful OSA treatment significantly reduces the risk of comorbid health conditions and premature death. However, it is generally accepted that the risk of severe sequelae from OSA positively correlates with the OSA severity (Marin et al., 2005), and is reduced by effective OSA treatment given adequate compliance to treatment (McEvoy et al., 2016, Qaseem et al., 2013, Patil et al., 2019b). Residual AHI < 15 in OSA treatment may be acceptable in respect to serious long-term sequelae (Chowdhuri et al., 2016, Marshall et al., 2008), suggesting that remaining mild OSA may be an adequate treatment result in patients with good compliance to treatment. On the other hand, mild and moderate OSA should be treated if possible, especially in patients with subjective symptoms of OSA. Besides, OSA is likely to worsen with increasing age (Leppanen et al., 2017, Beiske and Stavem, 2018, Lindberg et al., 1999) and a long-term follow-up study by Marklund (2016), found that the efficacy of MAS treatment deteriorated after 17 years, accompanied by increasing baseline AHI in most patients. This highlights the importance of periodic monitoring of the treatment efficacy in patients using MAS and suggests early

intervention, preferably in combination with causal measures for preventing worsening of the OSA severity (Gottlieb and Punjabi, 2020, Sutherland and Cistulli, 2019). How compliance to MAS treatment change in the long term remains elusive (Sharples et al., 2016).

When discussing sequelae from untreated and inadequately treated OSA, it is important to acknowledge that the AHI is merely a surrogate measure for nocturnal hypoxia, which seems to be a key variable in the relationship between OSA and many of the associated health conditions (Dewan et al., 2015). It could be argued that reducing the duration and severity of desaturation events, is of greater importance than reducing the AHI per se (Azarbarzin et al., 2019, Muraja-Murro et al., 2013, Oldenburg et al., 2016, Patel and Mehra, 2015). In this context, using AHI as the sole variable to evaluate treatment efficacy is indeed questionable. Moreover, changes in AHI are not always correlated to subjective improvement in OSA treatment (Kang et al., 2017, Mehta et al., 2001). In this RCT, similar improvement was observed in the patient-reported outcomes between treatment groups, also when exclusively studying the patients being compliant to treatment. If the AHI is practically eliminated by the treatment, as in most OSA patients receiving CPAP treatment, the AHI successfully functions as a surrogate measure for sleep fragmentation, apnea-hypopnea duration, and hypoxia. However, despite the residual AHI often found in treatments such as MAS, the characteristics of apnea and hypopnea events and the severity of desaturations may improve more than indicated by the AHI (Kulkas et al., 2017, Veasey and Rosen, 2019). An example of this could be observed in this RCT where 5 of the 8 MAS patients with no improvement in AHI from baseline to the 12-month follow-up, had their T-90% more than halved. Based on this, the treatment success in non-severe OSA treatment should be interpreted with caution when solely evaluated by AHI.

4.2.1.1 Post hoc analyses concerning compliance to treatment

Since only 52% of the patients in this RCT were compliant to treatment at the 12-month follow-up visit, possible associations between baseline variables other than Friedman score and treatment compliance were explored post hoc. Post hoc analyses provide an insight in trends and patterns regarding compliance to treatment and possible reasons for non-compliance. However, results from post hoc analyses should always be interpreted with caution and no conclusions should be based on these results.

The CPAP usage patterns indicate that non-compliant patients using the CPAP device struggle with both using the device enough hours a night and using it an adequately number of nights. The non-compliant patients in the MAS treatment group primarily struggle using the device enough number of nights, but when the patients first use the device, the MAS is mostly worn throughout

the whole night. These usage patterns were most evident when excluding those who quit treatment completely: The median use of the CPAP device was 2.8 (1.8 – 3.8) hours a night compared to the median use of MAS which was 7.0 (4.8 – 7.3) hours a night among non-compliant patients. It should also be noted that 52.7% of patients in the CPAP treatment groups quit treatment or used the device less than 25% of nights. This was significantly more patients compared to the 16.3% of patients quitting MAS treatment or using the MAS less than 25% of nights (Chi square $p < 0.001$).

The compliance to treatment among patients allocated to CPAP treatment in this RCT were notably worse than reported in most previous studies (Jacobsen et al., 2017, Madbouly et al., 2014). The inclusion of non-severe OSA patients only and patients hoping to be allocated to one specific treatment alternative may have contributed to the low compliance rates, as well as the absence of frequent follow-ups with motivational purposes the first weeks of treatment (Kushida et al., 2006a, Sawyer et al., 2011). On the other hand, the compliance rate was not significantly different (chi-square test, $p = 0.50$) between the patients using CPAP who received an intermediate follow-up (38.9%) compared to those who were not scheduled for any follow-ups between treatment start and the 4-month follow-up (29.7%). This indicates that the lack of the motivational follow-ups before the 4-month follow-up was not the main reason for the poor CPAP compliance in this RCT and had only minor potential to considerably bias the results. The intermediate follow-up may nonetheless have had some positive effects on CPAP compliance for some of those attending (Askland et al., 2020), since patients vulnerable for being non-compliant to CPAP treatment are particularly likely to benefit from supplementary support in the initial phases of treatment (Olsen et al., 2008).

Post hoc analyses are inappropriate for identifying predictors for non-compliance with sufficient certainty in either treatment group. However, in this RCT, smoking was unsurprisingly the baseline variable coming closest to characterizing patients being non-compliant (Jacobsen et al., 2017, Mehrtash et al., 2019). Baseline variables like sex, age, BMI, AHI, daytime sleepiness (PSQI question 8) and motivation and expectations to treatment were overall similar between compliant and non-compliant patients. These baseline variables have previously been shown to affect compliance to CPAP, but to a varying degree, and in varying directions. Nonetheless, higher AHI, higher BMI and more daytime sleepiness are generally associated with better CPAP compliance (Copur et al., 2018, Jacobsen et al., 2017, Mehrtash et al., 2019, Sawyer et al., 2011). Although not found for patients in the CPAP treatment group, non-compliant patients in the MAS treatment group tended to have higher mean BMI (36.4 ± 8.9) and AHI (20.0 ± 4.9) at baseline than those compliant to MAS treatment (31.0 ± 6.0 and 16.6 ± 5.5 respectively, Student's *t*-test

p = 0.06 in both cases). A probable mechanism behind this trend is that higher BMI contribute to higher baseline AHI and thus a potentially higher residual AHI in MAS treatment. High BMI may also independently limit the efficacy of MAS treatment through larger neck circumferences (Ngiam et al., 2013, Saboisky et al., 2009). For some patients, a high residual AHI may be accompanied by poor relief from OSA symptoms and then a reduced motivation for continuing MAS treatment, resulting in poor compliance (Marklund et al., 2004). In general, it could be hypothesized that patients with higher BMI do benefit more from CPAP treatment and less from MAS treatment, and vice versa for patients with lower BMI. Unfortunately, individual variations and conflicting results regarding the relationship between AHI improvement and MAS compliance render this assumption less suitable for clinical decision-making (Marklund, 2017, Sutherland and Cistulli, 2019). A higher percentage of women were found to be non-compliant to MAS treatment compared to men in this RCT. However, this is not in line with previous studies finding no differences between men and women in compliance to MAS treatment (Geer and Hilbert, 2021). No clear reason for the difference between men and women was found in the post hoc analyses on compliance to treatment.

At baseline, nearly all patients in this RCT were optimistic and motivated for treatment, making expectations and motivation for OSA treatment prior to randomization unsuitable for predicting compliance to treatment. However, when the OSA treatment for some patients turns out to be associated with adverse effects, or being more cumbersome or unpleasant than expected, the way the patients cope with these negative experiences associated with the allocated OSA treatment may become an increasingly important factor in treatment compliance (Olsen et al., 2008, Sawyer et al., 2011). At follow-up, 90.7% of patients compliant to treatment reported that successful treatment of OSA was perceived as somewhat to very necessary, compared to only 62.5% of non-compliant patients (Chi square p = 0.002). The patient's own perception of OSA as a health risk may thus affect the ability to stay motivated and compliant to OSA treatment (Crawford et al., 2014). Support from bed partners may also play an important role in compliance to treatment of non-severe OSA, particularly in treatment with CPAP (Lewis et al., 2004, Weaver and Grunstein, 2008). Like findings in previous studies, none of the patients living alone (n = 11) managed to achieve adequate compliance to CPAP treatment (Mehrtash et al., 2019, Lewis et al., 2004), but marital status was not associated with compliance to MAS treatment in this RCT.

Adverse effects from treatment are known risk factors related to poor compliance to CPAP and MAS treatment (Mullane and Loke, 2019, Olsen et al., 2008, Park et al., 2017, Patil et al., 2019b, Sutherland and Cistulli, 2019). The adverse effects reported in this RCT coincided with the adverse effect profile discussed by Schwartz et al. (2018). Similarly, to previous studies, the

adverse effect profiles also differed slightly between CPAP and MAS treatment (Giles et al., 2006, Sutherland et al., 2014). While patients in the MAS treatment group predominately reported pain and discomfort as the most frequent adverse effects, patients in the CPAP treatment group reported more problems related to insomnia, the sensation of claustrophobia or suffocating, noise from the CPAP device, discomfort related to the mask, hose and difficulties interacting with the bedpartner. Xerostomia was similarly prevalent in both treatment groups and a similar portion of patients using CPAP and MAS reported no adverse effects. Among the 74% of patients who reported experiencing adverse effects, most reported experiencing two or more adverse effects during the first 12 months of treatment. Compliant patients reported more adverse effects than non-compliant patients, which was not surprising since both effects and adverse effects from treatment presupposes use of CPAP and MAS. Hence, more use should lead to both better treatment effect, but also more adverse effects (Weaver and Grunstein, 2008).

Most patients will experience some degree of transient pain or discomfort lasting for days, weeks or even a few months when first starting MAS treatment (Doff et al., 2012, Doff et al., 2013b, Marklund et al., 2012, Sutherland et al., 2014). In this RCT, many patients in the MAS treatment group reported the jaw pain to fade away after only a few days. Some of the patients may thus have experienced jaw discomfort without reporting it as an adverse effect, perhaps regarding it as a negligible problem. Adverse effects affecting the dentition have previously been reported in both CPAP and MAS treatment (Doff et al., 2013a, Giles et al., 2006, Uniken Venema et al., 2020). Among these, changes in dental occlusion from MAS treatment are by far the most prevalent adverse effect (Chan et al., 2020, Hamoda et al., 2019, Serra-Torres et al., 2016). In this RCT, only 2 patients reported noticeable changes in dental occlusion, of which 1 noticed changed tooth position. The low number of reported bite changes is most likely reflecting that most patients do not notice bite changes even though they may be objectively observed (Marklund, 2017, Marklund, 2020). Also, 12 months may in many patients not be enough time period for noticeable tooth movement to occur (Araie et al., 2018). However, tooth movements are expected to occur in more patients compliant to MAS treatment as treatment continues beyond 12 months (Araie et al., 2018, Fransson et al., 2017, Hamoda et al., 2019, Marklund et al., 2019, Patel et al., 2019).

In total, 68% of non-compliant patients reported one or more adverse effects from treatment as a reason for not using their allocated treatment device. Seemingly, more patients in the CPAP treatment group (76%) reported one or more adverse effect from treatment as a reason for non-compliance compared to the MAS treatment group (62%). This is in line with Ramar et al. (2015) who reported discontinuation of treatment due to adverse effects are more common in

CPAP treatment than MAS treatment. Insomnia and the sensation of claustrophobia or suffocating was the most reported reasons for non-compliance in the CPAP treatment group, followed by the group of adverse effects gathered under the label "device being troublesome in bed". In the MAS treatment group, pain and discomfort associated with using the treatment device was clearly the most important reason for non-compliance. In both treatment groups, xerostomia was reported as a reason for non-compliance by some patients. How patients are asked to report adverse effects, and the selection of adverse effects listed in e.g., questionnaires do differ between studies. This complicates direct comparisons of the adverse effect's impact on treatment compliance and may be one reason why some studies have found minimal associations between adverse effects and treatment compliance (Engleman et al., 1996, Pepin et al., 1995). Nevertheless, it is very likely that some of the adverse effects reported in this RCT are at least part of the reason why patients are non-compliant or quit OSA treatment (Ulander et al., 2014).

4.2.2 Symptoms of anxiety and depression

Anxiety and depression may be associated with OSA, and symptoms of anxiety and depression are shown to affect sleep quality, compliance to OSA treatment and do overlap with some typical OSA symptoms such as daytime sleepiness and fatigue (Bjorvatn et al., 2017, Corfield et al., 2016, Diaz and Brown, 2016, Harris et al., 2009, Macey et al., 2010, Shapiro et al., 2014, Wells et al., 2004). Hence, studying symptoms of anxiety and depression using the HADS questionnaire was at first planned as a secondary aim in this RCT. However, the patients in this RCT had mean baseline HADS scores slightly higher than, but within the range of the normal population in several previous Norwegian studies (Grav et al., 2012, Kjaergaard et al., 2014, Leiknes et al., 2016, Nortvedt et al., 2006, Torske et al., 2016), including the HUNT4 survey where > 41 000 randomly selected inhabitants in mid-Norway completed the HADS questionnaire between 2017 and 2019 (NTNU HUNT Research Centre). Notably, the mean HADS scores at baseline were well below the recognized thresholds for both "possible" and "probable" cases of anxiety or depression (Bjelland et al., 2002, Herrmann, 1997). Furthermore, the HADS scores in this RCT were comparable to larger previous studies on Norwegian OSA populations (Bjorvatn et al., 2017, Kjelsberg et al., 2005). In other words, the patients recruited to this RCT had healthy levels of symptoms related to anxiety and depression at group level. Since few patients were "possible" or "probable" cases of anxiety- or depression disorder according to their HADS scores, the clinical potential and need to improve symptoms of anxiety and depression among patients in this RCT was very limited. The HADS data collected in this RCT was thus not published in any peer reviewed papers and is presented in this thesis only.

Some previous studies have found CPAP and MAS treatment to improve symptoms of anxiety and depression in OSA patients, but this finding remains inconclusive (Povitz et al., 2014, Saunamaki and Jehkonen, 2007). Statistically significant improvements from baseline to the 12-month follow-up visit was found in both treatment groups in this RCT, but these changes are clinically insignificant at group level due to the high number of patients with healthy HADS scores at baseline. Furthermore, when included as independent variables in regression analyses, the baseline HADS scores did not significantly impact the subjective sleep quality or HRQoL in this RCT. No meaningful associations between the OSA treatment and changes in HADS scores can thus be derived from this RCT, although individual patients may have experienced positive changes in respect to symptoms of anxiety and depression after OSA treatment with either CPAP or MAS. It is possible that significant associations between HADS scores and OSA treatment could be found if patients with higher HADS scores or severe psychiatric disorders were to be included in this RCT.

The items in the HADS questionnaire do not cover symptoms associated with somatic disorders such as OSA, but the overlapping symptoms between OSA, anxiety and depression illustrate the complex interaction between these conditions (Bjelland et al., 2002, Macey et al., 2010, Saunamaki and Jehkonen, 2007). The changes in HADS scores from baseline to the follow-up visits may therefore reflect improvements of OSA symptoms, not actual improvements of anxiety or depression disorders in patients with HADS scores ≥ 8 at baseline. Furthermore, previous studies have found high HADS anxiety- and depression scores to be associated with poor CPAP compliance (Diaz and Brown, 2016, Kjelsberg et al., 2005, Law et al., 2014), suggesting that results regarding changes in HADS scores are particularly susceptible to attrition bias in the PP analysis. However, no statistically significant association was found between HADS anxiety or depression score and compliance to CPAP and MAS treatment in this RCT using logistic regression analyses.

Missing entries in the HADS questionnaire were found in 3 patients at baseline, but imputed data in the baseline HADS questionnaire was only used when including symptoms of anxiety and depression as independent variables in multivariable regression analyses. Hence, the results presented in section 3.2.2 was based on complete HADS data analyses, i.e., without imputed data. Nevertheless, it is highly unlikely that the 3 patients who failed to complete the HADS questionnaire at baseline could significantly alter the mean baseline scores since no patients with severe psychiatric disease were enrolled in this RCT. For the same reason, the eligibility criteria may have contributed to the relatively uniform normal HADS mean scores at baseline in this RCT. On the other hand, Bjorvatn et al. (2017) who included a broader selection of newly

diagnosed OSA patients, found a prevalence of anxiety- or depression scale scores ≥ 8 very similar to this RCT. This indicates that the expected HADS scores in patients with untreated non-severe OSA are likely to be within a healthy range regardless of the eligibility criteria used in this RCT.

It should be noted that the HADS questionnaire was intended for screening symptoms associated with anxiety and depression disorders but is not suited for diagnosing anxiety- or depression disorders (Bjelland et al., 2002, Leiknes et al., 2016). Associations between anxiety and depression disorders and OSA could thus not be studied in this RCT.

4.2.3 Self-reported sleep quality (Paper I & III)

Sleep quality was reported through the PSQI questionnaire at baseline and both follow-up visits. Both CPAP and MAS treatment improved the PSQI global score from baseline to the follow-up visits, but no statistically significant differences between the treatment groups were found in the PSQI global score at the 12-month follow-up visit. At the 4-month follow-up visit, the PSQI global score was not significantly different between the treatment groups when using the Student's *t*-test. However, patients in the MAS treatment group had a slightly better PSQI global score compared to the CPAP treatment group after adjusting the difference for relevant baseline variables as described in section 2.7.8. The same trend was seen at the 12-month follow-up, but the difference between the treatment groups were statistically non-significant ($p = 0.6$). The MAS treatment group seemingly being slightly better at improving the PSQI global score in the ITT analysis at the 4-month follow-up, and otherwise being comparable to the CPAP treatment group was somewhat surprising. Especially since the CPAP treatment was undisputable better at improving the AHI than the MAS treatment. The most likely explanation for this finding in the ITT analysis is the relative worse AHI at follow-up being counterbalanced by a relative better compliance to treatment in the MAS treatment group compared to the CPAP treatment group. However, the CPAP treatment group was not found to have a better PSQI global score than the MAS treatment groups at any follow-up visits in the PP analyses, despite all patients being regarded compliant to treatment. The lack of statistical difference between the treatment groups may thus be attributed to a type II statistical error, particularly in the PP analyses. In other words, the lack of statistically significant differences between the treatment groups does not confirm that there really are no differences between the treatment groups.

Since the risk of type II statistical error in this RCT was considerable, a more robust study with better statistical power should attempt to recreate the results to either confirm or reject the findings and conclusions in Paper I and III. This issue should perhaps have been stressed in both

papers. Contrary to Paper III, the hypothesis testing performed in Paper I should also have considered the risk of random differences appearing between the treatment groups at baseline. The RCT design should ideally prevent this from being an issue, but should nevertheless be considered due to the low number of patients enrolled in this RCT. Hence, the results presented in Paper I should have been adjusted for baseline variables such as age, sex, smoking, baseline AHI and daytime sleepiness. Adjusting for baseline variables is especially important in the PP analyses due to the large number of patients being non-compliant to treatment at follow-up, and simultaneously missing out on the benefits of randomization when comparing the treatment groups.

The adjusted mean PSQI global score was 1.3 points lower in the MAS treatment group compared to the CPAP treatment group after 4 months of treatment ($p = 0.02$). This tend to support the results reported in Paper I: The MAS treatment seems to be at least as effective as the CPAP treatment at improving PSQI global score after 4 months of treatment. However, when comparing the OR for having a significantly improved PSQI global score at the 4-month follow-up, wide confidence intervals indicate that the results are unreliable. This also indicates that the statistically significant differences between the treatment groups are somewhat uncertain and that the risk of type II statistical error is noteworthy.

At the 12-month follow-up, there was no statistically significant difference in the number of patients having improved PSQI global score between the treatment groups. Wide confidence intervals in both the ITT and PP analyses indicate a low statistical power and high risk of type II error when comparing the PSQI global score between the treatment groups at the 12-month follow-up as well.

Comparing the treatment groups by the number of patients having significant RCI improvements may be considered a supplementary method to the main hypothesis testing. Instead of comparing the mean values between the treatment groups it indicates how many of the patients in each treatment group is responsible for a given change in mean values from baseline to follow-up. The RCI thereby indicates if a change in mean value is caused by few patients having huge improvements or many patients having small improvements. However, since no sham treatment group was included in the RCT design, it is not known how much of the changes in RCI do arise from placebo effects rather than true treatment effects. Moreover, the comparisons using RCI presented in Paper I and III are susceptible for bias since they were not adjusted for baseline variables. On the other hand, when adjusting for baseline variables, the results were still similar to the unadjusted results. However, the OR confidence intervals for having significantly improved

PSQI global score were very wide in all analyses when adjusted for baseline variables. This indicates that the findings presented using the RCI should be interpreted with caution, regardless of being adjusted for baseline variables or not.

Very little research is previously published on the association between changes in PSQI global score and OSA treatment. Lusic Kalcina et al. (2017) showed that patients with mild to severe OSA on average have a worse PSQI global score compared to a non-OSA population. The patients described in this RCT had a mean baseline PSQI global score at 7.8 ± 3.3, being above the upper limit of normal sleep quality, which is defined as a PSQI global score < 5 by Buysse et al. (1989). The findings in this RCT therefore suggest that successful OSA treatment improves the PSQI global score which is in line with findings from previous studies. Indeed, improved PSQI global score has even been demonstrated in trials showing modest improvements in AHI from exercise training and Tai chi/Qigong (Kline et al., 2011, Yilmaz Gokmen et al., 2019).

El-Solh et al. (2017) performed a RCT comparing CPAP and MAS treatment and found results like this RCT, with both treatments improving PSQI global score and being similar at follow-up, CPAP being better at improving AHI and the MAS treatment group showing better compliance to treatment. However, El-Solh et al. (2017) studied severe OSA in war veterans with post-traumatic stress syndrome, making their study population non-comparable to the patients in this RCT.

Based on the limited volume of relevant literature, it is not known why the PSQI global score are so similar between treatment compliant patients in the CPAP and MAS treatment group. MAS being good at improving sleep quality despite a less effective reduction in AHI may be one possible mechanism, as observed in studies investigating exercise training (Kline et al., 2011). Also, self-reported sleep quality may rely less on AHI and more on other HSAT variables that may improve more than the AHI in the MAS treatment group. Another possible mechanism is that improved sleep quality facilitates the compliance to CPAP and MAS treatment, thus similar results between the treatments may arise from survivor bias. Somiah et al. (2012) showed that good objective sleep quality at the first night of CPAP treatment is associated with short-term and long-term adherence to CPAP treatment. However, the direction of this association is unknown. It could be hypothesized that using the CPAP device itself negatively affect sleep quality, counteracting some of the benefits CPAP treatment have on sleep quality. If this is the case, there is likely an association between self-reported sleep quality and compliance to treatment, with CPAP or MAS device comfort being a common denominator.

4.2.3.1 Post-hoc analyses regarding typical OSA symptoms

Interpretation of the Epworth's sleepiness scale in this RCT would depend on multiple imputations being made in 44% of the questionnaires at baseline, rendering the results unreliable. Daytime sleepiness was therefore assessed post hoc using the PSQI question 8 which asked the patients how often they have had trouble staying awake while driving, eating meals, or engaging in social activities during the last month. Similarly, snoring and difficulties breathing comfortable during sleep were assessed by the PSQI questions 5d and 5e respectively.

Since the scores in the PSQI questionnaire are non-continuous, the numeric interval between the Likert scale scores may not be homogenous. Hence, the Wilcoxon signed ranks test was used to analyze the changes from baseline to follow-up in these individual PSQI questions. Fisher's exact test was used to cross check the results and showed results comparable to the Wilcoxon signed ranks test with only slightly different p-values (results from the Fisher's exact test are not shown). It should also be noted that changes from baseline to follow-up in the PSQI sub-scores may be subject to test-retest variability since the PSQI questionnaire is not validated on the individual sub-score level. Hence, these results from the post hoc analyses must also be interpreted with care.

At the 12-month follow-up, there were no differences in daytime sleepiness between the CPAP and MAS treatment groups in neither the ITT nor the PP analyses using the Mann-Whitney U-test. Similarly, no difference between the treatment groups was found when comparing the percentage of patients reporting changed frequency of excessive daytime sleepiness at the 12-month follow-up using the Fisher's exact test. The median PSQI question 8 score did significantly improve in the MAS treatment group, but not in the CPAP treatment group in the ITT analysis and vice versa in the PP analysis. In the ITT analysis, the poor compliance to CPAP treatment likely contributes to the change being non-significant. However, the non-significant changes were close to the significance cut-off at $\alpha = 0.05$ in both the ITT (CPAP) and the PP (MAS) analyses. Furthermore, the change in the CPAP treatment group was barely significant in the PP-analysis. The change in daytime sleepiness being borderline significant may suggest that the potential for improved daytime sleepiness is limited among patients with non-severe OSA (Marshall et al., 2006).

Although the PSQI question 8 measures sleep-related daytime dysfunction, the PSQI sub- and global scores have shown only weak correlation with the Epworth's Sleepiness Scale (Buysse et al., 2008). Hence, the average sum of the 7 questions from the Epworth's Sleepiness Scale that after all was completed by all patients in this RCT are presented in Table 21. The mean sums are

not to be confused with the Epworth's Sleepiness Scale total score and can thus not be compared with studies reporting the Epworth's Sleepiness Scale. As with the PSQI question 8, no statistical differences in the mean sums were found between the treatment groups after 12 months of treatment in neither the ITT nor the PP analysis. Differences between treatment groups were explored using Student's *t*-test and multivariable linear regression analysis adjusted for the baseline variables age, BMI, sex, smoking, education level, baseline AHI, incomplete Epworth Sleepiness Scale (missing one question), and symptoms of anxiety and depression according to HADS (Table 21). The mean sum at the 12-month follow-up were significantly lower than baseline in both the CPAP treatment group ($p_{ITT} < 0.001$, $p_{PP} = 0.003$) and MAS treatment group ($p_{ITT} < 0.001$, $p_{PP} < 0.001$) using then Paired samples *t*-test. This indicates that the improvement in daytime sleepiness may be underestimated by the PSQI question 8. However, the findings from the incomplete, non-validated version of the Epworth's Sleepiness Scale presented in this thesis must be interpreted with care.

Table 21 Mean sum of the 7 questions from the Epworth's Sleepiness Scale completed by all patients.

	Baseline		*12-month follow-up*		
	CPAP n^{ITT}=55 n^{PP}=18	MAS n^{ITT}=49 n^{PP}=36	CPAP n^{ITT}=55 n^{PP}=18	MAS n^{ITT}=49 n^{PP}=36	Adj. difference MAS – CPAP (95% CI)§, P value§
Mean sum ITT*	8.3 (3.5)	8.4 (3.4)	5.6 (3.2)	5.4 (3.3)	-0.6 (-1.8 – 0.5), .30
Mean sum PP*	8.1 (3.2)	7.8 (3.1)	5.0 (3.4)	4.6 (2.9)	-0.8 (-2.7 – 1.2), .42

**Incomplete Epworth's Sleepiness Scale sum (missing one question).*
§Difference between MAS and CPAP treatment groups at follow-up, based on linear regression analysis adjusted for baseline variables (Age, BMI, sex, smoking, education level, baseline AHI, Epworth Sleepiness Scale and symptoms of anxiety and depression according to HADS), reference group: CPAP.*

Regardless of which daytime sleepiness data used in the analyses, the difference between the treatment groups at the 12-month follow-up was clearly non-significant. Although not evidence for treatments being equal at improving daytime sleepiness, the results do concur with the sleep adjusted residual AHI being similar in the treatment groups in this RCT. This suggests that the similar overall effectiveness of CPAP and MAS may be reflected in daytime sleepiness reported at follow-up (Schwartz et al., 2018, Sutherland et al., 2015). Finding no difference in daytime sleepiness between CPAP and MAS treatment at follow-up also corresponds with the findings in 7 previous meta-analyses comparing the daytime sleepiness after CPAP and MAS treatment (Cammaroto et al., 2017, Gupta et al., 2016, Iftikhar et al., 2017, Li et al., 2013, Liu et al., 2017, Schwartz et al., 2018, Sharples et al., 2016). Schwartz et al. (2018) found CPAP to be better than MAS at improving the Epworth's Sleepiness Scale in their meta-analysis but found no difference

when comparing the treatment groups post treatment. Hence, Schwartz et al. (2018) concluded that the results from the Epworth's sleepiness scale were unclear. Common for the meta-analyses comparing daytime sleepiness after CPAP and MAS treatment all included patients with severe OSA at baseline. Sharples et al. (2016) reported findings for severe and moderate OSA separately and found no difference between CPAP and MAS treatment when only comparing patients with moderate OSA. From the post hoc analyses of the PSQI question 8 and the sum of the 7 questions from the Epworth's Sleepiness Scale, it is thus reasonable to believe that patients being at least partially compliant to treatment in this RCT experienced an improvement in daytime sleepiness. The difference in daytime sleepiness at the 12-month follow-up between the treatment groups seems to be non-significant in this RCT.

The percentage of patients reporting a changed symptom frequency regarding difficulties breathing during sleep and snoring was also presented in this thesis. Most patients in both treatment groups seemingly report no change or improved frequency of these OSA symptoms. Pearson chi square test/Fisher's exact test showed that a similar percentage of patients in the CPAP and MAS treatment groups reported changed snoring frequency. Like previous studies, both treatments improved snoring in most patients compliant to treatment (Ferguson et al., 1996, Marklund et al., 2015, Marklund, 2017). Meanwhile, fewer patients in the CPAP treatment group compared to the MAS treatment group seems to improve the frequency of reported breathing difficulties during sleep in both the ITT ($p = 0.002$) and PP ($p = 0.02$) analyses at the 12-month follow-up.

Although the comparison of treatment groups regarding the change in symptom frequency may be unreliable, the results are mainly supported by the results found when comparing the treatment groups using the Mann-Whitney U-test: At the 12-month follow-up, there were no differences between the CPAP and MAS treatment groups in the PP analyses, but when including the non-compliant patients, more patients in the CPAP treatment groups experienced difficulties breathing comfortably during the last month compared to the MAS treatment group. This difference is likely to arise due to the difference in treatment compliance between the treatment groups (Sutherland et al., 2015).

4.2.4 Health-related quality of life (Paper III)

The HRQoL was assessed with the widely used SF36 questionnaire (Kuhn et al., 2017, Shahid et al., 2011). The results were presented in Paper III and in this thesis using the norm-based SF36 domain scores. The norm-based SF36 domain scores allow for direct comparison between the individual SF36 domain scores, contrary to the 0-100 scale domain scores which arguably may be

more intuitive and easier to read. Besides, the norm-based scores are easy to compare to previous research in other populations and directly assess the trial population's score in relation to the general healthy population's score, which is 50 ± 10 in any given domain (Ware et al., 2000).

At baseline, patients in this RCT scored on average worse than, but within the standard deviation of the Norwegian general population's average in all SF36 domains (Jacobsen et al., 2018). This concurs with existing literature showing a reduced HRQoL in patients with OSA (Fornas et al., 1995, Lacasse et al., 2002). However, the OSA diagnosis is only one of several possible reasons for impaired HRQoL in OSA patients, since the OSA diagnosis is often accompanied by comorbid health conditions, which also may impair the HRQoL (Beiske and Stavem, 2018, Pauletto et al., 2021). Improving all health conditions that potentially reduce the HRQoL in an OSA population after 12 months of OSA treatment is unrealistic. Thus, restoring all aspects of HRQoL to the level found in a generally healthy population solely through OSA treatment may not be expected. Besides, Kang et al. (2017) showed that the HRQoL was closer related to the subjective sleep quality and symptoms of OSA than to the objective OSA severity, which indicates that the subjective perceptions of the individual OSA patient's general health and social life are important elements in the reporting of HRQoL (Lacasse et al., 2002). Furthermore, the SF36 is a generic questionnaire that may not be adequately sensitive to HRQoL changes related to OSA and OSA treatment (Pauletto et al., 2021).

At the 12-month follow-up visit, the CPAP and MAS treatment groups seemed overall to be similarly effective at improving SF36 domain scores, and no statistically significant differences in any of the SF36 domain scores were found in neither the ITT nor the PP analysis. This was in line with the findings in the meta-analyses by Kuhn et al. (2017) and Schwartz et al. (2018). In the CPAP treatment group, the ITT analysis showed more improvement in the role-physical domain of the SF36 than the MAS treatment, despite 67.3% of patients being non-compliant to treatment. Since this change was not found in the PP analysis, the improvement primarily took place in the non-compliant patients (Figure 11 and Figure 12). Possible mechanisms responsible for the improved HRQoL in non-compliant patients could be an effect, or placebo effect in patients with partial compliance to treatment (Crawford et al., 2012), alternatively an effect from becoming aware of their OSA diagnosis (Isidoro et al., 2015). It is also possible that some of the non-compliant patients in the CPAP treatment group have compensated for poor CPAP compliance with physical exercise, improving on the physical domains in SF36 (Iftikhar et al., 2017). It may also be a random statistically significant finding, which is a concern when collectively analyzing all SF36 domains, without correcting the significance level (Farcomeni, 2008). Indeed, when using the Bonferroni correction (excluding the aggregated component scores) the SF36 vitality

domain would be the only domain considered significantly improved in the ITT analysis in both treatment groups. With Bonferroni corrections in the PP analysis, the vitality domain would again be the only SF36 domain to significantly improve, but then in the MAS treatment group only.

The significant improvement found in the mental component score in the CPAP (PP analysis) and MAS treatment group (ITT and PP analyses) is mainly the result of the improvement found in the vitality domain. However, it could be hypothesized that the mental component score also improved by the patients' recognition of OSA, and the sense of receiving proper health care (Isidoro et al., 2015).

In the PP analysis, the two treatment groups had similar SF36 domain scores at follow-up, indicating that the treatments have a similar ability to improve the HRQoL. Although the PP analysis is susceptible to attrition bias and statistical type II error, the results may be representative for patients with the ability to be compliant to CPAP and MAS treatment, considering that several previous studies suggest that CPAP and MAS treatment have a similar effect on the HRQoL (Barnes et al., 2004, Doff et al., 2013b, El-Solh et al., 2017, Gagnadoux et al., 2009, Kuhn et al., 2017, Schwartz et al., 2018). Nevertheless, previous RCTs comparing the SF36 between CPAP and MAS treatment have individually shown conflicting results. Barnes et al. (2004) and El-Solh et al. (2017) both found similar SF36 scores in patients using CPAP and MAS, but CPAP improved 6 subdomains from baseline in the study by El-Solh et al. (2017) while MAS improved 4 subdomains. The subdomains improved did not match the subdomains that improved in our RCT, which is likely due to El-Solh et al. (2017) studying war veterans having post-traumatic stress disorder combined with mild to severe OSA. The study by Engleman et al. (2002) reported significantly more improvement in the mental component score with CPAP treatment compared to MAS treatment, while the treatments were similar at improving the physical component score. This difference from our study may result from the inclusion of severe OSA patients in the study by Engleman et al. (2002). Phillips et al. (2013) showed that CPAP treatment were inferior to MAS treatment in 4 SF36 subdomains (Bodily Pain, Vitality, Social Function and Mental Health) and the mental component score and being comparable to MAS treatment in the remaining domains and the physical component score. However, the study by Phillips et al. (2013) was a short-term crossover trial including patients with severe OSA and are thus not directly comparable to our RCT. Overall, based on previous studies and findings from this RCT, CPAP and MAS treatments seem equally suitable in the treatment of non-severe OSA from a HRQoL perspective.

Since this RCT did not allocate patients to any placebo control group, the improvement in HRQoL observed in both treatment groups could be a result of placebo effects of various degrees. Moreover, the sample size in this RCT might be too low to find differences in SF36 domain scores between CPAP and MAS treatment. This is apparent in the wide confidence intervals found in some of the SF36 domains when comparing the treatment groups, in both the ITT and PP analyses. The confidence intervals were particularly wide when comparing the number of patients reporting a significant change according to RCI in the individual SF36 domains (Table 17 and Table 18). Hence, the comparison between the number of CPAP and MAS patients with improved SF36 domains should be interpreted with caution (Levine and Ensom, 2001).

When comparing HRQoL and self-reported sleep quality, the improvement in the SF36 vitality domain was the only one correlated to the improvement in PSQI global score. This finding was reflected in the ITT analysis as a weak to moderate correlation between the mental component score and PSQI global score as well. Since the vitality domain is constructed from questions addressing sleepiness, fatigue and daytime energy, the correlation between the vitality domain in SF36 and PSQI global score seems reasonable and does correspond with previous studies reporting a correlation between subjective sleep quality and HRQoL (Kang et al., 2017). Moderate correlations between the general health domain, social functioning domain and PSQI global score were also found in the ITT analysis of the CPAP treatment group (data not shown). However, these correlations are clinically insignificant due to the lack of significant improvement in the general health and social functioning domain scores (Figure 11) and is thus likely to be random findings or a result of the number of variables not being corrected for in the statistical models.

4.2.5 Friedman tongue position (Paper II)

As demonstrated in this RCT, the treatment of non-severe OSA with CPAP is associated with poor compliance to treatment. On the other hand, knowing which patients will adequately improve AHI with MAS seems elusive in a pretreatment clinical setting seems. In that sense, the findings discussed in this thesis support the need for reliable methods that can predict the treatment outcome in non-severe OSA patients. Only then is it possible to tailor the treatment to each patient and start moving beyond a “trial-and-error approach” to non-severe OSA treatment (Eastwood et al., 2010, Sutherland et al., 2018).

Based on the pathophysiological mechanisms leading to OSA and the previously shown association between tongue position and OSA severity (Friedman et al., 2013), it seemed plausible that the Friedman score could be associated with the effectiveness of CPAP and MAS

treatment. Besides, Friedman score is easy to implement in clinical practice since it requires minimal effort and no equipment to perform and is already widely used by otorhinolaryngologists. Although previous studies have shown some conflicting results regarding the inter-examiner agreement for Friedman score (Friedman et al., 2008, Sundman et al., 2018), the ability of Friedman score to predict outcomes in CPAP and MAS treatment seemed promising.

Although the Friedman score seemed theoretically promising, this trial found no association between the Friedman score and compliance to treatment, and no association between Friedman score and adequate AHI improvement. The CPAP and MAS treatment groups showed similar patterns in the relation between Friedman score and compliance to treatment (Figure 9). Since all patients in the CPAP treatment group achieved adequate AHI improvement, only the MAS treatment group had a variable number of patients with adequate AHI between Friedman scores (Figure 10). The Fisher's exact test showed no differences in the compliance to treatment or the number of patients with adequately improved AHI across Friedman scores in either treatment group. Furthermore, the logistic regression showed no associations between increasing Friedman score and compliance to treatment nor adequate AHI improvement in any treatment group. This was also the case when merging the CPAP and MAS treatment groups in the analyses. Neither results in the logistic regression analyses had notably wide confidence intervals, indicating a modest risk of type II error (Levine and Ensom, 2001). Confidence intervals could not be produced in the analysis between increasing Friedman score and AHI improvement in the CPAP treatment group since all patients reached adequate AHI improvement.

There are several possible explanations for the lacking association between Friedman score and compliance to treatment and AHI improvement. Jacobsen et al. (2017) found better compliance to CPAP treatment with higher AHI, while tongue base reduction is demonstrated to improve both AHI and the compliance to CPAP treatment (Friedman et al., 2009, Mulholland et al., 2019). Seemingly, compliance to CPAP treatment could in theory potentially both increase and decrease with increased Friedman score. However, a more plausible explanation for the absence of associations in both treatment groups, may be that Friedman score does not give an accurate description of the volume in the velo- and oropharyngeal lumen (Friedman et al., 2017). The Friedman score could for example best represent soft tissue crowding in the hypo-pharyngeal region, while the primary site for obstruction in most patients enrolled in the trial could be in the velo- and oropharyngeal region. The Friedman score would then seem independent from treatment effectiveness in the studied population. Furthermore, an increased Friedman score may not sufficiently reduce the pharyngeal cross-section to have a clinically significant effect on the intraluminal airway pressure in patients with non-severe OSA. Hence, Friedman score may not

reflect the collapsibility of the pharyngeal walls as can be observed through inconvenient procedures such as remotely controlled mandibular protrusion during sleep, awake nasendoscopy or drug-induced sleep endoscopy (Kotecha and De Vito, 2018, Remmers et al., 2013, Sutherland and Cistulli, 2019, Vroegop et al., 2013).

The Friedman score has been described as both a 4-grade classification and a 5-grade classification of the tongue size and position in the oral cavity. In the 5-grade version, Friedman score grade II is split into grade IIa and IIb (Friedman et al., 2008, Friedman et al., 2017). However, in this trial the 4-grade Friedman score was used since this version was already established in the clinical routine at the ENT departments involved in the trial. This decision is unlikely to affect the results in any way.

4.3 Evidence regarding outcomes in this thesis

Between the outcomes AHI, treatment compliance/preference, subjective sleep quality, HRQoL as well as the post hoc outcomes anxiety- and depression symptoms and daytime sleepiness, several research groups have published results from clinical trials investigating OSA treatment. Studies published prior to the planning of this RCT represent the evidence at the time the first patients were recruited in this RCT in 2014. Between 2014 and the publications of Paper I, II and III in 2020, several new studies have added to the current evidence in OSA treatment.

Findings presented in this thesis should be interpreted in the context of the current evidence. Hence, a brief presentation of the most relevant findings from previous RCTs comparing CPAP and MAS treatment to each other and to placebo treatments are presented below. The most relevant RCTs published prior to the planning of this RCT are presented in Table 22 and RCTs published after the planning of this RCT are presented in Table 23.

As acknowledged by several meta-analyses (Giles et al., 2006, Li et al., 2013, Lim et al., 2006), RCTs performed prior to 2014 had established that AHI, minimum SpO_2 and OSA symptoms such as daytime sleepiness are effectively improved by both CPAP and MAS compared to placebo, given adequate treatment compliance. RCTs comparing CPAP to MAS had shown that CPAP was significantly better than MAS at improving AHI and minimum SpO_2. This difference between CPAP and MAS treatment was found to be more pronounced in severe OSA than mild OSA, thus MAS was suggested as a second-string alternative to CPAP, primarily in non-severe OSA. It was also shown that most patients in crossover RCTs preferred MAS treatment over CPAP treatment, and that compliance to treatment was similar or slightly better in MAS treatment than in CPAP treatment. Both CPAP and MAS treatment had shown to improve objective and subjective sleep quality, HRQoL and mood in patients with OSA. However, not all RCTs

investigating sleep quality, HRQoL and mood found any significant improvement in either treatment options, and no clear difference between CPAP and MAS treatment was found regarding the ability to improve these parameters (Table 22).

Table 22 A selection of relevant clinical trials published prior to this RCT.

Author (year)	*N / RCT-design*	*Mean age*	*Mean AHI at baseline*	*Interventions*	*Treatment duration*	*Reported findings (relevant for this thesis)*
Aarab et al. (2011)	43 / Parallel	52.2 ± 9.6	20.8 ± 9.9	CPAP/MAS	12 months	Both treatments improved AHI and daytime sleepiness. CPAP improved AHI more than MAS.
Barnes et al. (2004)	104 / Crossover	47.0 ± 0.9	21.3 ± 1.3	CPAP/MAS/ Placebo tablet	3 months	CPAP and MAS both improved AHI, daytime sleepiness, SF36. CPAP improved AHI more than MAS. MAS may not improve HRQoL and mood more than placebo. Compliance better in MAS treatment than CPAP.
Craig et al. (2012)	391 / Parallel	~58 ± ~7.5	-	CPAP/ Standard care	6 months	CPAP improves both daytime sleepiness and SF36.
Doff et al. (2013b)	103 / Parallel	49 ± 10	~40 ± ~30	CPAP/MAS	24 months	Both treatments showed similar improvements in daytime sleepiness and SF36. CPAP improved AHI more than MAS, but less difference between treatments in non-severe OSA.
Drager et al. (2007)	24 / Parallel	46 ± 6	~58 ± ~22	CPAP/No treatment	4 months	CPAP improved AHI and daytime sleepiness. No improvement with no treatment.
Engleman et al. (2002)	51 / Crossover	46 ± 9	31 ± 26	CPAP/MAS	2 months	CPAP improved AHI, daytime sleepiness and SF36 more than MAS. HADS only slightly, but similarly improved by CPAP and MAS. Patients preferred CPAP.
Ferguson et al. (1996)	27 / Crossover	46.2 ± 10.9	24.5 ± 8.8	CPAP/MAS	4 months	Both treatments improved AHI and daytime sleepiness, but CPAP more than MAS. Other OSA symptoms similarly improved by CPAP and MAS. Patients preferred MAS.

Ferguson et al. (1997)	24 / Crossover	44.0 ± 10.6	26.8 ± 11.9	CPAP/MAS	4 months	Both treatments improved AHI and daytime sleepiness. CPAP improved AHI more than MAS. Patients preferred MAS.
Gagnadoux et al. (2009)	59 / Crossover	50.3 ± 9.1	34 ± 13	CPAP/MAS	2 months	Both treatments improved AHI, daytime sleepiness, and HRQoL. CPAP improved AHI more than MAS. Patients preferred MAS.
Hoekema et al. (2008)	103 / Parallel	>20	~40 ± ~30	CPAP/MAS	12 weeks	CPAP improved AHI more than MAS. CPAP and MAS similar at improving daytime sleepiness, SF36 and HADS.
Hoyos et al. (2012)	65 / Parallel	49 ± 12	39.9 ± 17.7	CPAP/Sham CPAP	12 weeks	CPAP and sham CPAP both improved daytime sleepiness, but CPAP improved AHI in contrast to sham CPAP.
Kushida et al. (2012)	1098 / Parallel	~52 ± ~12	~40 ± ~25	CPAP/Sham CPAP	6 months	CPAP improved AHI and daytime sleepiness more than sham CPAP. This was most pronounced in moderate and severe OSA.
Lam et al. (2007)	101 / Parallel	~45 ± ~2	21.4 ± 1.1	CPAP/MAS/ Sleep hygiene	10 weeks	All treatments improved daytime sleepiness. MAS improved AHI more than sleep hygiene alone. CPAP improved both AHI and daytime sleepiness more than MAS and sleep hygiene. Same trend, but no clear differences between treatments regarding SF36.
Marshall et al. (2005)	31 / Crossover	50.5 ± ?	21.6 ± 7.5	CPAP/Sham CPAP	3 weeks	CPAP improved daytime sleepiness. No overall improvements in SF36 or HADS in neither treatment group. Sham CPAP did not improve AHI.
Mehta et al. (2001)	24 / Crossover	48 ± 9	27 ± 17	MAS/Sham MAS	1 week	MAS improved AHI, daytime sleepiness, and subjective sleep quality. Sham MAS did not.
Monasterio et al. (2001)	125 / Parallel	54 ± 9	20 ± 6	CPAP/ conservative therapy	6 months	Both treatments improved AHI, but CPAP more than conservative therapy. No significant change in daytime sleepiness and HRQoL in any treatment group.

Montserrat et al. (2001)	45 / Parallel	54.2 ± 10.2	53.8 ± 19.3	CPAP/Sham CPAP	6 weeks	Both CPAP and sham CPAP improved daytime sleepiness and some SF36 domains, but CPAP improved sleepiness and other symptoms of OSA more than sham CPAP.
Petri et al. (2008)	93 / Parallel	~50 ± ~10	34.7 ± 29.7-39.6	MAS/Sham MAS/No treatment	4 weeks	MAS and sham MAS improved daytime sleepiness, but MAS more than sham MAS. Only MAS improved AHI and the mental component of SF36.
Phillips et al. (2011)	38 / Crossover	49 ± 13	41.2 ± 23.9	CPAP/Sham CPAP	8 weeks	CPAP improved AHI and daytime sleepiness. Sham CPAP did not.
Phillips et al. (2013)	126 / Crossover	49.5 ± 11.2	25.6 ± 12.3	CPAP/MAS	1 month	CPAP improved AHI more than MAS. Both treatments improved daytime sleepiness and SF36. Patients preferred MAS.
Tan et al. (2002)	24 / Crossover	50.9 ± 10.1	22.2 ± 9.6	CPAP/MAS	2 months	Both treatments improved AHI and daytime sleepiness. CPAP improved AHI insignificantly more than MAS. Patients preferred MAS.
Weaver et al. (2012)	239 / Parallel	~50 ± ~12	~12.5 ± ~6.5	CPAP/Sham CPAP	8 weeks	CPAP improved AHI, daytime sleepiness and SF36. Sham CPAP did not.
Woodson et al. (2003)	90 / Parallel	~49 ± ~9	~19 ± ~10	CPAP/ TCRFTA/ Placebo	8 weeks	Both treatments improved AHI, daytime sleepiness and SF36 compared to placebo surgery.

AHI = Apnea-hypopnea-index, CPAP = Continuous Positive Airway Pressure, HADS = Hospital Anxiety and Depression Scale, HRQoL = Health related quality of life, N = Number of patients randomized at baseline, MAS = Mandibular advancement splints, RCT = Randomized clinical trial, SF36 = Short Form 36, TCRFTA = Temperature controlled radiofrequency tissue ablation.

Since 2014, some new RCTs (Table 23) and several meta-analyses relevant to the outcomes reported in this thesis have been published (Cammaroto et al., 2017, Iftikhar et al., 2017, Patil et al., 2019b, Ramar et al., 2015, Schwartz et al., 2018, Sharples et al., 2016). These publications have mainly confirmed previous findings, further founding CPAP as the gold standard treatment in moderate-severe OSA and simultaneously demonstrated a more similar efficacy between CPAP and MAS treatment in mild OSA cases. More recent publications have also suggested CPAP and MAS treatments to be more similar than previously thought at improving subjective outcomes such as daytime sleepiness and HRQoL (Trzepizur et al., 2021, Kuhn et al., 2017). This may be attributed to the good compliance in modern MAS treatment partly counterbalancing the suboptimal efficacy of MAS treatment compared to CPAP treatment (Sutherland et al., 2018). Observational studies have revealed a more complex relationship between anxiety and depression symptoms and OSA (Bjornsdottir et al., 2016, Bjorvatn et al., 2017, Diaz and Brown, 2016), reflected in meta-analyses reporting a small to moderate impact on depression from CPAP and MAS treatments, but minimal to no impact on anxiety (Gupta et al., 2016, Labarca et al., 2020, Povitz et al., 2014).

Table 23 A selection of relevant clinical trials published after the planning of this RCT.

Author (year)	*N / RCT-design*	*Mean age*	*Mean AHI at baseline*	*Interventions*	*Treatment duration*	*Reported findings (relevant for this thesis)*
de Vries et al. (2019)	85 / Parallel	50.7 ± 9.7	20.9 ± 4.5	CPAP/MAS	12 months	Both treatments improved daytime sleepiness and SF36 but had minimal impact on HADS. CPAP improved AHI more than MAS.
El-Solh et al. (2017)	44 / Crossover	52.7 ± 11.6	34.7 ± 29.7	CPAP/MAS	4 weeks	CPAP and MAS showed similar improvements in PSQI and SF36. CPAP improved AHI more than MAS.
Huang et al. (2015)	73 / Parallel	32.4 ± 6.7	~29 ± ~13	CPAP/No therapy	36 months	CPAP improved AHI and daytime sleepiness, while no therapy did not.
McMillan et al. (2014)	278 / Parallel	71.1 ± 4.6	-	CPAP/best supportive care	12 months	CPAP improved daytime sleepiness and the vitality-domain in SF36 more than best supportive care.
Mok et al. (2020)	126 / Parallel	51 ± 11	42.4 ± 22.6	CPAP/Sham CPAP	12 weeks	CPAP did not improve symptoms of depression more than sham CPAP.
Ponce et al. (2019)	145 / Parallel	74.9 ± 4.6	21.7 ± 4.8	CPAP/No treatment	3 months	CPAP improved AHI, daytime sleepiness, and some aspects of QoL, but did not improve HADS.
Quinnell et al. (2014)	90 / Crossover	50.9 ± 11.6	13.8 ± 6.2	3 types of MAS/No treatment	6 weeks	MAS, boil-and-bite type MAS and semi bespoke MAS all improved AHI and daytime sleepiness, but MAS performed better than the other treatments. Patients disapproved boil-and-bite type MAS.

AHI = Apnea-hypopnea-index, CPAP = Continuous Positive Airway Pressure, HADS = Hospital Anxiety and Depression Scale, PSQI = Pittsburgh Sleep Quality Index, QoL = Quality of life, N = Number of patients randomized at baseline, MAS = Mandibular advancement splints, RCT = Randomized clinical trial, SF36 = Short Form 36.

4.3.1 What does this RCT add to the current literature in OSA research?

The call for clinical trials evaluating efficacy of OSA treatment with CPAP or MAS was evident both prior to the planning of this RCT (Ferguson et al., 2006, Giles et al., 2006, McDaid et al., 2009, Marklund et al., 2012, Qaseem et al., 2013) and the publication of the Papers I, II and III (Marklund, 2017, Schwartz et al., 2018, Sharples et al., 2016, Veasey and Rosen, 2019). This trial aimed to meet some of the demand for new knowledge, in particular issues regarding daytime sleepiness (Lim et al., 2006, McDaid et al., 2009), HRQoL (Kuhn et al., 2017, Lim et al., 2006, Machado et al., 2004) and predictors for treatment success (Giles et al., 2006, Lim et al., 2006, Ramar et al., 2015). Unfortunately, too many patients in this RCT had completed the faulty version of the Epworth's sleepiness scale rendering the daytime sleepiness data unsuitable for publication. Even more important, compliance to treatment was considerably poorer than expected, leading to low statistical power in this RCT. This means that the risk of finding incorrect insignificant differences between treatment groups in this RCT was substantial. It can thus be argued that most comparisons between treatment groups in this RCT adds little to the current literature on OSA.

On the other hand, the similarities between the treatment groups regarding HRQoL and subjective sleep quality, and the apparent difference in treatment efficacy between CPAP and MAS devices coincide with the current evidence in OSA research. This RCT therefore adds more data to the already established knowledge base. The findings in this RCT also expose issues that raise new questions about OSA treatment: Most importantly, are the compliance to treatment in this RCT representative for patients with non-severe OSA in Norway? If so, the compliance to CPAP treatment in previous studies may tend to overestimate the compliance to non-severe OSA treatment, at least in mid- and northern Norway. Moreover, little is known about the possible reasons for this. This trial seems to be the first to investigate the association between Friedman score and treatment efficacy/compliance in CPAP and MAS treatment among patients with non-severe OSA. The results regarding Friedman score can be recognized as an addition to the current knowledge about treatment of OSA with CPAP or MAS.

5 Conclusions, clinical implications, and further research

5.1 Main conclusions

The overall objective of clinical research is to gain knowledge that ideally improve on the philosophy and methods used in the clinical management of patients. Through clinical research, the prevention and treatment of diseases and disorders keep getting better, safer, easier to implement, more efficient, and with a more predictable outcome for both patients and health-care providers. This thesis contributes to the knowledge of the treatment of non-severe OSA, and the clinical decision-making process related to choosing between treatment alternatives for OSA. Under reservations regarding the risk of statistical type II error related to suboptimal number of patients participating in the trial, the following conclusions may be drawn from the findings presented in this thesis:

- The ability to practically eliminate apnea- and hypopnea events in non-severe OSA patients makes the CPAP a more predictable and effective treatment than MAS given good compliance to treatment.
- At group level, the subjectively reported compliance to CPAP treatment was lower compared to MAS treatment.
- After both 4 and 12 months of treatment, there were no conclusive differences between CPAP and MAS treatment regarding self-reported sleep quality.
- After 12 months of treatment, there were no differences found between CPAP and MAS treatment regarding health-related quality of life.
- Tongue size according to Friedman tongue position seems to be unsuitable for predicting treatment success and compliance to treatment in neither CPAP nor MAS treatment in patients with non-severe OSA.

5.2 Clinical implications

The results presented in this thesis agree with existing knowledge and guidelines regarding the ability to reduce AHI with CPAP and MAS treatment and the compliance pattern to these treatment options (Ramar et al., 2015). Since overall treatment effectiveness depends on both AHI reduction and the compliance to treatment (Sutherland et al., 2015), the differences between CPAP and MAS treatment effectiveness may be less pronounced than indicated by the AHI differences at follow-up. This is supported by findings in this RCT suggesting that the subjective sleep-quality and HRQoL may be similar in CPAP and MAS treatment after 12 months of treatment.

Even though group-level data suggests that the effectiveness of CPAP and MAS treatment may be somewhat comparable, the individual patient may experience either treatment alternative as far superior. This emphasizes the importance of tailoring OSA treatment to the specific patient, taking severity of OSA, device efficacy, subjective sleep-quality, and compliance to treatment into account. Unfortunately, there is still no reliable way to predict the compliance and efficacy in CPAP and MAS treatment in an outpatient clinic setting in patients with non-severe OSA. Despite Friedman score being able to predict OSA severity, and indirectly predicting surgical treatment success in OSA (Friedman et al., 2004, Friedman et al., 2013), this RCT shows that tongue position and size according to Friedman score is associated with neither AHI reduction nor compliance to CPAP and MAS treatment in non-severe OSA.

If there are no known methods that precisely predict who will benefit the most from either CPAP or MAS treatment, the primary treatment choice should be the most effective treatment option in ideal treatment conditions. This implies that CPAP should still be regarded the primary treatment choice in addition to causal interventions such as physical exercise, weight-loss and avoiding supine sleep position. However, due to the poor compliance to CPAP treatment reported in this RCT, MAS should be considered a standard treatment option in non-severe OSA in all hospital clinics treating primary OSA. Patients being non-compliant to CPAP treatment should in other words be offered MAS treatment. Similarly, patients with unsatisfactory subjective and objective response to MAS treatment should be encouraged to comply with CPAP treatment.

5.2.1 Further research

Methods for clinically predicting which OSA patients will benefit the most from MAS treatment is a current issue in contemporary OSA research (Sutherland and Cistulli, 2019). The results presented in this thesis highlight the challenges in predicting treatment success and compliance in CPAP and MAS treatment. Accurate prediction of treatment success is key to tailored treatment in non-severe OSA patients. Hence, future research should continue the search for reliable methods for identifying patients likely to be compliant to- and benefit the most from MAS and CPAP treatment respectively.

As part of the quest for a better tailored treatment of OSA, reasons for quitting CPAP and MAS treatment, and predictors for compliance, including adverse effects and comfort related to both treatment options should be further investigated. Moreover, the impact on treatment compliance from the patient's internal and external motivation to carry through with treatment should be investigated. Further research is also needed to identify HSAT variables and patient characteristics associated with the change in self-reported sleep quality and HRQoL. Associations

between self-reported sleep quality and daytime sleepiness and the role of self-reported sleep quality in OSA treatment in relation to the patient's motivation and compliance to treatment in general should be studied. Importantly, since this RCT may not have answered all research questions as intended, there is a need for larger non-inferiority trials comparing placebo, CPAP and MAS treatment.

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Papers I-III

Paper I

ORIGINAL ARTICLE

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Self-Reported Sleep Quality With Mandibular Advancement Device or Continuous Positive Airway Pressure: A Randomized Clinical Trial on Patients With Mild and Moderate Obstructive Sleep Apnea

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Study Objectives: To compare self-reported sleep quality, treatment compliance, and respiratory event index (REI) after 4 months of treatment with mandibular advancement device (MAD) or continuous positive airway pressure (CPAP) in mild and moderate obstructive sleep apnea (OSA).

Materials and Methods: A total of 104 patients with mild or moderate OSA were randomly allocated to MAD or CPAP treatment and followed for 4 months. Data were collected through type 3 polygraphic sleep recordings, CPAP recordings, medical examination, and the Pittsburgh Sleep Quality Index (PSQI). Chi-square test, t-test, and Mann-Whitney U test were used to analyze compliance, PSQI global score and REI, respectively. Reliable change index (RCI) was used to evaluate change in PSQI global score.

Results: Six patients were lost to follow-up. More patients were compliant with MAD treatment (79.5%) than CPAP treatment (38.9%) at follow-up (P<0.001). Both groups had improved PSQI global scores: MAD (8.0±3.1 to 5.7±2.5, P<0.001) and CPAP (7.7±3.5 to 6.7±3.4, P=0.01). More patients had improved PSQI global score according to the RCI in the MAD group (38.6%) than in the CPAP group (16.7%) (P=0.01). Both treatments reduced REI (P<0.001), but CPAP (REI=1.1) more so than MAD (REI=7.9) (P<0.001).

Conclusions: Both MAD and CPAP treatment improve self-reported sleep quality in patients with mild and moderate OSA. More patients comply with MAD treatment, which improves sleep quality in more patients than does CPAP, despite REI being lower in the CPAP group. With respect to sleep quality, MAD treatment should be considered a better treatment option than CPAP in mild and moderate OSA.

Keywords: adult; continuous positive airway pressure; mandibular advancement; obstructive sleep apnea; occlusal splints; patient compliance; respiratory disorders; self-report; sleep hygiene

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INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by repeated collapse of the soft tissues in the upper airway and leads to sleep fragmentation and reduced sleep quality.[1-3] The severity of OSA is measured by the apnea-hypopnea index (AHI) and is graded as mild (AHI 5-14.9 events/h), moderate (AHI 15-29.9 events/h) and severe (AHI >30 events/h).[4] When OSA is diagnosed through unattended sleep apnea testing the AHI is substituted by the respiratory event index (REI).[5] Continuous positive airway pressure (CPAP) reduces respiratory events by eliminating the negative respiratory pressure that collapses the upper airways.[6] Despite challenges regarding patient adherence, CPAP is currently regarded as the gold standard for treatment of all patients with OSA,[7] whereas exercise training and weight loss are recommended as adjunct treatments for all patients with OSA who are overweight.[8,9] In addition, surgical interventions are indicated in selected groups of patients with OSA.[10-12] For patients with primary snoring or mild OSA or those who are unable or unwilling to use CPAP, a mandibular advancement device (MAD) is regarded as an adequate alternative.[7,13,14] MADs relocate and fixate the mandible in a protruded position when used, thus increasing the retropalatal and retroglossal volume and thereby reducing the collapsibility of the upper airways.[15,16] Although CPAP treatment is known to be superior to MAD treatment in regard to respiratory event reduction,[7,10,17] several studies have shown patients adhering better to MAD and preferring MAD over CPAP when given the choice.[18-21] Both CPAP and MAD treatments are associated with only mild and transient adverse effects such as

pressure in the face, mild pain in teeth and jaw, or changes in salivation,[10,16,19,22] suggesting that factors other than adverse effects from CPAP and MAD have an effect on the patient's preferences and motivation in OSA treatment.[15,20] The patient's perceived sleep quality while using CPAP or MAD might be one such factor, but self-reported sleep quality during OSA treatment is not extensively studied.[17,23] Contrary to polysomnographic analysis of sleep quality, which shows sleep efficacy and changes in sleep stages during OSA treatment,[24,25] self-reported sleep quality shows how the patient experiences the effect of OSA treatment on sleep quality. It is currently not clear which OSA treatment is better at improving self-reported sleep quality, or how much improvement could be expected in patients with mild and moderate OSA.[2] To our knowledge, no randomized controlled trial has previously measured and compared the effect of CPAP and MAD treatment on self-reported sleep quality in patients with mild and moderate OSA.

Aim

In this study we aimed to compare self-reported sleep quality after initial phase (4 months) of MAD or CPAP treatment in mild and moderate OSA. Secondary aims were to compare treatment compliance and change in REI from baseline to follow-up.

MATERIALS AND METHODS

Study Design

This study was a two-centered parallel arm randomized controlled clinical trial, with 50/50 allocation ratio. Blinding of the patients and clinical personnel was not feasible because of the nature of the OSA treatment.

Ethical Approval

The trial was approved by the Norwegian Regional Committee for Medical and Health Research Ethics, REC Central (registration #2014/956) and was registered in ClinicalTrials.gov (registration #NCT02953028).

Calibration

Two researchers (LMB and TKSA) calibrated all personnel involved in the patient treatment and data collection according to the trial protocol. The protocol checklists complied with the later updated American Academy of Sleep Medicine practice guidelines for diagnostic testing for OSA.[26]

Recruitment and Randomization

All patients in the trial were referred from primary health care to the ear-nose-throat departments at the University hospital of Northern Norway (UNN) in Tromsø, St. Olavs University Hospital (St. Olavs), and Aleris Hospital in Trondheim, Norway. All patients were screened for OSA by ambulatory type 3 sleep recording devices (Embletta® or Nox T3™, ResMed Norway AS) at home or at a hotel. Respiratory events were defined as >90% reduction in respiratory flow or >50% reduction in respiratory flow combined with ≥3% oxygen desaturation from baseline respectively. The sleep recordings were manually analyzed by sleep technicians at the three hospitals before otorhinolaryngologists at UNN and St. Olavs Hospitals performed a medical examination of the patients. All patients meeting the inclusion criteria were invited to participate in the study by the otorhinolaryngologist.

Inclusion criteria were age 20 to 75 years, REI between 10.0 and 29.9, and ability to protrude the mandible at least 5 mm. Exclusion criteria were pregnancy, drug abuse, daily use of sedative medication, preexisting severe psychiatric disorders, or somatic health issues such as temporomandibular dysfunction that prevented the use of CPAP or MAD.

After providing informed written consent to participate, the patients were randomized to treatment with either CPAP or MAD. The patients drew lots from a masked envelope for random allocation. Block-randomization with 30 lots per block at each of the two study sites was used to prevent skewed distribution between CPAP and MAD groups across seasons and study sites.

Treatment Protocol and Questionnaires

The treatment protocol was based on the recommendations from the Standards of Practice Committee and the Board of Directors of the American Academy of Sleep Medicine.[27] Patients allocated to the CPAP group met a sleep technician on 2 consecutive days for adaptation and adjustment of the CPAP-machine (Resmed®, San Diego, California, USA). A facemask or nose mask was used depending on the patient's needs and preference. The patients had the opportunity to see the sleep technicians for adjustments of the CPAP machine when necessary.

Patients allocated to the MAD group met a dentist and dental hygienist or dental nurse for impression of the dentition, bite registration using the George gauge™ (Scheu-dental GmbH, Iserlohn, Germany) and ordering the MAD (Respire Medical, New York, New York, USA and SomnoDent®, Sydney, New South Wales, Australia). At the second visit to the dental team the MAD was set between 60% and 65% of maximum protrusion of the mandible. Necessary changes to the MAD based on patient feedback were made after 2 to 3 weeks. The patients had the opportunity to see the dental team for further

adjustments of the MAD when necessary.

At the medical examination prior to treatment, all patients completed the Pittsburgh Sleep Quality Index (PSQI) a 19-item validated questionnaire measuring self-perceived sleep quality during the previous month. PSQI assess 7 aspects of sleep quality: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medicine, and daytime dysfunction, which are transformed into a global score. The PSQI global score has a possible range of 0-21 points, with ≤5 points representing good sleep quality.[28]

To evaluate whether the change in PSQI for each individual patient was clinically and statistically significant, the reliable change index (RCI) as described by Jacobson and Truax[29] was used. The RCI was calculated by using the standard deviation from pretreatment PSQI global score and a test-retest reliability at 0.85.[28] An RCI value <-1.96 indicate that the patient's reduction in PSQI global score is statistically significant on a 5% level, and thus not likely to occur due to expected test-retest variations. The patients also completed a 12-item questionnaire assessing general health, socioeconomic status, and smoking and alcohol habits.

At follow-up after approximately 4 months, all patients completed the PSQI questionnaire and a questionnaire covering self-reported compliance to both the CPAP and MAD group. Recordings of usage and REI were downloaded from the CPAP machine, whereas patients using MAD recorded REI through a new polygraphic sleep recording while using the MAD. Sleep technicians at UNN and St. Olavs hospitals analyzed both CPAP recordings and the new polygraphic sleep recordings. Patients were regarded as compliant with treatment if they reported using the CPAP or MAD more than 4 hours during more than 50% of nights.

Statistical Analysis

Both intention-to-treat (ITT) analyses (all included patients) and per-protocol (PP) analyses (patients compliant with treatment) are presented for the primary aim and compliance.[30] REI was analyzed according to ITT only. At follow-up, the MAD and CPAP groups were compared using the *t*-test (PSQI), Mann-Whitney *U* test (REI), and Pearson chi-square test (compliance with treatment). Change within treatment groups in PSQI global score and REI from baseline to follow-up was analyzed using paired-samples *t*-test and Wilcoxon signed-rank test, respectively. Missing entries in PSQI were replaced by multiple imputations as recommended by CONSORT 2010.[31,32] The number of patients with RCI<-1.96 in each treatment group was compared using Pearson chi-square test. All statistical analyses were done using SPSS 25 statistical software package (IBM Corp, Armonk, New York, USA) and a two-sided value of $P<0.05$ was considered statistically significant.

Sample Size

Based on an expected 15% difference in PSQI global score between treatment groups at follow-up and a common standard deviation within groups at 25%, a sample size of 45 patients in each treatment group was needed to detect differences in a *t*-test between the groups at a 5% significance level (two-tailed analysis) and reaching 80% power. Assuming a 10% dropout rate, a minimum of 99 patients was needed for the trial.

RESULTS

Participant Flow, Dropouts, and Treatment Compliance

Patients were recruited to the study between October 2014 and February 2018. A total of 104 patients satisfied the inclusion criteria and signed a written consent to participate in the trial. Forty-nine patients were allocated to MAD treatment and 55 were allocated to CPAP treatment. The flow of patients in the study is illustrated in Figure 1. Thirty-eight patients with a MAD and 45 patients using CPAP had no missing data throughout the trial. After replacing missing PSQI entries through imputations, 44 patients using a MAD and 54 patients using CPAP were included in the PSQI analyses at 4 months. Median time from treatment start to follow-up was 4 months, range 2 to 8 months. Follow-up was ended in January 2019.

The 11 patients ceasing treatment before follow-up were demographically similar to the remaining study population at baseline and were evenly distributed between mild and moderate OSA. Information on compliance was available for 98 patients. The chi-square test showed more patients being compliant with MAD treatment (79.5%) than CPAP treatment (38.9%) at follow-up ($P<0.001$).

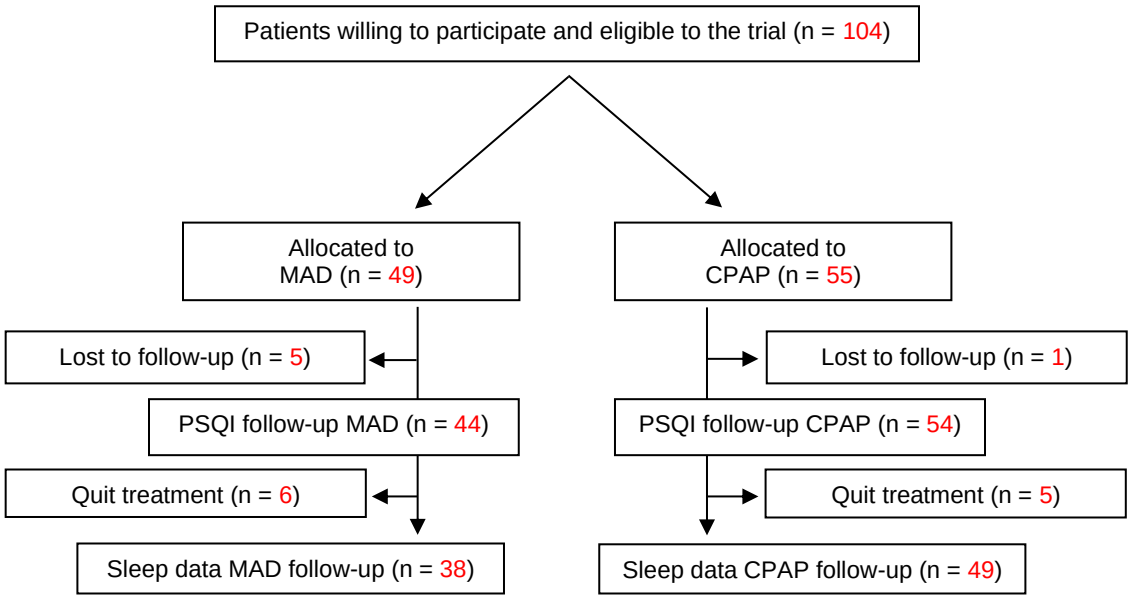
Baseline Data and Outcome Variables

Demographic patient data at baseline are presented in Table 1 and were uniformly distributed between the treatment groups. The distribution was similar in the ITT and PP analysis (supplementary Table S 1).

PSQI Global Score

From baseline to follow-up, mean PSQI global score was reduced in both treatment groups in the ITT analysis: MAD group from 8.0±3.1 to 5.7±2.5, $P<0.001$ and CPAP group from 7.7±3.5 to 6.7±3.4, $P=0.01$. PP analysis including only patients with treatment compliance also showed reduced PSQI global score in both treatment groups: MAD group from 8.1±3.1 to 5.3±2.5, $P<0.001$ and CPAP group from 7.1±3.5 to 5.8±3.3, $P=0.02$. The PSQI global score did not differ between the treatment groups at follow-up (Table 2).

Figure 1. Patient flow chart



MAD: Mandibular Advancement Device
CPAP: Continuous Positive Airway Pressure

Table 1. Demographic patient data at baseline, all included patients

Baseline variables	**MAD (n=49)**	**CPAP (n=55)**
Age at inclusion [a]	49.6 (9.0)	53.3 (10.2)
BMI at inclusion [a]	32.4 (7.2)	30.8 (6.2)
Sex		
Female	20 (40.8)	17 (30.9)
Male	29 (59.2)	38 (69.1)
Marital status		
Cohabitant	37 (75.5)	44 (80.0)
Living alone	12 (24.5)	11 (20.0)
OSA severity		
Mild	19 (38.8)	13 (23.6)
Moderate	30 (61.2)	42 (76.4)
Allergy		
Yes	8 (16.3)	9 (16.4)
No	51 (83.7)	46 (83.6)
Self-reported health		
Good-Excellent	13 (26.5)	16 (29.1)
Poor-Fair	36 (73.5)	39 (70.9)
Education level		
College or university	27 (55.1)	23 (41.8)
Other education	22 (44.9)	32 (58.2)
Alcohol consumption		
≤ Once per week	40 (81.6)	43 (78.2)
> Once per week	9 (18.4)	12 (21.8)
Smoking status		
Nonsmoking	42 (85.7)	41 (74.5)
Smoking	7 (14.3)	14 (25.5)

[a]Mean (standard deviation), all other variables: n (%).
BMI, body mass index (kg/m^2); CPAP, continuous positive airway pressure; MAD, mandibular advancement device; OSA, obstructive sleep apnea. (kg/m^2).

Table 2. PSQI and REI at baseline and follow-up.

	Baseline		Follow-up (4 months)		
	MAD (n=49)	CPAP (n=55)	MAD (n=44)	CPAP (n=54)	*P*
PSQI ITT	8.0 (3.1)	7.7 (3.5)	5.7[a] (2.5)	6.7[a] (3.4)	.11
PSQI PP[b]	8.1 (3.1)	7.1 (3.5)	5.3[a] (2.5)	5.8[a] (3.3)	.55
REI[c]	16.3 (12.4-23.0)	18.1 (15.3-24.6)	7.9[a] (6.0-13.7)	1.1[a] (0.6-1.6)	<.001

P indicates *t*-test/Mann-Whitney *U* test between MAD and CPAP group at follow-up. Mean (standard deviation). median (interquartile range).

ITT, intention to treat; PP, per protocol; PSQI, Pittsburgh Sleep Quality Index (global score); REI, respiratory event index (events/h).

[a]Statistically significant change from baseline within treatment group ($P<0.05$).
[b]MAD n=35 at follow-up, CPAP n=21 at follow-up.
[c]MAD n=38 at follow-up, CPAP n=49 at follow-up.

Reliable Change in PSQI Global Score

According to the RCI, significantly more patients in the MAD group than in the CPAP group reported improvement in sleep quality, that is, having RCI <-1.96 for the change in PSQI global score from baseline to follow-up. This was found in both the ITT and PP analyses (Table 3).

Table 3. Number of patients with significantly improved PSQI global score (RCI<-1.96).

	Significantly improved PSQI global score (RCI<-1.96)		
	MAD	CPAP	*P*
PSQI ITT	38.6% (17/44)	16.7% (9/54)	.014
PSQI PP	45.7% (16/35)	19.0% (4/21)	.044

ITT, intention to treat; PP, per protocol; P, Pearson chi-square test; PSQI, Pittsburgh Sleep Quality Index (global score); RCI, reliable change index.

Respiratory Event Index

Both treatment groups had a reduction in median REI from baseline to follow-up: MAD group from 16.3 (12.4 – 23.0) to 7.9 (6.0 – 13.7), $P<0.001$ and CPAP group from 18.1 (15.3 – 24.6) to 1.1 (0.6 – 1.6), $P<0.001$ (Table 2). The CPAP group had a lower REI score than the MAD group at follow-up ($P<0.001$).

DISCUSSION

In this randomized controlled clinical trial we compared the effect of CPAP and MAD treatment on self-reported sleep quality in patients with mild and moderate OSA. After 4 months of treatment, self-reported sleep quality was improved in both treatment groups. Although PSQI global score at follow-up was similar between the treatment groups, the difference in the number of patients reporting a reliable improvement in PSQI global score was significant. Patients reporting an improved PSQI global score according to the RCI are assumed to also have clinically improved sleep quality from baseline to follow-up.[33] This means that 38.6% of patients using a MAD and 16.7% of patients using CPAP in our trial experienced an improvement in perceived sleep quality, even though the absolute change in PSQI global score seem modest. By using the RCI, we counteract the effect from possible outliers in PSQI change, thereby limiting the possible influence from factors not related to OSA on the PSQI change at group level.

It is reasonable to believe that effective treatment of OSA should improve sleep quality.[24,34] Both treatment groups in this trial significantly reduced the REI, indicating that both MAD and CPAP have a considerable positive effect on mild and moderate OSA. In the CPAP group the REI was reduced to 1.1, well below the limit for having OSA.[4] The MAD group had on average a residual REI at 7.9, which is unsurprising as the MAD by increasing the volume of the upper airway merely reduce the negative respiratory pressure, not fully eliminate the collapsibility of the upper airways.[16] Although reducing the REI by more than 50%, the residual REI may be contributing to PSQI global score remaining above 5.0 in the MAD group at

follow-up. However, CPAP treatment also did not reduce PSQI global score below 5.0, showing that the PSQI global score is dependent on more factors than REI.[2,23] The limited reduction of PSQI global score in the CPAP group may be due to low CPAP compliance in the ITT analysis. However, the PP analysis showed that when only including patients who used the MAD or CPAP more than 4 hours, more than 50% of nights, more patients using MAD than using CPAP report improved sleep quality according to the RCI (Table 3). This trend was even more pronounced when using 4 hours and 70% of nights as the lower limit for compliance (P=0.02, table not shown), indicating that MAD treatment, despite having higher residual REI, is better than CPAP treatment at improving self-reported sleep quality. Previous studies have indicated that MAD is perceived as a less invasive treatment alternative and is preferred over CPAP treatment in most studies where patients have been treated with both appliances.[8,15,18] This is not only in line with our findings regarding treatment compliance, but also indicates why MAD seems to be better at improving sleep quality, given that CPAP treatment may be uncomfortable and thus impair sleep quality while simultaneously lowering REI.[35,36]

This study deviates from the more common cutoff level for treatment compliance being >4 hours, >70% of nights[21] because only 33 MAD patients (76.7%) and 17 CPAP patients (31.5%) would be regarded as compliant with treatment, further reducing statistical power in the PP analyses. Regardless of compliance cutoff level, treatment compliance in this study was better with MAD than with CPAP, a finding that also was found in a recent meta-analysis.[37] Furthermore, the poor compliance with CPAP treatment in this trial is in line with another meta-analysis where CPAP compliance became worse with reduced OSA severity.[21] Fortunately, the risk of serious cardiovascular events and death seems to be small in mild and moderate OSA compared to severe OSA.[38-40] This finding, and the debated role of respiratory events as a predictor for cardiovascular events and early death, suggests that good compliance with treatment may be more important than optimal reduction of respiratory events, as long as the residual REI is within preferably mild and perhaps moderate OSA.[41,42] Achieving patient- perceived benefits of OSA treatment such as improved sleep quality should therefore be considered part of the treatment goal, especially in mild and moderate OSA, where factors other than disease severity seem to be important for motivation and compliance to treatment.[21,35,43] To bypass concerns related to treatment compliance, mandibular advancement surgery may be considered in patients in whom REI is effectively reduced and sleep quality is improved with MAD treatment. Surgical mandibular advancement reduces REI through mechanisms similar to MAD treatment, but the invasive nature of such a surgical procedure makes it more suited for patients having severe OSA and should not be considered in patients where there are high risks of postsurgical malocclusion or poor facial esthetics.[12,44]

The randomization procedure in this trial was successful; thus, any first-night effects in the polygraphic sleep recordings[26,45] or placebo effects on sleep quality in this initial phase of treatment should be equal in the two treatment groups because of the study design.[46] However, there was a risk of recruitment bias because the study was unblinded and some patients could be familiar with either MAD or CPAP treatment before agreeing to participate in the trial. To minimize this risk, only patients who had not in any way been treated for OSA previously were invited to the trial. Patients in this trial deviated from the Norwegian general population by having higher average body mass index and worse self-reported general health at baseline.[47,48]

One major limitation of this study is the uncertainty of using self-reported compliance. Objectively measured compliance was available for the CPAP group only, which showed minor discrepancies between self-reported and objectively measured compliance for 6 patients. There are no reasons to believe that patients in the MAD group are less honest than those in the CPAP group when reporting on their use of the appliance. Moreover, very good agreement between subjective and objective measured compliance in MAD patients was found in previous studies.[49] PP analyses using objectively measured compliance for the CPAP group are presented in the supplementary Table S 2 and supplementary Table S3.

Imputed data were used in the primary analysis as recommended by the CONSORT 2010 statement to avoid compromising the methodologic strengths of the randomization.[31] Results from analysis only including patients with no imputed data are presented in the supplementary Table S 4 and supplementary Table S 5. Fisher exact test showed that the 6 patients without any information on compliance were similar to the rest of the patients at baseline (data not shown). Furthermore, the 5 patients who were lost to follow-up in the MAD group were missing at random. The missing patients in this trial are therefore unlikely to create any bias at follow-up. Although sleep data on follow-up was available in fewer patients in the MAD group (77.6%) than in the CPAP group (89.1%), this difference was not statistically significant (chi-square test, P=0.11) and unlikely to affect the results.

CONCLUSION

In summary, both MAD and CPAP treatment improve self-reported sleep quality in patients with mild and moderate OSA. When using the CPAP device, the CPAP group achieved a lower REI than the MAD group. Nevertheless, significantly more patients in the MAD group comply with the treatment and report a significant improvement in PSQI global score compared to the CPAP group. Regarding sleep quality, MAD should be considered

a better treatment option than CPAP in mild and moderate OSA.

ABBREVIATIONS

AHI – apnea-hypopnea index
CPAP – continuous positive airway pressure
ITT – intention to treat
MAD – mandibular advancement device
OSA – obstructive sleep apnea
PP – per protocol
PSQI – Pittsburgh Sleep Quality Index
RCI – reliable change index
REI – respiratory event index

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DISCLOSURE STATEMENT

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SUPPLEMENTARY TABLES

Table S 1. Distribution of patient characteristics in intention-to-treat and per protocol analysis

Baseline variables	MAD ITT (n=49)	CPAP ITT (n=55)	MAD PP (n=35)	CPAP PP (n=21)
Age at inclusion[a]	49.6 (9.0)	53.3 (10.2)	49.9 (9.2)	55.1 (10.9)
BMI at inclusion[a]	32.4 (7.2)	30.8 (6.2)	32.2 (7.1)	30.4 (5.1)
Sex				
Female	20 (40.8)	17 (30.9)	13 (37.1)	7 (33.3)
Male	29 (59.2)	38 (69.1)	22 (62.9)	14 (66.7)
Marital status				
Cohabitant	37 (75.5)	44 (80.0)	27 (77.1)	19 (90.5)
Living alone	12 (24.5)	11 (20.0)	8 (22.9)	2 (9.5)
OSA severity				
Mild	19 (38.8)	13 (23.6)	15 (42.9)	4 (19.0)
Moderate	30 (61.2)	42 (76.4)	20 (57.1)	17 (81.0)
Allergy				
Yes	8 (16.3)	9 (16.4)	3 (8.6)	4 (19.0)
No	51 (83.7)	46 (83.6)	32 (91.4)	17 (81.0)
Self-reported health				
Good-Excellent	13 (26.5)	16 (29.1)	13 (37.1)	6 (28.6)
Poor-Fair	36 (73.5)	39 (70.9)	22 (62.9)	15 (71.4)
Education level				
College or university	27 (55.1)	23 (41.8)	19 (54.3)	8 (38.1)
Other education	22 (44.9)	32 (58.2)	16 (45.7)	13 (61.9)
Alcohol consumption				
≤ Once per week	40 (81.6)	43 (78.2)	29 (82.9)	17 (81.0)
> Once per week	9 (18.4)	12 (21.8)	6 (17.1)	4 (19.0)
Smoking status				
Nonsmoking	42 (85.7)	41 (74.5)	31 (88.6)	19 (90.5)
Smoking	7 (14.3)	14 (25.5)	4 (11.4)	2 (9.5)

BMI, body mass index (kg/m^2); CPAP, continuous positive airway pressure; ITT, intention to treat; MAD, mandibular advancement device; OSA, obstructive sleep apnea; PP, per protocol.

[a]Mean (standard deviation), all other variables: n (%).

Table S 2. PSQI and REI at baseline and follow-up (Objectively measured CPAP compliance and self-reported MAD compliance, >4 hours, >50% of nights).

	Baseline		Follow-up (4 months)		
	MAD (n=49)	CPAP (n=55)	MAD (n=44)	CPAP (n=54)	*P*
PSQI PP[b]	8.1 (3.1)	6.7 (3.4)	5.3[a] (2.5)	5.5 (3.0)	.81

CPAP, continuous positive airway pressure; MAD, mandibular advancement device; PP, per protocol; PSQI, Pittsburgh Sleep Quality Index (global score). *P* indicates t-test between MAD and CPAP group at follow-up.

[a]Statistically significant change from baseline within treatment group ($P<0.05$).

[b]MAD n=35 at follow-up, CPAP n=17 at follow-up.

Table S 3. Number of patients with significantly improved PSQI global score (RCI<-1.96) (objectively measured CPAP compliance and self-reported MAD compliance, >4 hours, >50% of nights).

	Improved PSQI global score		
	MAD	CPAP	*P*
PSQI ITT	38.6% (17/44)	16.7% (9/54)	.014
PSQI PP	45.7% (16/35)	17.6% (3/17)	.049

CPAP, continuous positive airway pressure; ITT, intention to treat; MAD, mandibular advancement device; PP, per protocol; PSQI, Pittsburgh Sleep Quality Index (global score). *P* indicates Pearson chi-square test.

Table S 4. PSQI and REI at baseline and follow-up (no patients with imputed data).

	Baseline		Follow-up (4 months)		
	MAD (n=43)	CPAP (n=46)	MAD (n=38)	CPAP (n=46)	*P*
PSQI ITT	7.7 (2.9)	7.8 (3.6)	5.4 [a] (2.3)	6.9 [a] (3.6)	.026
PSQI PP[b]	7.8 (2.7)	6.7 (3.5)	5.2 [a] (2.3)	5.5 (3.1)	.74
REI[c]	17.1 (12.5-22.8)	17.5 (14.6-23.0)	7.9 [a] (6.0-13.2)	1.1 [a] (0.6-1.6)	<.001

CPAP, continuous positive airway pressure; ITT, intention to treat; MAD, mandibular advancement device; PP, per protocol; PSQI, Pittsburgh Sleep Quality Index (global score); REI, respiratory event index (events/h). *P* indicates Difference between MAD and CPAP group at follow-up.

[a]Statistically significant change from baseline within treatment group (*P*<0.05).

[b]MAD n=33, CPAP n=16.

[c]MAD n=36 at follow-up, CPAP n=43 at follow-up.

Table S 5. Number of patients with significantly improved PSQI global score (RCI<1.96) (no patients with imputed data).

	Statistically significant improvement		
	MAD	CPAP	*P*
PSQI ITT	39.5% (15/38)	17.4% (8/46)	.024
PSQI PP	42.4% (14/33)	18.8% (3/16)	.10

CPAP, continuous positive airway pressure; ITT, intention to treat; MAD, mandibular advancement device; PP, per protocol; PSQI, Pittsburgh Sleep Quality Index (global score). *P* indicates Pearson chi-square test.

CORRIGENDA

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Correction: Self-Reported Sleep Quality With Mandibular Advancement Device or Continuous Positive Airway Pressure: A Randomized Clinical Trial on Patients With Mild and Moderate Obstructive Sleep Apnea

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The article titled "Self-Reported Sleep Quality With Mandibular Advancement Device or Continuous Positive Airway Pressure: A Randomized Clinical Trial on Patients With Mild and Moderate Obstructive Sleep Apnea" [*J Dent Sleep Med*. 2020; 7(2)] contained an error in the description of respiratory flow and oxygen desaturation. The error was as follows:

"Respiratory events were defined as >90% reduction in respiratory flow or >50% reduction in respiratory flow combined with ≥3% oxygen desaturation from baseline respectively."

The prior section should be replaced with: "Respiratory events were defined as >90% reduction in respiratory flow or >30% reduction in respiratory flow combined with ≥3% oxygen desaturation from baseline respectively."

The description was corrected in the manuscript, which was re-published on the JDSM website on November 18, 2020.

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Paper II

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Clinical Study

Friedman Score in Relation to Compliance and Treatment Response in Nonsevere Obstructive Sleep Apnea

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Nonsevere obstructive sleep apnea (OSA) is most often treated with a continuous positive airway pressure (CPAP) device or a mandibular advancement splint (MAS). However, patient compliance with these treatments is difficult to predict. Improvement in apnea-hypopnea index (AHI) is also somewhat unpredictable in MAS treatment. In this study, we investigated the association between Friedman tongue position score (Friedman score) and both treatment compliance and AHI improvement in patients with nonsevere OSA receiving CPAP or MAS treatment. 104 patients with nonsevere OSA were randomly allocated to CPAP or MAS treatment and followed for 12 months. Data were collected through a medical examination, questionnaires, sleep recordings from ambulatory type 3 polygraphic sleep recording devices, and CPAP recordings. Associations between Friedman score, treatment compliance, and AHI improvement were analysed with logistic regression analyses. Friedman score was not associated with treatment compliance (odds ratio [OR]: 0.85, 95% confidence interval [CI]: 0.59–1.23), or AHI improvement (OR: 1.05, 95% CI: 0.62–1.76) in the overall study sample, the CPAP treatment group, or the MAS treatment group. Adjustment for socioeconomic factors, body mass index, and tonsil size did not significantly impact the results. Although Friedman score may predict OSA severity and contribute to the prediction of success in uvulopalatopharyngoplasty, we found no association between Friedman score and treatment compliance in patients with nonsevere OSA receiving CPAP or MAS treatment, nor did we find any association between Friedman score and AHI improvement. Factors other than Friedman score should be considered when deciding whether a patient with nonsevere OSA should be treated with CPAP or MAS.

1. Introduction

Obstructive sleep apnea (OSA) is characterised by breathing cessations during sleep due to transient obstructions in the upper airways [1]. The use of surgical procedures in the upper airways to treat OSA is reserved for only a few, selected patient groups [2, 3]. The most common OSA treatment is continuous positive airway pressure (CPAP). A mandibular advancement splint (MAS) is an alternative for patients with primary snoring or mild OSA or those who are

unable or unwilling to use a CPAP device [4, 5]. CPAP treatment significantly lowers the number of breathing cessations in most patients by equalising the negative respiratory pressure that can cause the pharyngeal region to collapse [6]. Unfortunately, poor compliance with CPAP treatment is a significant challenge, especially among patients with nonsevere OSA [7, 8]. Ideally, the CPAP device should be used all night, every night [9]. However, compliance with CPAP treatment is usually regarded as "good" or "adequate" when patients are able to use the CPAP device for more than 4 hours a night [7], at least 70% of nights [10]. MAS treatment, which improves pharyngeal patency by protruding the mandible, shows better compliance, but less predictable improvements in breathing cessations [5, 11–13]. However, both CPAP and MAS treatment can successfully treat nonsevere OSA, as long as patient compliance is adequate [12, 14, 15]. Therefore, tools are needed to help clinicians predict whether the patient is more likely to comply with CPAP or MAS treatment, and if the patient will successfully respond to MAS treatment [16–19]. The Friedman tongue position score (Friedman score) was developed to describe and classify the morphology of the oropharynx with the tongue in a natural relaxed position [20]. A higher Friedman score has been found to predict higher OSA severity [21], which is associated with better compliance with CPAP treatment [8]. In the Friedman Grade staging system, which combines body mass index (BMI), tonsil size, and Friedman score, a low Friedman score has been reported to predict treatment success after uvulopalatopharyngoplasty (UPPP) [2]. In other studies, anatomical obstructions in the nasal cavity and oropharynx have been found to reduce both the effect of and compliance with CPAP treatment [22, 23]. Comparing these findings to the treatment mechanisms of MAS, which relies on relocating the tongue to an anterior position through mandibular protrusion [11], it seems plausible that the Friedman score could be associated with both treatment compliance and apnea-hypopnea index (AHI) improvement in both CPAP and MAS treatment. The Friedman score may therefore be a potential clinical tool for predicting treatment compliance and AHI improvement in CPAP and MAS treatment. In this study, we investigated the association between Friedman score and both treatment compliance and AHI improvement in patients with nonsevere OSA receiving CPAP or MAS treatment.

2. Materials and Methods

2.1. Study Design and Sample. This prospective, observational study took place in a clinical trial setting and is based on data from a two-centred, parallel-arm randomised controlled trial (RCT), with a 50 : 50 allocation ratio. Due to the nature of CPAP and MAS treatment, the clinical personnel and patients had to know which treatment was received; thus, a blinded RCT was not feasible. All patients in the RCT participated in the current observational study. The patients were recruited to the study after being referred from primary health care to the Ear-Nose-Throat Department of the University Hospital in Northern Norway, Tromsø, and St. Olavs and Aleris Hospitals in Trondheim, Norway. Referred patients were screened for OSA by ambulatory type 3 polygraphic sleep recording devices (Embletta® or Nox T3™, ResMed Norway AS) over night, at home or at a hotel, between October 2014 and February 2018. Resultant sleep recordings were manually analysed by sleep technicians. An otorhinolaryngologist performed a medical examination of the patients and assigned them a Friedman score, which is assessed by a passive, visual inspection of the patient's oral cavity while positioned across from the patient. The 4-grade Friedman score was chosen for this study: grade (I), the entire uvula and palatal tonsils visible; grade (II), the complete soft palate and parts of the uvula visible; grade (III), the uvula not visible and parts of the soft palate visible; and grade (IV), only the hard palate visible [24]. Two researchers (LMB and TKSA) calibrated all involved sleep technicians, dentists, and physicians at the three hospitals according to the study protocol. The protocol checklists complied with updated American Academy of Sleep Medicine practice guidelines for diagnostic testing for OSA [25]. Apnea events were defined as >90% reduction of respiratory flow lasting ≥10 seconds; hypopnea events were defined as ≥50% reduction in respiratory flow lasting ≥10 seconds combined with ≥3% reduction from baseline peripheral blood oxygenation. Nonsevere OSA was defined as AHI <30 events/hour [26].

Inclusion criteria were age 20 to 75 years, AHI between 10.0 and 29.9, and ability to protrude the mandible at least 5 mm. Exclusion criteria were severe OSA (AHI ≥30), pregnancy, drug abuse, daily use of sedative medication, preexisting severe psychiatric disorders, or somatic health issues, such as temporomandibular dysfunction and nasal obstructions, which would interfere with the use of the CPAP device or MAS. Patients who had received previous CPAP or MAS treatment were also excluded.

All patients who met the aforementioned criteria were invited to participate in the study by the otorhinolaryngologist after performing the medical examination. Informed written consent to participate was obtained from 104 patients, who drew lots from a masked envelope for random allocation to either CPAP or MAS treatment. To prevent skewed distribution between treatment groups, across seasons and across study sites, block-randomization with 30 lots per block was used. The number of patients recruited to the study was based on a power calculation for health related quality of life in the RCT which this study was based upon. Baseline characteristics were obtained from a self-administered questionnaire, in which an allergic rhinitis was defined as any respiratory complaint attributed to allergic rhinitis, and smoking was defined as current occasional use or current daily use of smoking tobacco.

The treatment protocol was based on recommendations from the Standards of Practice Committee and the Board of Directors of the American Academy of Sleep Medicine [27]. For patients allocated to the CPAP treatment group, a sleep technician calibrated each CPAP device to the individual patient (Resmed®, San Diego, CA, USA). A facemask or nose mask was used depending on the patient's needs and preference. Patients returned for a follow-up visit 4 months

after treatment initiation, during which adjustments were made to the CPAP device if needed, and providers gave patients a motivational talk to advocate the use of the device.

For patients allocated to MAS treatment, a dentist ordered and adapted the MAS (Respire Medical, New York, NY, USA or SomnoDent®, Sydney, NSW, Australia). At treatment initiation, the MAS was set to 60–65% of maximum mandibular protrusion. After 2 to 3 weeks, the MAS was set to the maximum comfortable protrusion, based on feedback from the patient. Patients returned for a follow-up visit 4 months after treatment initiation, during which a new sleep recording was taken while using the MAS, adjustments were made to the MAS if needed, and providers gave patients a motivational talk to advocate its use.

A final follow-up visit occurred at about 12 months after treatment initiation in both treatment groups, at which time all patients completed a questionnaire on treatment compliance. Patients were categorised as compliant if they reported using the CPAP device or MAS more than 4 hours per night, more than 70% of nights [10, 28]. Successful AHI improvement was defined as AHI <10 or AHI <15 when subsequently reducing more than 50% from the AHI at baseline [29].

2.2. Statistical Analysis. The associations between Friedman score and treatment compliance and AHI improvement at the final follow-up visit were evaluated with logistic regression in the overall study sample, the CPAP treatment group, and the MAS treatment group. Friedman score was treated as an ordinal variable in the logistic regression analyses, as the associations did not deviate from linearity ($p > 0.34$ for all likelihood ratio tests). The multivariable logistic regression analyses were performed in two models: model 1 was adjusted for sex, age, BMI, education level, and smoking; model 2 was adjusted for all the variables in model 1 as well as tonsil size and was regarded as the main model. The results are presented as odds ratios (ORs) with 95% confidence intervals (CIs) for the outcome per 1-point increase in Friedman score.

All statistical analyses were performed using SPSS 25 statistical software package (IBM Corp, Armonk, NY, USA) and a two-sided $p < 0.05$ was considered statistically significant.

2.3. Ethical Approval. The RCT, including the current observational study, was approved by the Norwegian Regional Committee for Medical and Health Research Ethics, REC Central (registration #2014/956) and is registered in ClinicalTrials.gov (registration #NCT02953028).

3. Results

Friedman score and baseline characteristics were available for all 104 RCT participants. The final follow-up visit occurred between 10 and 20 months (median 12 month). One patient in the MAS treatment group was lost to follow-up, making compliance data available for 55 and 48 patients in the CPAP and MAS treatment groups, respectively. Prior to follow-up, 24 patients had discontinued treatment and were noncompliant, 17 in the CPAP treatment group and seven in the MAS treatment group. Another two patients in the MAS treatment group declined the sleep recording at final follow-up, despite reporting adequate treatment compliance. Therefore, AHI at final follow-up was available for 38 and 39 patients in the CPAP and MAS treatment groups, respectively (Figure 1).

Baseline patient characteristics were evenly distributed across Friedman scores, except for smoking and tonsil size. Fewer patients with a Friedman score of III were smokers, and more patients with a Friedman score of II had tonsil size grade >1 when compared to those with other Friedman scores (Table 1).

In the logistic regression analyses, Friedman score was not associated with treatment compliance or AHI improvement (Tables 2 and 3). In the main model, the OR for treatment compliance was 0.85 (95% CI 0.59–1.23) per 1-point increase in Friedman score, while the OR for AHI improvement was 1.05 (95% CI 0.62–1.76). No association between Friedman score and treatment compliance/AHI improvement was found when analyses were stratified by treatment group (Tables 4 and 5). The OR for CPAP and MAS treatment compliance was 0.90 (95% CI 0.53–1.54) and 0.98 (95% CI 0.39–2.48), respectively, per 1-point increase in Friedman score. All patients in the CPAP treatment group had an AHI <10 at follow-up; thus no OR was produced for AHI improvement in the CPAP treatment group. OR for MAS treatment was 1.02 (95% CI 0.53–1.98) per 1-point increase in Friedman score.

4. Discussion

In this prospective observational study, we found no association between Friedman score and CPAP or MAS treatment compliance. Good treatment compliance is essential for CPAP and MAS treatment to be effective, but achieving adequate compliance is challenging, especially in CPAP treatment [9, 12, 30]. To limit unnecessary treatment failures and poor compliance, tools are needed to guide clinicians to choose which treatment is best suited for each individual patient [18, 19]. Surgical reduction of airway obstructions, including the tongue base, has been shown to increase CPAP treatment compliance [22]. To our knowledge, no previous studies have investigated the direct association between Friedman score and MAS treatment, but a high Friedman score imply that a larger mandibular protrusion might be necessary for successful MAS treatment [31]. Unfortunately, an increased mandibular protrusion is known to increase side effects, which may decrease MAS treatment compliance [11, 32]. Therefore, an association between Friedman score and CPAP and MAS treatment compliance seems plausible. However, when comparing our findings to previous studies, factors such as the patient's and their bed partner's positive attitude towards OSA treatment, patient's increased use of active coping strategies, larger nasal volume and reduced nasal resistance, increased daytime sleepiness, no smoking, and realistic treatment expectations may be better than Friedman score at predicting treatment compliance [7, 8, 30, 33, 34].

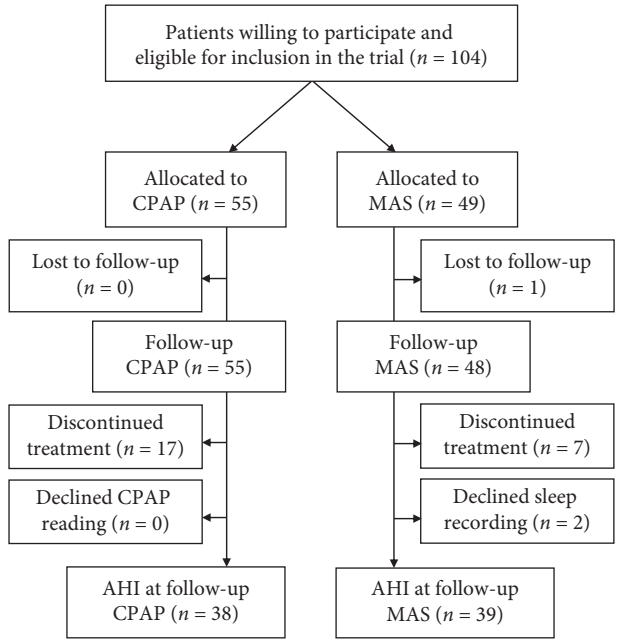

Figure 1: Patient flow chart CPAP: continuous positive airway pressure; MAS: mandibular advancement splint; AHI: apnea-hypopnea index.

Table 1: Patient characteristics at baseline ($n = 104$).

	Friedman score				
Baseline variables	I $n = 22$	II $n = 23$	III $n = 32$	IV $n = 27$	Total
Age at inclusion*	52.6 (10.8)	50.4 (11.6)	52.5 (9.1)	50.7 (8.3)	51.7 (9.8)
BMI at inclusion*	32.0 (6.8)	28.5 (4.2)	33.2 (8.0)	31.9 (6.2)	31.5 (6.7)
AHI at inclusion*	19.1 (6.4)	17.0 (5.6)	18.6 (5.5)	19.2 (5.3)	18.5 (5.6)
Sex					
Female	6 (27.3)	7 (30.4)	14 (43.8)	10 (37.0)	37 (35.6)
Male	16 (72.7)	16 (69.6)	18 (56.3)	17 (63.0)	67 (64.4)
Marital status					
Cohabitating	16 (72.7)	17 (73.9)	25 (78.1)	23 (85.2)	81 (77.9)
Living alone	8 (27.3)	6 (26.1)	7 (21.9)	4 (14.8)	23 (22.1)
Allergic rhinitis					
Yes	5 (22.7)	2 (8.7)	2 (6.3)	8 (29.6)	17 (16.3)
No	17 (77.3)	21 (91.3)	30 (93.8)	19 (70.4)	87 (83.7)
Self-reported health					
Good-excellent	4 (18.2)	8 (34.8)	10 (31.3)	7 (25.9)	29 (27.9)
Poor-fair	18 (81.8)	15 (65.2)	22 (68.8)	20 (74.1)	75 (72.1)
Education level					
College or university	9 (40.9)	13 (56.5)	17 (53.1)	11 (40.7)	50 (48.1)
Other education	13 (59.1)	10 (43.5)	15 (46.9)	16 (59.3)	54 (51.9)
Alcohol consumption					
≤1 time/week	18 (81.8)	18 (78.3)	25 (78.1)	22 (81.5)	83 (79.8)
>1 time/week	4 (18.2)	5 (21.7)	7 (21.9)	5 (18.5)	21 (20.2)
Smoking status					
Nonsmoking	14 (63.6)	18 (78.3)	30 (93.8)	21 (77.8)	83 (79.8)
Smoking	8 (36.4)	5 (21.7)	2 (6.3)	6 (22.2)	21 (20.2)
Tonsil size					
Tonsils absent	2 (9.1)	0 (0)	3 (9.4)	4 (14.8)	9 (8.7)
Grade 1	18 (81.8)	12 (52.2)	20 (62.5)	16 (59.3)	66 (63.5)
Grade 2	1 (4.5)	10 (43.5)	9 (28.1)	7 (25.9)	27 (26.0)
Grade 3	1 (4.5)	1 (4.3)	0 (0)	0 (0)	2 (1.9)
Grade 4	0 (0)	0 (0.0)	0 (0)	0 (0)	0 (0.0)

BMI: body mass index (kg/m2); AHI: apnea-hypopnea index. Tonsil size according to Brodsky grade. * Mean (standard deviation), all other variables: n (%). Allergic rhinitis = any respiratory complaints attributed to allergic rhinitis. Smoking = current occasional or daily use of smoking tobacco.

Table 2: Association between Friedman score and treatment compliance evaluated by logistic regression analysis, $n = 103$.

		Treatment compliance (>4 hours, >70% nights)		
	n (%)	Crude OR (95% CI)	Model 1 OR (95% CI)	Model 2 Or (95% CI)
1-point increase in Friedman score	54 (52.4)	0.83 (0.58–1.19)	0.86 (0.60–1.24)	0.85 (0.59–1.23)

n (%): using CPAP/MAS >4 hours, >70% of nights, OR: odds ratio, CI: confidence interval. Model 1: adjusted for age, sex, body mass index at inclusion, education level, and smoking. Model 2: adjusted for tonsil size + model 1.

Table 3: Association between Friedman score and AHI improvement evaluated by logistic regression analysis, $n = 77$.

		AHI <10 or AHI <15 and reduced >50% at final follow-up		
	n (%)	Crude OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
1-point increase in Friedman score	59 (76.6)	0.99 (0.61–1.60)	1.05 (0.62–1.76)	1.05 (0.62–1.76)

AHI: apnea-hypopnea index. OR: odds ratio, CI: confidence interval. N (%): AHI <10 or 15 and reduced >50%. Model 1: adjusted for age, sex, body mass index at inclusion, education level, and smoking. Model 2: adjusted for tonsil size + model 1.

Table 4: Association between Friedman score and treatment compliance evaluated by logistic regression analysis, stratified by treatment group, CPAP $n = 55$, MAS $n = 48$.

		Treatment compliance (>4 hours, >70% nights)		
	n (%)	Crude OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
1-point increase in Friedman score, CPAP	18 (32.7)	0.89 (0.53–1.47)	0.96 (0.57–1.62)	0.90 (0.53–1.54)
1-point increase in Friedman score, MAS	36 (75.5)	0.68 (0.35–1.30)	1.03 (0.42–2.52)	0.98 (0.39–2.48)

CPAP: continuous positive airway pressure; MAS: mandibular advancement splint; OR: odds ratio, CI: confidence interval. N (%): using CPAP/MAS >4 hours, >70% of nights. Model 1: adjusted for age, sex, body mass index at inclusion, education level, and smoking. Model 2: adjusted for tonsil size + model 1.

Table 5: Association between Friedman score and AHI improvement evaluated by logistic regression analysis, stratified by treatment group, CPAP $n = 38$, MAS $n = 39$.

		AHI <10 or AHI <15 and reduced>50% at final follow-up		
	n (%)	Crude OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)
1-point increase in Friedman score, CPAP	38 (100)	N.A.	N.A.	N.A.
1-point increase in Friedman score, MAS	21 (53.8)	1.01 (0.56–1.81)	1.02 (0.53–1.98)	1.02 (0.53–1.98)

CPAP: continuous positive airway pressure; MAS: mandibular advancement splint; AHI: apnea-hypopnea index. OR: odds ratio, CI: confidence interval n (%): AHI <10 or 15 and reduced >50%. N.A.: all patients achieved AHI <10 at follow-up. Model 1: adjusted for age, sex, body mass index at inclusion, education level, and smoking. Model 2: adjusted for tonsil size + model 1.

Similarly, we found no association between Friedman score and AHI improvement in the CPAP or MAS treatment groups. Previous studies have shown that when combining Friedman score, tonsil size, and BMI into the modified Friedman staging system for patients with OSA [24], lower Friedman score contributes to better results after UPPP in those with nonsevere OSA [3, 23]. Also, surgical reduction of obstructions in the upper airways—such as tonsillectomy in cases of large palatal tonsils [35], or UPPP in cases of large palatal tonsils, excessive tissue in the soft palate, and tongue base [22]—have shown improved AHI and improved CPAP efficacy, particularly in patients with nonsevere OSA. All patients in the CPAP treatment group with AHI measures at final follow-up had successfully reduced their AHI below 10, regardless of their Friedman score at baseline, while patients in the MAS treatment group showed more variation in residual AHI at final follow-up. However, other studies have suggested that younger age, lower BMI, smaller upper airways, less collapsibility in the upper airways, high hyoid bone position, and non-REM dominated and nonpositional OSA may be more important than Friedman score for predicting AHI improvement in MAS treatment [11, 19, 29]. Nevertheless, there are still uncertainties regarding the significance of predictors in successful MAS treatment [19, 36]. Therefore, Friedman score cannot be used to decide whether CPAP or MAS treatment is the most suitable for individual patients with nonsevere OSA.

In our study, we had information on BMI and tonsil size [37]. However, 98.1% of the patients had tonsil size < grade 3, thus limiting our ability to combine Friedman score and tonsil size into the Friedman staging system for patients with OSA in the analyses. Moreover, it is unlikely that the two

patients with large palatal tonsils (1.9%) impacted the association between Friedman score and treatment compliance and AHI improvement in this study, even though tonsil size grades 3 and 4 may contribute to nonsevere OSA [35]. All patients in need of surgical intervention that could impact CPAP or MAS treatment were excluded from the RCT this study was based upon, which may have resulted in the skewed distribution of tonsil size in this study. Patients who were likely to benefit from nasal surgery were excluded from our study for the same reason, although OSA patients in general have a more narrow nose than a healthy population [38].

Treatment compliance was significantly lower, while AHI improvement was significantly better in the CPAP treatment group than the MAS treatment group (chi square test, $p < 0.001$). However, the regression analyses in each treatment group showed the same lack of association between Friedman score and treatment compliance/AHI improvement as in the overall study sample. Thus, possible associations in one treatment group were not concealed by the other treatment group in the analysis of the overall study sample. Moreover, the random allocation to the treatment groups ensured that the choice of treatment was not a confounder in the analyses. AHI <10 and AHI <15 with >50% AHI reduction was chosen as criteria of successful AHI improvement, since AHI <15 is likely to present a low risk of health sequelae compared to severe OSA [15, 39–42] and is regarded an adequate goal in MAS treatment [19, 29]. In total, 27 patients did not have an AHI measure at final follow-up. However, 17 had an AHI measure at 4-month follow-up, which was not included in the main analysis. Using these 4-month follow-up measures to replace the missing AHI measures in these 17 patients at final follow-up did not change the lack of association between Friedman score and AHI improvement (Supplementary Table S1).

We chose not to divide Friedman score II into IIa and IIb as described by Friedman et al. [43]; but this decision is unlikely to impact our results. Due to the inclusion criteria, the relatively small number of patients, and the fact that the patients in the study were recruited following a referral from primary health care, the results from this study may not be generalised to all patients with nonsevere OSA. However, the patients were similar to the Norwegian general population in terms of the demographic variables listed in Table 1, although they had higher BMI and worse self-reported general health at baseline [44, 45]. The patients in our study are probably representative of nonsevere OSA patients without need of nasal or oropharyngeal surgical corrections referred to Norwegian public and private hospitals.

5. Conclusions

Although the Friedman score may predict OSA severity and when combined with tonsil size and BMI can predict success in UPPP, we found no association between Friedman score and CPAP and MAS treatment compliance in patients with nonsevere OSA. Neither did we find any association between Friedman score and AHI improvement. Therefore, factors other than Friedman score alone should be considered when deciding whether a patient with nonsevere OSA should be treated with CPAP or MAS.

Data Availability

The datasets generated and/or analysed during the current study are not publicly available due to planned publications based on data included in the present datasets but are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Supplementary Materials

Table S1: association between Friedman score and AHI improvement evaluated by logistic regression analysis, missing replaced, $n = 94$. (*Supplementary Materials*)

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Paper III

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Research Article

Health-Related Quality of Life and Sleep Quality after 12 Months of Treatment in Nonsevere Obstructive Sleep Apnea: A Randomized Clinical Trial with Continuous Positive Airway Pressure and Mandibular Advancement Splints

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In this randomized controlled trial, patients with nonsevere obstructive sleep apnea (OSA) were treated with continuous positive airway pressure (CPAP) or a twin block mandibular advancement splint (MAS). The primary objective was to compare how CPAP and MAS treatments change the health-related quality of life (HRQoL) and self-reported sleep quality of patients after 12 months of treatment. In total, 104 patients were recruited: 55 were allocated to the CPAP treatment group and 49 to the MAS treatment group. We used the SF36 questionnaire to evaluate HRQoL and the Pittsburgh Sleep Quality Index (PSQI) to evaluate sleep quality. All patients were included in the intention-to-treat analyses. These analyses showed improvements in the SF36 physical component score (from 48.8 ± 7.6 at baseline to 50.5 ± 8.0 at follow-up, $p = 0.03$) in the CPAP treatment group and in the mental component score (from 44.9 ± 12.1 to 49.3 ± 9.2, $p = 0.009$) in the MAS treatment group. The PSQI global score improved in both the CPAP (from 7.7 ± 3.5 to 6.6 ± 2.9, $p = 0.006$) and the MAS (8.0 ± 3.1 to 6.1 ± 2.6, $p < 0.001$) treatment groups. No difference was found between the treatment groups in any of the SF36 scores or PSQI global score at the final follow-up ($p > 0.05$) in any analysis. The improvement in the SF36 vitality domain moderately correlated to the improvement in the PSQI global score in both groups (CPAP: $|r| = 0.47$, $p < 0.001$; MAS: $|r| = 0.36$, $p = 0.01$). In the MAS treatment group, we also found a weak correlation between improvements in the SF36 mental component score and PSQI global score ($|r| = 0.28$, $p = 0.05$). In conclusion, CPAP and MAS treatments lead to similar improvements in the HRQoL and self-reported sleep quality in nonsevere OSA. Improvements in aspects of HRQoL seem to be moderately correlated to the self-reported sleep quality in both CPAP and MAS treatments.

1. Introduction

Obstructive sleep apnea (OSA) is a sleep condition associated with reduced health-related quality of life (HRQoL) [1–3]. This may be related to poor sleep quality due to repeated breathing cessations and fragmented sleep [4, 5] or to the characteristics of a typical OSA population, including high body mass index (BMI) and poor subjective health status [2, 6]. Although not universally defined, the term HRQoL is used for describing an individual's somatic, mental, and social well-being, in contrast to the general QoL, which also considers aspects such as economy and living conditions, in addition to health and social status [7]. One widely used questionnaire showing reduced subjective health status and HRQoL in patients with OSA is the "Medical Outcomes Study Short-Form 36-Element Health Survey" (SF36) [1, 8]. Previous studies have shown conflicting effects of OSA treatment on the HRQoL [9–12].

In the adult Norwegian population, the prevalence of OSA is estimated to 16%, of which the majority have nonsevere OSA [13]. In addition to positional therapy in patients with supine-dependent OSA [14, 15], the most common treatments for nonsevere OSA in patients noneligible for surgical intervention are continuous positive airway pressure (CPAP) devices or mandibular advancement splints (MAS) [16, 17]. CPAP treatment effectively reduces the number of pharyngeal soft tissue collapses, which cause the breathing cessations, by creating a pneumatic splint in the upper airways, regardless of OSA severity [18]. By comparison, the efficacy of the MAS treatment is harder to predict without using less accessible procedures such as remotely controlled mandibular protrusion during sleep [19] or drug-induced sleep endoscopy [20, 21], especially in moderate and severe OSA [22, 23]. However, better compliance with MAS treatment makes the overall effectiveness of the two treatments comparable [24] and they are probably equally effective at preventing negative health outcomes associated with OSA [25–27]. Whether the prevention of negative health outcomes with CPAP and MAS treatments is reflected in the HRQoL is uncertain. A meta-analysis by Kuhn et al. [28] presented evidence for the positive effect of CPAP treatment on the HRQoL of patients with OSA when measured using the SF36 questionnaire, while the results regarding MAS treatment were less certain. Thus, more trials investigating the effects of MAS on the HRQoL are needed, preferably in comparison with CPAP treatment [28].

Although commonly used in OSA research, the SF36 questionnaire may not directly evaluate sleep or sleep quality. Questionnaires such as the Pittsburgh Sleep Quality Index (PSQI) evaluate the subjective sleep quality but not the HRQoL [29]. Kang et al. [3] showed that the HRQoL is more associated with sleep quality than with the objectively measured treatment effects on OSA and that sleep quality is also likely to impact the HRQoL. Whether or not the SF36 is sensitive to changes in self-reported sleep quality is not clear, but the SF36 seems to be associated with daytime sleepiness [30], indicating that it may also reflect changes in sleep quality. The aim of this randomized controlled trial was to compare CPAP and MAS after 12 months of treatment in patients with nonsevere OSA, in terms of their HRQoL and self-reported sleep quality, and to investigate the correlation between HRQoL and sleep quality.

2. Materials and Methods

2.1. Trial Design. This was a two-centered, parallel-arm, randomized, controlled clinical trial, with a 50 : 50 allocation ratio. Blinding of the patients and clinical personnel was not feasible due to the nature of CPAP and MAS treatments.

2.2. Participants. Inclusion criteria for participation in the trial were age 20–75 years, apnea-hypopnea-index (AHI) between 10.0 and 29.9, and the ability to protrude the mandible at least 5 mm. Exclusion criteria were severe OSA (AHI ≥30), nasal obstruction, pregnancy, drug abuse, daily use of sedative medication, previous treatment with CPAP or MAS, and preexisting severe psychiatric disorders or somatic health issues interfering with the use of CPAP or MAS, including subjective signs of temporomandibular dysfunction, exaggerated gag reflex, and <10 teeth in the mandible with good periodontal support.

2.3. Study Setting and Randomization. Patients participating in the trial were referred from primary healthcare to the ear-nose-throat-departments at the University Hospital of Northern Norway (UNN) in Tromsø, St. Olavs University Hospital (St. Olavs), or Aleris Hospital and Medical Center in Trondheim, Norway. The Aleris Hospital and Medical Center transferred eligible patients to St. Olavs for random allocation and interventions. Two researchers (LMB and TKSA) calibrated all healthcare personnel involved in the trial, according to the study protocol. For random allocation, the patients drew lots from a masked envelope made by one of the researchers (TKSA). Block randomization with 30 lots per block at each study site was used to prevent skewed distribution between treatment groups across seasons and study sites.

2.4. Interventions. All patients were screened for OSA overnight at home or at a hotel, using an ambulatory, type 3, polygraphic sleep recording device (Embletta® or Nox T3™, ResMed Norway AS). Sleep technicians manually analyzed the sleep recordings according to the American Academy of Sleep Medicine practice guidelines for diagnostic testing for OSA [31]. Apnea events were defined as ≥90% reduction in respiratory flow lasting ≥10 s. Hypopnea events were defined as ≥50% reduction in respiratory flow lasting ≥10 s, with a simultaneous ≥3% reduction in peripheral blood oxygen saturation from baseline. All patients were medically examined by an otorhinolaryngologist at UNN or St. Olavs Hospitals and were invited to participate in the trial if they met the inclusion criteria. After giving an informed written consent to participate, the patients were randomized to either the CPAP or MAS treatment group. The study protocol for the two treatment groups complied with the recommendations from the Standards of Practice

Committee and the Board of Directors of the American Academy of Sleep Medicine [32, 33].

For patients allocated to CPAP treatment, an auto-CPAP device (ResMed®, San Diego, CA, USA) was adapted and calibrated by a sleep technician. A nose mask or face mask was used, based on the needs and preferences of the individual patient. Patients returned for a follow-up visit 4 months after treatment onset. A sleep technician downloaded efficacy data from the CPAP device, made necessary adjustments to the CPAP device, and gave a motivational talk to advocate further use of the CPAP device.

For patients allocated to MAS treatment, an intraoral examination followed by a bite registration using the George Gauge™ (Scheu-Dental GmbH, Iserlohn, Germany) and an impression of the dentition was made by a dentist. The impressions and bite registration were sent to a dental technician for the production of the MAS (Respire Medical, New York, NY, USA, or SomnoDent®, Sydney, NSW, Australia). All MAS had the same twin block design, although produced by two different manufacturers. The MAS was set to 60–65% of maximum mandibular protrusion at treatment onset and titrated to maximal comfortable mandibular protrusion after two to three weeks by the dentist. Patients in the MAS treatment group also returned for a follow-up visit 4 months after treatment onset. A sleep technician performed and analyzed a new overnight polygraphic sleep recording and gave a motivational talk to advocate further use of the MAS. The MAS was used during the overnight polygraphic sleep recording at follow-up. Necessary adjustments to the MAS were subsequently made by a dentist.

About 12 months after the treatment was initiated, all patients returned for a final follow-up visit, during which efficacy data were downloaded from the CPAP device for the CPAP treatment group and a new overnight polygraphic sleep recording was performed for the MAS treatment group while using the MAS.

2.5. Outcomes. The HRQoL was evaluated at baseline and at both follow-up visits using the SF36 questionnaire (version 2). This questionnaire is a widely used, multipurpose, generic, and validated questionnaire, consisting of 36 questions that measure the relative burden of disease and health conditions [28, 34]. The SF36 yields eight HRQoL domains scored on a 0–100 scale, where zero represents the worst and 100 represents the best HRQoL. The 0–100 scales are standardized into norm-based scores to allow direct comparison among different domains and in relation to the general population. A norm-based score more or less than 50 represents a better or worse HRQoL, respectively, than the average general population. The eight norm-based domains were united into one physical and one mental aggregated health scale [34]. We present the norm-based scores, while the 0–100 scales are presented in Supplementary Tables S1–S3.

The self-reported sleep quality was measured using the PSQI questionnaire at baseline and at both follow-ups. The PSQI is a validated questionnaire consisting of 19 questions, assessing seven aspects of sleep quality: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medicine, and daytime dysfunction. These aspects were transformed into a sum score ranging from zero to 21 points, where good sleep quality is defined as ≤5 points [29].

To make results in the SF36 and PSQI comparable, the reliable change index (RCI) was used to calculate a standardized change in the SF36 domains and PSQI global score from baseline to final follow-up in each individual patient, as described by Jacobson and Truax [35]. The RCI was calculated using the test-retest figures by Stavem et al. [36] and Buysse et al. [29] and the pretreatment standard deviation in each SF36 domain and PSQI global score. A |RCI-value| >1.96 indicated a statistically significant change from baseline on a 5% significance level, i.e., a change not likely to occur due to test-retest variations. Statistical significant changes in the RCI corresponded to clinically significant changes, with a bigger |RCI value| also indicating a bigger clinical change [35]. The RCI enabled correlation analysis between changes in the SF36 domain scores and those in the PSQI global score after OSA treatment.

Demographic characteristics of the patients were collected through a questionnaire at the time of the medical examination prior to treatment. Compliance with treatment was self-reported at the final follow-up and defined as using the CPAP device or MAS for more than 4 hours per night, more than 70% of the nights [37, 38].

2.6. Sample Size. Based on an expected 10% difference between the treatment groups in the SF36 domain scores at final follow-up [39] and a common standard deviation within groups at 20%, a sample size of 69 patients in each treatment group at the final follow-up was needed to detect between-group differences at a 5% significance level and reaching 80% power in a two-tailed *t*-test. Similarly, to detect a difference in the PSQI global score between the treatment groups, 45 patients were needed in each treatment group, based on an expected difference of 15% between groups, and a 25% standard deviation within groups at the final follow-up.

2.7. Statistical Analysis. Both intention-to-treat (all included patients) and per-protocol (patients compliant to treatment at final follow-up) analyses are presented. Differences between the two treatment groups regarding average SF36 scores and the PSQI global score at final follow-up were analyzed using multivariable linear regression and adjusted for age, BMI, sex, smoking, AHI, and the SF36 domain/PSQI global score at baseline. A paired sample *t*-test was used to analyze changes from baseline at the final follow-up within each treatment group. Mann–Whitney *U*-test and paired sample Wilcoxon test were used to compare changes in the AHI between and within treatment groups. The correlation between significantly changed SF36 domain scores and the PSQI global score was examined using Pearson correlation analysis on RCI values. Larger RCI values represented larger changes from baseline at the final follow-up in the respective

scales. Differences in the number of patients with improved scores between treatment groups were analyzed using Pearson chi-square and Fisher's exact tests. Any missing entries in the SF36 questionnaire were replaced in accordance with Ware et al. [34].

Missing entries in the PSQI questionnaire were replaced through multiple imputations, as recommended by CONSORT 2010 [40, 41]. Data missing at the final follow-up in patients who discontinued treatment were replaced by data from baseline or the 4-month follow-up for the intention-to-treat analysis.

All statistical analyses were performed using SPSS 26 statistical software package (IBM Corp, Armonk, NY, USA) and a two-sided $p < 0.05$ was considered statistically significant.

2.8. Ethical Approval. This randomized controlled trial was approved by the Norwegian Regional Committee for Medical and Health Research Ethics, REC Central (registration #2014/956), and is registered in ClinicalTrials.gov (registration #NCT02953028).

3. Results

3.1. Recruitment and Participant Flow. The patients were recruited between October 2014 and February 2018. Informed written consent to participate was obtained from 104 patients, of which 55 were allocated to the CPAP treatment group and 49 to the MAS treatment group. The final follow-up visit occurred between 10 and 20 months (median 13 months) after treatment onset and completed by October 2019. Figure 1 illustrates the distribution and flow of patients in the study.

At the final follow-up, 18 patients (32.7%) in the CPAP treatment group and seven (14.3%) in the MAS treatment group had quit treatment, all reporting not being compliant to treatment. One patient (2.0%) in the MAS treatment group withdrew from the trial before the final follow-up for no specific reason, being compliant to treatment up to that point. There were more smokers (35.1%) among patients discontinuing treatment before the final follow-up than among those continuing treatment (11.9%) ($p = 0.005$). Patients discontinuing treatment did not differ from the remaining study population in any other way at baseline. Among patients discontinuing treatment, no improvement was found in any SF36 domain at a group level, but the PSQI global score was improved from 7.8 to 6.6 points ($p = 0.03$).

3.2. Number of Participants Analyzed. All recruited patients were included in the intention-to-treat analysis of SF36 and PSQI scores. In the per-protocol analysis, 18 patients (32.7%) in the CPAP treatment group and 36 (73.5%) in the MAS treatment group were regarded as compliant and included in the analysis. When only including cases with complete data, i.e., excluding patients with imputations in the scores of any questionnaire at the final follow-up, 34 and 39 patients were included in the CPAP and MAS treatment groups, respectively (Supplementary Table S4). The baseline characteristics of all recruited patients are presented in Table 1 and were similar between treatment groups.

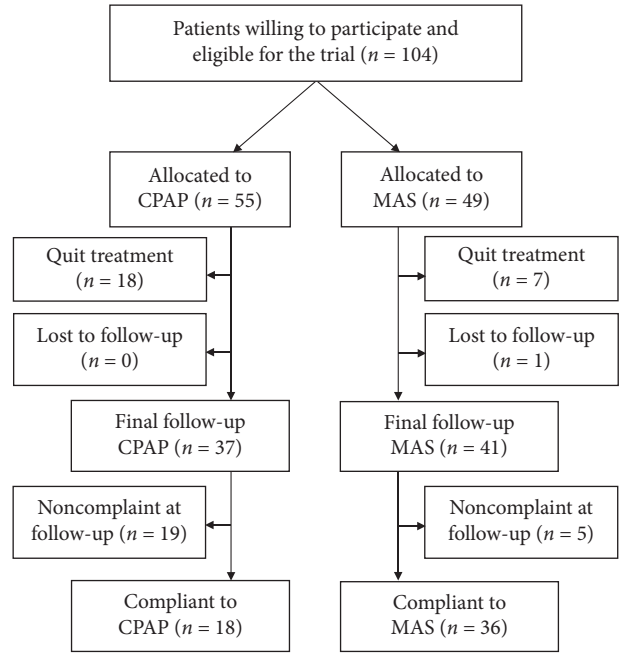

Figure 1: Patient flowchart.

3.3. SF36 Domains. At the final follow-up, there were no statistically significant differences between the CPAP and MAS treatment groups in any of the SF36 domains or component scores. This was the case for both the intention-to-treat (Table 2) and per-protocol analyses (Table 3). In the intention-to-treat analysis, the SF36 role-physical ($p = 0.04$) and vitality ($p = 0.006$) domains and the physical component score ($p = 0.03$) were improved in the CPAP treatment group, while the SF36 vitality ($p < 0.001$) and social functioning ($p = 0.04$) domains and the mental component score ($p = 0.009$) were improved in the MAS treatment group. In the per-protocol analysis, the SF36 vitality ($p = 0.03$) and social functioning domains ($p = 0.02$) and the mental component score ($p = 0.003$) were improved in the CPAP treatment group, while the SF36 vitality ($p < 0.001$), social functioning ($p = 0.02$), and mental health ($p = 0.02$) domains and the mental component score ($p = 0.003$) were improved in the MAS treatment group.

3.4. PSQI Global Score and AHI. At the final follow-up, there were no statistically significant differences between the CPAP and MAS treatment groups in the PSQI global score, which was improved by both CPAP ($p = 0.006$) and MAS ($p < 0.001$) treatments based on both the intention-to-treat (Table 2) and per-protocol analysis (CPAP: $p = 0.03$; MAS: $p < 0.001$; Table 3).

In the per-protocol analysis, the median AHI at the final follow-up was significantly better ($p < 0.001$) in the CPAP (0.9, 0.7–1.4) than in the MAS treatment group (10.1, 6.1–16.5). Both treatment groups showed significant

Table 1: Patient characteristics at baseline, n (%).

Baseline variables	Total ($n = 104$)	CPAP ($n = 55$)	MAS ($n = 49$)
Age at inclusion[a]	51.7 (9.8)	53.3 (10.2)	49.6 (9.0)
BMI at inclusion[a]	31.5 (6.7)	30.8 (6.2)	32.4 (7.2)
AHI at inclusion[b]	17.6 (13.2–23.5)	18.1 (15.3–24.6)	16.3 (12.4–23.0)
Sex			
Female	37 (35.6)	17 (30.9)	20 (40.8)
Male	67 (64.4)	38 (69.1)	29 (59.2)
Marital status			
Cohabitating	81 (77.9)	44 (80.0)	37 (75.5)
Living alone	23 (22.1)	11 (20.0)	12 (24.5)
Allergic rhinitis			
Yes	17 (16.3)	9 (16.4)	8 (16.3)
No	87 (83.7)	46 (83.6)	51 (83.7)
Self-reported health			
Good-excellent	29 (27.9)	16 (29.1)	13 (26.5)
Poor-fair	75 (72.1)	39 (70.9)	36 (73.5)
Education level			
College or university	50 (48.1)	23 (41.8)	27 (55.1)
Other education	54 (51.9)	32 (58.2)	22 (44.9)
Alcohol consumption			
≤1 time/week	83 (79.8)	43 (78.2)	40 (81.6)
>1 time/week	21 (20.2)	12 (21.8)	9 (18.4)
Smoking status			
Nonsmoking	83 (79.8)	41 (74.5)	42 (85.7)
Smoking	21 (20.2)	14 (25.5)	7 (14.3)

CPAP: continuous positive airway pressure; MAS: mandibular advancement splint; BMI: body mass index (kg/m^2); AHI: apnea-hypopnea index. [a]Mean (standard deviation); [b]median (25–75 percentiles). Allergic rhinitis: any respiratory complaints attributed to allergic rhinitis; smoking: current occasional or daily use of smoking tobacco.

Table 2: SF36 domains (norm-based scales) and PSQI global score at baseline and final follow-up (12 months), based on intention-to-treat analysis.

SF36 domains	Baseline		Follow-up		Adj. difference (95% CI)[§]	p[§]
	CPAP ($n = 55$)	MAS ($n = 49$)	CPAP ($n = 55$)	MAS ($n = 49$)		
Physical functioning	48.2 (8.9)	47.5 (8.2)	50.0 (8.4)	48.2 (9.6)	−1.6 (−4.4–1.1)	0.23
Role-physical	49.6 (6.8)	48.6 (8.3)	51.4* (6.3)	49.7 (8.2)	−1.9 (−4.4–0.5)	0.13
Bodily pain	49.2 (11.4)	46.3 (10.1)	50.0 (10.7)	46.8 (11.4)	−1.0 (−4.5–2.5)	0.59
General health	45.4 (9.8)	45.8 (10.6)	48.2 (9.9)	46.9 (10.7)	−1.1 (−4.1–2.0)	0.48
Vitality	42.8 (11.4)	39.8 (10.1)	47.4* (10.8)	47.7* (10.5)	2.0 (−1.9–5.9)	0.32
Social functioning	44.5 (12.4)	42.2 (12.2)	47.5 (12.4)	46.5* (10.2)	0.3 (−4.1–4.6)	0.91
Role-emotional	48.4 (8.1)	48.4 (8.1)	49.5 (8.6)	49.6 (7.4)	0.2 (−2.7–3.0)	0.91
Mental health	47.7 (10.0)	47.8 (11.4)	48.9 (11.7)	50.4 (8.5)	1.9 (−1.8–5.7)	0.30
Physical component score	48.8 (7.6)	47.0 (9.4)	50.5* (8.0)	47.5 (10.4)	−1.8 (−4.1–0.5)	0.13
Mental component score	45.6 (10.3)	44.9 (12.1)	47.8 (12.3)	49.3* (9.2)	2.5 (−1.3–6.3)	0.20
PSQI global score	7.7 (3.5)	8.0 (3.1)	6.6* (2.9)	6.0* (2.6)	−0.8 (−1.8–0.1)	0.09

CPAP: continuous positive airway pressure; MAS: mandibular advancement splint; PSQI: Pittsburgh Sleep Quality Index; SF36: Medical Outcomes Study Short-Form 36-Element Health Survey; SF36 domains and PSQI global score: mean (standard deviation). *Statistically significant change from baseline to follow-up within treatment group, paired t-test ($p < 0.05$). [§]Difference between MAS and CPAP treatment groups at follow-up, based on linear regression analysis adjusted for baseline variables (age, BMI, sex, smoking, baseline AHI, and the baseline SF36 domain/PSQI global score), reference group: CPAP.

improvements in the AHI from baseline at the final follow-up ($p < 0.001$).

3.5. Correlations between SF36 Domain Scores and PSQI Global Score. The improvement in the SF36 vitality domain score was moderately correlated to that in the PSQI global score in both the CPAP ($|r| = 0.47$, $p < 0.001$) and MAS treatment groups ($|r| = 0.36$, $p = 0.01$). In the latter, there was a weak correlation between improvements in the SF36 mental component score and PSQI global score ($|r| = 0.28$, $p = 0.05$). In the per-protocol analysis, the improvement in the SF36 vitality domain was strongly correlated with that in the PSQI global score in the CPAP treatment group ($|r| = 0.51$, $p = 0.03$). Other SF36 domains or component scores with significant improvement after treatment were not correlated to the improvement in the PSQI global

Table 3: SF36 domains (norm-based scales) and PSQI global score at baseline and final follow-up (12 months), based on per-protocol analysis (compliant patients only).

SF36 domains	Baseline		Follow-up		Adj. difference (95% CI)[§]	$p^{§}$
	CPAP ($n = 18$)	MAS ($n = 36$)	CPAP ($n = 18$)	MAS ($n = 36$)		
Physical functioning	47.9 (9.0)	48.3 (7.7)	49.8 (8.3)	49.7 (9.1)	−0.8 (−4.5–2.8)	0.64
Role-physical	49.4 (6.3)	48.4 (9.0)	50.4 (7.2)	50.2 (8.3)	−0.3 (−4.1–3.6)	0.89
Bodily pain	48.4 (12.4)	46.7 (10.3)	47.7 (11.7)	46.9 (11.5)	0.1 (−5.8–6.0)	0.97
General health	45.9 (10.2)	46.9 (10.5)	49.1 (10.5)	49.2 (10.1)	−0.4 (−4.9–4.2)	0.88
Vitality	43.2 (13.7)	39.8 (10.1)	51.0* (9.4)	50.2* (8.4)	0.0 (−5.3–5.2)	0.99
Social functioning	46.6 (12.7)	41.9 (13.0)	51.8* (8.7)	47.7* (9.3)	−1.7 (−6.9–3.5)	0.51
Role-emotional	49.5 (7.3)	48.0 (8.8)	51.3 (6.4)	50.0 (7.4)	0.3 (−3.6–4.1)	0.89
Mental health	49.2 (8.8)	47.2 (12.4)	53.3 (8.1)	51.5* (8.2)	−0.8 (−5.1–3.5)	0.71
Physical component score	47.7 (8.3)	47.9 (9.1)	48.2 (8.7)	48.5 (10.0)	0.0 (−3.6–3.7)	0.99
Mental component score	47.6 (9.6)	44.1 (12.5)	53.2* (4.9)	50.5* (8.0)	−0.2 (−3.9–3.4)	0.91
PSQI global score	7.1 (3.4)	7.7 (3.3)	5.7* (2.3)	5.4* (2.5)	−0.6 (−1.7–0.5)	0.25

CPAP: continuous positive airway pressure; MAS: mandibular advancement splint; PSQI: Pittsburgh Sleep Quality Index SF36: Medical Outcomes Study Short-Form 36-Element Health Survey; SF36 domains and PSQI global score: mean (standard deviation). *Statistically significant change from baseline to follow-up within treatment group, paired t-test ($p < 0.05$). [§]Difference between MAS and CPAP treatment groups at follow-up, based on linear regression analysis adjusted for baseline variables (age, BMI, sex, smoking, baseline AHI, and the baseline SF36 domain/PSQI global score), reference group: CPAP.

Table 4: Number of patients with improved SF36 scores according to RCI (>1.96) and PSQI global score according to RCI (<−1.96), based on intention-to-treat analysis.

	Significantly improved HRQoL or sleep quality		
	CPAP ($n = 55$)	MAS ($n = 49$)	p
Physical functioning	16.4% (9/55)	12.2% (6/49)	0.55
Role-physical	12.7% (7/55)	12.2% (6/49)	0.94
Bodily pain	7.3% (4/55)	10.2% (5/49)	0.73[F]
General health	21.8% (12/55)	28.6% (14/49)	0.43
Vitality	36.4%* (20/55)	44.9%* (22/49)	0.38
Social functioning	12.7% (7/55)	18.4% (9/49)	0.43
Role-emotional	9.1% (5/55)	12.2% (6/49)	0.60
Mental health	14.5% (8/55)	22.4% (11/49)	0.30
Physical component	10.9% (6/55)	8.2% (4/49)	0.75[F]
Mental component	18.2% (10/55)	20.4%* (10/49)	0.77
PSQI global score	18.2% (10/55)	32.7% (16/49)	0.09

HRQoL: health-related quality of life; RCI: reliable change index; PSQI: Pittsburgh Sleep Quality Index (global score); SF36: Short Form 36 (8 domains + 2 aggregated scales); CPAP: continuous positive airway pressure; MAS: mandibular advancement splint; P: Pearson chi-square test; F: Fisher's exact test. *Significant correlation to PSQI global score.

Table 5: Number of patients with improved SF36 scores according to RCI (>1.96) and PSQI global score according to RCI (<−1.96), compliant patients only.

	Significantly improved HRQoL or sleep quality		
	CPAP ($n = 18$)	MAS ($n = 36$)	p
Physical functioning	11.1% (2/18)	11.1% (4/36)	1.00[F]
Role-physical	5.6% (1/18)	13.9% (5/36)	0.65[F]
Bodily pain	5.6% (1/18)	11.1% (4/36)	0.66[F]
General health	27.8% (5/18)	36.1% (13/36)	0.54
Vitality	38.9%* (7/18)	50.0% (18/36)	0.44
Social functioning	5.6% (1/18)	19.4% (7/36)	0.26[F]
Role-emotional	11.1% (2/18)	13.9% (5/36)	1.00[F]
Mental health	16.7% (3/18)	25.0% (9/36)	0.73[F]
Physical component	5.6% (1/18)	11.1% (4/36)	0.66
Mental component	22.2% (4/18)	22.2% (8/36)	1.00[F]
PSQI global score	16.7% (3/18)	33.3% (12/36)	0.20

HRQoL: health-related quality of life; RCI: reliable change index; PSQI: Pittsburgh Sleep Quality Index (global score); SF36: Short Form 36 (8 domains + 2 aggregated scales); CPAP: continuous positive airway pressure; MAS: mandibular advancement splint; P: Pearson chi-square test; F: Fisher's exact test. *Significant correlation to PSQI global score.

score. The number of patients in each treatment group showing improvement according to the RCI in SF36 domains and the PSQI global score is presented in Table 4 (intention-to-treat) and Table 5 (per-protocol).

4. Discussion

In this randomized controlled trial, we compared changes in the HRQoL and self-reported sleep quality after 12 months of CPAP or MAS treatment in patients with nonsevere OSA. All patients in this trial were recruited after a referral from primary healthcare services. The randomization procedure was successful and created comparable groups at baseline. Baseline variables were similar in the intention-to-treat and per-protocol analyses. It is likely that the included patients are representative of patients with nonsevere OSA, who do not need nasal or pharyngeal surgical corrections, and are referred to Norwegian public and private hospitals. The patients had higher BMI and worse self-reported general health than the Norwegian general population at baseline [42, 43], but were comparable to OSA populations in other recent Norwegian studies [2, 44]. The mean values for all SF36 domains at baseline were lower than but within one standard deviation from the mean values of the Norwegian general population [45]. The PSQI global score was above the cutoff for good sleep quality in both treatment groups, which is defined as a global score of 5 points or below according to the developers of the PSQI [29].

4.1. SF36 and PSQI. Both CPAP and MAS treatments improved the SF36 vitality domain, which is in line with the findings of the meta-analysis by Kuhn et al. [28]. In the intention-to-treat analysis, CPAP treatment also improved the SF36 role-physical domain and physical

component scores, while MAS treatment improved the SF36 social functioning domain and mental health component scores. In the per-protocol analysis, both CPAP and MAS treatments improved the SF36 domains of vitality and social functioning and the mental component score, while only MAS treatment improved the SF36 mental health domain score. The PSQI global score was also significantly improved after 12 months of treatment in both treatment groups and in both the intention-to-treat and per-protocol analyses.

Although improvements in several SF36 domain scores were found, the SF36 is a generic questionnaire and thus not specific to OSA [1]. Hence, SF36 does not directly measure sleep quality [34] and may not be representative of patients with sleep disorders, such as OSA. Previous studies have shown lacking association between OSA severity (measured in AHI) and the impairment in the HRQoL [3, 6]. Besides, it is not clear whether it is unspecific symptoms overlapping with OSA symptoms or true OSA symptoms that lower the SF36 scores among OSA patients [2]. Communicating the OSA diagnosis to patients may itself improve the HRQoL, with no other treatment [46]. This suggests that the change in SF36 domain scores after treatment of OSA may be attributed to the patients being diagnosed and cared for or to placebo effects associated with OSA treatment, and not solely to the effect of CPAP or MAS treatment.

Nevertheless, patients compliant to CPAP and MAS treatments showed greater improvements in their HRQoL than those noncompliant to treatment. Furthermore, the SF36 vitality domain, which showed the biggest improvement in both treatments, likely reflects the patient's sleep quality, considering that the questions composing this domain are closely associated with daytime sleepiness: (1) "Did you feel full of life?" (2) "Did you have a lot of energy?" (3) "Did you feel worn out?" and (4) "Did you feel tired?". The correlation between the SF36 vitality domain score and PSQI global score also indicates that this SF36 domain is the one most likely to respond to changes in sleep quality, but this association does not imply a causal link between HRQoL and sleep quality.

Since the improvement in the physical component score in the CPAP treatment group was found in the intention-to-treat but not in the per-protocol analysis, this score is likely to have improved in some patients noncompliant to treatment. If so, the physical component score improved in noncompliant patients for reasons other than those in patients effectively treated with CPAP or MAS. For example, it is possible that some noncompliant patients started doing physical exercises or reduced their body weight after getting the OSA diagnosis, to compensate for not using CPAP or MAS [47, 48]. If doing so, it is likely that they improved the subjective sleep quality as well [49].

4.2. Compliance and AHI. Difficulties in maintaining compliance with treatment is a known challenge in the treatment of nonsevere OSA, especially in CPAP treatment [38, 50]; so, lower compliance in the CPAP than in the MAS treatment group could be expected [23, 26]. However, the compliance with CPAP in this study was lower than expected [51–54]. Discomfort related to the CPAP mask, choking sensation, and xerostomia were the most reported reasons for noncompliance. Nevertheless, investigating the reasons for the particularly poor compliance with CPAP treatment in this study was beyond the scope of this article. Based on the findings in the present trial, differences in compliance between treatment groups should be considered when planning and evaluating the success of CPAP and MAS treatments [26, 55].

Despite an unambiguous better AHI improvement in the CPAP treatment group, it is worth noticing that MAS treatment showed benefits similar to CPAP treatment regarding the HRQoL and self-reported sleep quality, even when comparing compliant patients only. Furthermore, RCI analyses showed that the number of patients experiencing an improvement in individual SF36 domain scores and PSQI global score was similar between the treatment groups. Changes according to the RCI are not likely to occur due to test-retest variations in repeated completion of the respective questionnaires. Therefore, a statistically significant change in the RCI also represents a clinically significant change on a patient level [35]. This suggests that MAS treatment provide subjective benefits equal to that from CPAP in the treatment of nonsevere OSA and may be considered first-line treatment in patients who are more motivated for MAS treatment than CPAP treatment.

4.3. Risk and Handling of Bias. In the current study, the results in the per-protocol analysis only included patients who used the CPAP device or MAS for more than 4 hours, 70% of the nights. Therefore, results from the per-protocol analysis should be representative of the efficacy of CPAP and MAS treatments in improving the HRQoL and sleep quality. However, in addition to having a small number of included patients, the per-protocol analysis is prone to bias due to exclusion of patients discontinuing or being semicompliant to treatment. Dropout analyses showed that patients discontinuing treatment had rather similar baseline characteristics to patients compliant to treatment. Hence, the treatment groups should be comparable in the per-protocol analysis. Although similarities between discontinuing and compliant patients indicate a low risk of dropout bias, it is possible that some patient characteristics other than those reported in this study were different between these patients.

In contrast to the per-protocol analysis, the intention-to-treat analysis maintains the strengths of the randomization, thus being less prone to bias. The disadvantage of the intention-to-treat analysis is the inclusion of noncompliant patients, some of whom were not using their assigned treatment device at all. Therefore, this analysis might underestimate the true effects of CPAP and MAS treatments on the HRQoL and sleep quality, especially in the CPAP treatment group where only 32.7% of the patients were regarded compliant to treatment. The discontinuing patients in this study had no significant change in any of the SF36 domains, but the noncompliant patients had a barely significant improvement in the PSQI global score. Although

unlikely, it is unclear whether this improvement is clinically significant on a group level.

The CPAP and MAS treatment groups were fairly similar at the final follow-up when comparing their HRQoL and sleep quality, but the two groups seemed to be more similar in the per-protocol than the intention-to-treat analysis. This could be because much fewer patients were included in the per-protocol analysis than the calculated number needed to show differences between treatment groups. To reduce the influence of potential confounders and bias, linear regression models were used to adjust the differences between the two treatment groups for baseline variables. Only minor changes were found regarding the differences between CPAP and MAS treatments in both SF36 scores and PSQI global score. Adjusting for baseline variables did not alter the lack of significant differences between the treatment groups.

Since this was an unblinded trial, risk of bias from the clinical handling of the patients was unavoidable. To avoid biasing common variables between the treatment groups, all clinical personnel were instructed to approach the patients in a standardized fashion. However, some of the possible biases from the lack of blinding are inherently entangled with the provided treatment. Thus, differences in the handling of patients related to the characteristics of CPAP and MAS treatments are inevitable in both clinical research and clinical practice.

5. Limitations

A major limitation of this study is the risk of being underpowered. Power analysis prior to the patient recruitment suggested that 69 patients in each treatment group were needed to show differences between CPAP and MAS treatments in the SF36 physical and mental component scores. The number of patients in the trial was the maximum that could be recruited within the time span of this trial, but may not have been sufficient to show differences between the two treatments, especially in the per-protocol analysis. Since 66% of the patients in the CPAP treatment group were considered noncompliant, approximately three times more patients should have been recruited to the study to find any differences between treatment groups in the per-protocol analysis according to the power calculation for the SF36 domain scores. The low number of patients in the per-protocol analysis suggested that a nonparametric test was more suitable to test the statistical differences between treatment groups. However, no differences were found when using the Mann–Whitney *U*-test instead of the regression analysis.

It is plausible that even with 69 patients in each treatment group, the null hypothesis would still not be falsified in this trial due to the similar results found between treatment groups. Moreover, the number of patients in the trial was larger than the calculated number needed to show differences in the PSQI global score between treatment groups; however, no significant differences were found between treatment groups in this score either.

Using self-reported compliance data is another limitation of the study. Objective compliance data were not available for the MAS treatment group, and thus, self-reported data were used for both treatment groups to enable the comparison of compliance data. In contrast to the compliance data downloaded from the CPAP device, four patients misreported themselves as compliant, all of whom had objective CPAP usage very close to 4 hours in 70% of the nights and slightly overestimated their compliance. Previous studies have shown that patients using MAS only slightly overestimate their compliance compared to the objectively measured compliance after 12 months of treatment [56]. Thus, the self-reported compliance is likely comparable between the CPAP and MAS treatment groups at the final follow-up.

6. Conclusions

In summary, both CPAP and MAS treatments seemed to improve vitality and mental aspects of the HRQoL, as well as the self-reported sleep quality in patients with nonsevere OSA. In this study, HRQoL and self-reported sleep quality were similar after 12 months of CPAP and MAS treatments. Between improvements in aspects of HRQoL and self-reported sleep quality, a moderate to strong correlation was found after CPAP treatment, while a weak to moderate correlation was found after MAS treatment.

Data Availability

The datasets generated and/or analyzed during the current study are not publicly available due to planned publications based on data included in the present datasets, but are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Supplementary Materials

Supplementary tables presenting SF36 domain scores at baseline and follow-up according to the 0–100 scales. Intention-to-treat analyses (Table S1), per-protocol analyses (Table S2), and complete case analyses (Table S3) are

provided. Table S4: present complete case analyses of the norm-based SF36 domain scores and PSQI global score at baseline and follow-up. (*Supplementary Materials*)

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Corrigendum

Corrigendum to "Health-Related Quality of Life and Sleep Quality after 12 Months of Treatment in Nonsevere Obstructive Sleep Apnea: A Randomized Clinical Trial with Continuous Positive Airway Pressure and Mandibular Advancement Splints"

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In the article titled "Health-Related Quality of Life and Sleep Quality after 12 Months of Treatment in Nonsevere Obstructive Sleep Apnea: A Randomized Clinical Trial with Continuous Positive Airway Pressure and Mandibular Advancement Splints" [1], the authors identified an error in Section 2.4 as follows:

"Hypopnea events were defined as ≥50% reduction in respiratory flow lasting ≥10 s, with a simultaneous ≥3% reduction in peripheral blood oxygen saturation from baseline" should be corrected to "Hypopnea events were defined as ≥30% reduction in respiratory flow lasting ≥10 s, with a simultaneous ≥3% reduction in peripheral blood oxygen saturation from baseline."

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Appendices

Appendix 1

Invitation letter

INVITASJONSBREV TIL PASIENTER HENVIST TIL ØRE-NESE-HALS-AVD. VED ST.OLAVS HOSPITAL

En studie om søvnapnébehandling, livskvalitet og etterlevelse

September 2014/2016

Bakgrunn og hensikt med studien

Du er henvist for utredning og eventuell behandling ved Øre-Nese-Hals-avdelinga (ØNH) ved Universitetssykehuset Nord-Norge i Tromsø/St.Olavs Hospital i Trondheim. I den forbindelse kan du bli forespurt om å delta i en forskningsstudie om behandlingstyper og livskvalitet ved sykdommen *obstruktiv søvnapnésyndrom* (OSA). Formålet med studien er å kartlegge hvilke forhold som kan påvirke om behandlingen blir vellykket. Studien foregår i regi av Universitetet i Tromsø (UiT), Universitetssykehuset Nord-Norge (UNN), St.Olavs Hospital og Tannhelsetjenestens kompetansesenter i Nord-Norge (TkNN). Dette er informasjon til deg om studien.

Studien er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk.

PLANLAGTE OPPMØTER VED ØNH GRUPPE 1 (Apnéskinne)		TID	TIDSPLAN
Utredning	Søvnregistrering Utfylling av spørreskjemaer	Over natten	
Tillaging av apparatur	Undersøkelse av munnhule/svelg	Poliklinisk time	Så snart som mulig etter utredning
Behandlingsstart	Utlevering og tilpasning av apparatur.	Poliklinisk time	1 mnd. etter tillaging
Første kontroll	Kontroll og eventuell justering av apparatur.	Poliklinisk time	1-3 uker etter behandlingsstart
Andre kontroll	Søvnregistrering Utfylling av spørreskjemaer	Over natten	4-6 mnd. etter behandlingsstart
Tredje kontroll	Søvnregistrering Utfylling av spørreskjemaer	Over natten	12 mnd. etter behandlingsstart
Videre kontroller	Ved behov		

PLANLAGTE OPPMØTER VED ØNH GRUPPE 2 (CPAP)		TID	TIDSPLAN
Utredning	Søvnregistrering Utfylling av spørreskjemaer	Over natten	
Behandlingsstart	Tilpasning av apparatur	Over natten	0-3,5 mnd. etter utredning
Første kontroll	Avlesning av apparatur Spørreskjema	Poliklinisk time	4 mnd. etter tilpasning
Andre kontroll	Avlesning av apparatur Spørreskjema	Poliklinisk time	12 mnd. etter tilpasning
Videre kontroller	Ved behov		

Hva innebærer studien?
Mens søvnapné kan behandles på flere forskjellige måter, er to spesifikke behandlingstyper de vanligste, hhv. ved hjelp av en apnéskinne (gruppe 1) eller en CPAP-maskin (gruppe 2). En apnéskinne vil holde underkjeven litt lenger frem enn utgangsstillingen, for dermed å hindre at tungen og ganen blokkerer luftveiene. En tannlege tar avtrykk av tennene, og skinnene fremstilles i akryl. En CPAP-maskin er en elektrisk innretning som gjennom en maske som dekker nese og/eller munn skaper et lite overtrykk i luftveiene, noe som fører til færre pustestopp pr. time. Deltakerne i studien vil bli tilfeldig utvalgt til én av disse to grupper. Som studiedeltaker blir du satt opp til behandling og påfølgende kontroller som tabellene på side 1 viser. Antall oppmøter ved ØNH vil variere etter behandlingstype. Utover dette er det ingen forskjell mellom gruppene i forhold til oppfølging.

Mulige fordeler og ulemper for deg som deltager i studien
Som deltaker i studien vil du ikke få noen nevneverdige fordeler, men du følger samme behandlingsregime som andre pasienter. Som for alle pasienter som behandles for OSA har du anledning til å gå videre med annen behandling hvis det senere skulle bli nødvendig. En mulig ulempe med å delta i studien er at du må fylle ut noen flere spørreskjemaer enn det som er vanlig ved ordinær behandling. Deltakere i denne studien kan ved en senere anledning bli invitert til å delta i en oppfølgingsstudie. Det vil selvfølgelig være frivillig om du ønsker å delta i nok en studie.

Kostnader knyttet til deltakelse i studien
Egenandeler for behandling er lik for de to behandlingstypene og må betales på vanlig måte. Utgifter til utredninger/undersøkelser utover egenandeler ved behandling ved dekkes av det offentlige. Reise- og overnattingsutgifter dekkes på samme måte som ved vanlig polikliniske timer.

Hva skjer med innsamlet informasjon om deg?
Innsamlet data vil bli gjort ikke-identifiserbar ved at personnavn og fødselsnummer erstattes med et identifikasjonsnummer. Kun de prosjektansvarlige i forskningsstudien har adgang til kodelisten med pasientnavn. Etter at dataene er analysert vil kodelisten oppbevares hos UNN i Tromsø. Som studiedeltaker har du rett til innsyn i alle opplysninger som blir registrert om deg og du kan kreve at innsamlet informasjon om deg slettes. Informasjonen som registreres skal kun brukes slik det er beskrevet under hensikten med studien. Resultatene av studien vil bli publisert i nasjonale og internasjonale tidsskrifter. Det vil ikke være mulig å identifisere din informasjon i resultatene av studien når disse publiseres.

Frivillig deltakelse
Det er frivillig å delta i studien. Dersom du takker ja, kan du likevel når som helst og uten å oppgi noen grunn, trekke deg fra studien. Du vil da igjen bli en ordinær pasient ved avdelingen og fulgt opp på normal måte. Dersom du trekker deg fra studien vil dette ikke få noen konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du en samtykkeerklæring når du kommer til utredning ved Øre-Nese-Hals-avdelinga.

Oppfølging etter avsluttet behandling
Etter at studien er avsluttet overføres du til ordinær oppfølging ved Øre-Nese-Hals-avdelinga.

Konfidensialitet
Alle opplysninger behandles konfidensielt og ingen vil kunne gjenkjennes i publikasjoner. Ved prosjektets slutt vil alle anonymiserte forskningsdata bli oppbevart på UNN i opptil fem år før de ødelegges.

Utdypende forklaring av hva studien innebærer
For å få delta i studien må deltakerne ha:

- $10 \leq AHI \leq 30$ påvist ved polygrafi
- Subjektiv symptom på OSA
  (Nedsatt konsentrasjonsevne, dagtretthet, morgenhodepine etc.)
- Alder ≥ 20 og ≤ 75 år med full samtykkekompetanse
- Evne til minst 5mm framskyting av underkjeven
- Akseptere tilfeldig valg av behandling
- Akseptere å møte til avtalte timer og å svare på planlagte spørreskjemaer

Deltakerne kan derimot ikke ha:

- Dominans av sentral søvnapné
- Ukontrollert periodontal sykdom (inadekvat støttevev rundt tenner/tannmobilitet)
- Alvorlig nedsatt almenntilstand
- Graviditet
- Helseproblemer som gjør at ordinær behandling av OSA ikke kan gjennomføres

Obstruktiv søvnapné (OSA) er en tilstand hvor de øvre luftveiene blokkeres av ulike anatomiske strukturer. *Obstruktiv* betyr i denne sammenheng at pusten hemmes. *Søvnapné* betyr pustepauser under søvn. OSA kan ofte gi utfall som snorking.

Det er normalt å ha noen pustepauser når man sover, men det gir nedsatt søvnkvalitet hvis man er urolig og har mange kortvarige oppvåkninger. For de som deler seng med noen, vil også partneren kunne bli plaget av dette. Konsekvensene av tilstanden er at du ofte på dagtid kan føle deg søvnig, ha konsentrasjonsvansker, opplever at det er vanskelig å tenke klart, har hodepine, og noen opplever oftere enn andre impotens. I tillegg er det vist at det å ha søvnapné gir økt risiko for hjerte-karsykdommer.

Gjennom å kartlegge pasientkarateristika og behandlingsresultat kan en studere hvilke pasienter som har mest nytte av hvilken type behandling for OSA. Denne informasjonen blir innhentet gjennom konsultasjoner og spørreskjema. Spesifikke mål for studien er å kartlegge hvordan de to behandlingsmetodene skiller seg fra hverandre mht. behandlingseffekt, behandlings-etterlevelse og hvordan behandlingstypen påvirker livskvalitet hos pasienter med mild til moderat OSA.

Ingen av behandlingstypene innebærer smerte, men kan noen ganger oppleves som litt ubehagelige, hver behandlingstype på sin måte. De vanligste bivirkningene ved behandling av OSA er tørr munn/hals, økt spyttproduksjon, forbigående ømhet i kjeve- og ansiktsmuskulatur, mens noen få kan oppleve at det presser på tennene. For at studien skal kunne gi gode og sikre resultat er det ønskelig at alle deltakerne møter opp til de planlagte kontrollene og fyller ut de nødvendige spørreskjemaene. Deltakerne vil bli orienterte dersom ny informasjon blir tilgjengelig som kan påvirke deltakernes villighet til å delta i studien.

Personvern, økonomi og forsikring

Opplysninger som registreres om deg er journalopplysninger som trenges for å kunne behandle din søvnapnésykdom samt opplysningene innsamlet ved spørreskjemaene. Innsamlet data vil bli gjort ikke-identifiserbar ved at personnavn og fødselsnummer erstattes med et identifikasjonsnummer. Informasjonen som registreres skal kun brukes slik som beskrevet i hensikten med studien. Så lenge studien pågår vil kun de prosjektansvarlige i forskningsstudien har adgang til navnelisten. Alle som får innsyn til opplysningene har taushetsplikt. Etter at dataene er analysert vil kodelisten som knytter navn til identifikasjons-nummer oppbevares hos UNN, slik at eventuelle oppfølgings-studier vil kunne gjennomføres. Etter at prosjektet er avsluttet vil kodelistene bli ødelagte. Som deltaker i studien har du rett til innsyn i alle opplysninger som blir registrert om deg, og du kan kreve at innsamlet informasjon slettes fra studieregisteret.

Hvis du sier ja til å delta i studien, har du også rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlet informasjon.

Som for all behandling av helse- og tannhelsepersonell i Norge er deltakerne i studien dekket av Norsk Pasientskadeerstatning (NPE). Informasjon om resultatene etter studien kan du få dersom du henvender deg til Øre-Nese-Hals-avdelinga på UNN, tlf.nr.: 77 62 74 02

Med hilsen

Lars Martin Berg	Prosjektansvarlig, cand. odont, spes.tannlege, IKO, UiT/TkMN	Tlf.: 941 33 180 E-post: osasstudie@gmail.com Postadr.: TkMN, Klæbuvn 70, 5. etg, 7030 TRONDHEIM
Torun Karina S. Ankjell	Prosjektansvarlig, cand. med., LiS-lege, NKØØ, UNN	Tlf.: 776 27 402 E-post: torun.karina.ankjell@unn.no Postadr.: ØNH-avd. UNN Tromsø, Pb. 100 Langnes, 9038 TROMSØ
Tordis A. Trovik	Hovedveileder og prosjektleder, professor, dr.odont. ISM, UiT	Tlf.:776 44 297 E-post: tordis.a.trovik@uit.no Postadr.:Institutt for samfunnsmedisin, Det helsevitenskapelige fakultet, UiT Norges arktiske universitet, 9037 TROMSØ

Appendix 2

Patient health declaration form (Helseskjema 1)

Medical examination checklist (Helseskjema 2)

Questionnaire regarding treatment compliance and patient-satisfaction at follow-up visits

Pittsburgh Sleep Quality Index (PSQI)

Medical Outcomes Study Short-Form 36-Element Health Survey (SF36)

Hospital Anxiety and Depression Scale (HADS)

BAKGRUNNSINFORMASJON/ HELSESKJEMA 1

En studie om søvnapnébehandling, livskvalitet og etterlevelse

ID nr.
Dato:

Utfylles av **pasienten** før konsultasjon med ØNH-lege. Kun et svar per spørsmål

1. I hvilket år er du født? ☐

2. Kjønn

1 ☐ Kvinne
2 ☐ Mann

3. Sivil status

1 ☐ Aleneboende
2 ☐ Gift/ sambo

4. Høyeste utdannelse

1 ☐ Folkeskole
2 ☐ 9-årig grunnskole
3 ☐ 1-2-årig videregående
4 ☐ Videregående yrkesfaglig utdanning
5 ☐ 3-årig videregående allmennfaglig
6 ☐ Universitetsutdanning (≤4 år)
7 ☐ Universitetsutdanning (> 4 år)
8 ☐ Annen utdanning?

Spesifiser:

5. Hvordan er den generelle helsetilstanden?

1 ☐ Utmerket
2 ☐ Meget god
3 ☐ God
4 ☐ Nokså god
5 ☐ Dårlig

6. Hvordan er tannhelsen din?

1 ☐ Utmerket
2 ☐ Meget god
3 ☐ God
4 ☐ Nokså god
5 ☐ Dårlig

7. Sover du godt om natten?

1 ☐ Svært ofte
2 ☐ Ofte
3 ☐ En gang i mellom
4 ☐ Sjelden
5 ☐ Svært sjelden

8. Har du noen av følgende plager?
(sett så mange kryss som nødvendig)

1 ☐ Generell søvnighet
2 ☐ Følelse av utslitthet
3 ☐ Hodepine om morgenen
4 ☐ Dårlig hukommelse
5 ☐ Irritabilitet
6 ☐ Nervøsitet
7 ☐ Manglende konsentrasjonsevne
8 ☐ Smerte i kroppen
9 ☐ Munntørrhet
10 ☐ Andre plager?

Spesifiser:

9. Røykevaner

1 ☐ Aldri røykt
2 ☐ Røykt tidligere
3 ☐ Røyker < 10 sigaretter per dag
4 ☐ Røyker ≥ 10 sigaretter per dag

*10. Hvor ofte drikker du alkohol?**

1 ☐ Omtrent 6–7 ganger pr. uke
2 ☐ Omtrent 4-5 ganger pr. uke
3 ☐ Omtrent 2-3 ganger pr. uke
4 ☐ Omtrent 1 ganger pr. uke eller sjeldnere

Fortsetter på baksiden av arket

*Kvinner: én alkoholenhet, Menn: to alkoholenheter. (Én alkoholenhet er én liten flaske øl, eller ett glass vin, eller én drink)

11. I hvor stor grad har du hatt plager med allergier (som innbefatter pustebesvær)?
Sett kryss i én rute

Små/ingen plager - store plager

1	2	3	4	5

12. I hvor stor grad har du forventninger til behandlingen?
Sett kryss i én rute

Små/ingen forventninger - store forventninger

1	2	3	4	5

*Kvinner: én alkoholenhet, Menn: to alkoholenheter. (Én alkoholenhet er én liten flaske øl, eller ett glass vin, eller én drink)

HELSESKJEMA 2

En studie om søvnapnébehandling, livskvalitet og etterlevelse

ID nr.
Dato:

Utfylles av **lege** 2. dag av søvnregistrering. Kun et svar per spørsmål

1. I hvilket år er pasienten født?

2. Har du inntrykk av at pasienten er motivert for behandlingen?

1 ☐ Svært motivert
2 ☐ Temmelig godt motivert
3 ☐ Ikke spesielt motivert
4 ☐ Nærmest likegyldig

3. Har du inntrykk av at pasienten har god støtte for behandlingen fra sine nærmeste (spesielt fra sengepartneren)?

1 ☐ Svært god støtte
2 ☐ Temmelig god støtte
3 ☐ Ikke spesielt god støtte
4 ☐ Nærmest likegyldig
5 ☐ Ikke aktuelt

4. BMI

Høyde (m)
Vekt (kg)

5. Tall fra søvnregistreringen

Total søvntid	min.
AHI	
Tot.antall obstruktive apnéer	
Totalantall miksede apnéer	
Totalantall sentrale apnéer	
Totalantall hypopnéer	
ODI	
Gj.snittlig SaO_2-verdi	%
Laveste målte SaO_2-verdi	%
Snorketid	%

6. Har pasienten protrusjonsevne på mer enn 5 mm?

1 ☐ Ja
2 ☐ Nei
3 ☐ Uklart

7. Antall tenner i munnen

Antall tenner i o.kj.
Antall tenner i u.kj.

8. Sovestilling i antall minutt

Rygg (Supine)
Annen (Non-supine)

9. Har pasienten palpasjonsømhet i tyggemuskulatur?

1 ☐ Nei
2 ☐ Grad I
3 ☐ Grad II
4 ☐ Grad III

10. Friedman grad

1 ☐ Friedman grad I
2 ☐ Friedman grad II
3 ☐ Friedman grad III
4 ☐ Friedman grad IV

11. Tonsillstørrelse

1 ☐ Grad I
2 ☐ Grad II
3 ☐ Grad III
4 ☐ Grad IV

5 ☐ Tonsillektomert

ETTERLEVELSE AV BEHANDLING (COMPLIANCE)

En studie om søvnapnébehandling, livskvalitet og etterlevelse
12-månederskontroll

ID nr.
Dato:

Her kommer noen spørsmål om hvorledes du opplevde din behandling. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser den siste uken. Ikke tenk for lenge på svaret – de spontane svarene er best.

1. Hvilken behandling har du fått?

1 ☐ CPAP (*pustemaskin*)*
2 ☐ MAS (*apnéskinne*)**

* Continuous Positive Airway Pressure
** Mandibular Advancement Splint

2. Hvor lenge etter at du fikk veiledningen startet du å bruke CPAP/ MAS?

1 ☐ Umiddelbart etter
2 ☐ 2 - 3 dager etter veiledning
3 ☐ 4 - 7 dager etter veiledning
4 ☐ > 7 dager etter veiledning

3. Hvor alvorlig opplever du din søvnapné?

1 ☐ Svært alvorlig
2 ☐ Moderat alvorlig
3 ☐ Litt alvorlig
4 ☐ Svært lite alvorlig

4. Hvor nødvendig er det for deg å bli fullstendig behandlet for din søvnapné?

1 ☐ Svært nødvendig
2 ☐ Moderat nødvendig
3 ☐ Litt nødvendig
4 ☐ Svært lite nødvendig

5. Nå har det gått omtrent ett år siden du fikk utlevert ditt behandlingsapparat. I hvor mange av disse nettene har du brukt apparatet du fikk utlevert – hele eller deler av natten?

1 ☐ Alle nettene
2 ☐ Omtrent alle nettene
3 ☐ Omtrent i 75 % av nettene
4 ☐ Omtrent i 50 % av nettene
5 ☐ Omtrent i 25 % av nettene
6 ☐ Mindre enn i 25 % av nettene
7 ☐ Bruker den ikke lengre

6. Hvor mange timer sover du i gjennomsnitt per natt?

timer

7. I hvor mange timer i gjennomsnitt per natt bruker du pustemaskinen / skinnen?

timer

Fortsetter på baksida!

8. Har behandlingen vært effektiv?

1 ☐ Ja
2 ☐ Nei
3 ☐ Usikker

9. Har behandlingen hatt noen bivirkninger (uønskede sideeffekter)?

1 ☐ Ja
2 ☐ Nei
3 ☐ Usikker

10. Hvilke bivirkninger (uønskede sideeffekter) har du opplevd? (sett så mange kryss som nødvendig)

1 ☐ Ubehag/smerte i kjeven
2 ☐ Ømme tenner
3 ☐ Irritasjon i gummene
4 ☐ Skinna/masken løsner/kommer ut av stilling mens jeg sover
5 ☐ Føler at jeg ser dum ut
6 ☐ Vanskelig i forhold til sengepartneren
7 ☐ Økt spyttmengde
8 ☐ Munntørrhet
9 ☐ Tannskjæring/gnissing
10 ☐ Kvelningsfornemmelser
11 ☐ Gnagsår
12 ☐ Andre bivirkninger?

Fortell:

11. Dersom du ikke har brukt behandlings-apparatet ditt hver natt eller nesten hver natt, hvilke (om noen) av bivirkningene gjorde at du ikke brukte apparatet hver natt? (sett så mange kryss som nødvendig)

1 ☐ Ubehag/smerte i kjeven
2 ☐ Ømme tenner
3 ☐ Irritasjon i gummene
4 ☐ Skinna/masken løsner/kommer ut av stilling mens jeg sover
5 ☐ Føler at jeg ser dum ut
6 ☐ Vanskelig i forhold til sengepartneren
7 ☐ Økt spyttmengde
8 ☐ Munntørrhet
9 ☐ Tannskjæring/gnissing
10 ☐ Kvelningsfornemmelser
11 ☐ Gnagsår
12 ☐ Andre årsaker

12. Har du merket noen forbedring i noen av plagene du kunne ha hatt før du startet med behandlingen? (sett så mange kryss som nødvendig)

1 ☐ Generell søvnighet
2 ☐ Følelse av utslitthet
3 ☐ Hodepine om morgenen
4 ☐ Dårlig hukommelse
5 ☐ Irritabilitet
6 ☐ Nervøsitet
7 ☐ Manglende konsentrasjonsevne
8 ☐ Smerte i kroppen
9 ☐ Munntørrhet
10 ☐ Andre plager?

Fortell:

13. Hvordan er den generelle helsetilstanden?

1 ☐ Utmerket
2 ☐ Meget god
3 ☐ God
4 ☐ Nokså god
5 ☐ Dårlig

PITTSBURG SLEEP QUALITY INDEX (PSQI)

En studie om søvnapnébehandling, livskvalitet og etterlevelse

ID nr.
Dato:

Instruksjoner: Følgende spørsmål har med ditt vanlige søvnmønster den siste måneden å gjøre. Du skal svare på hva som er mest riktig for de fleste dager og netter **den siste måneden**. Vennligst svar på alle spørsmål.

1. I løpet av den siste måneden, når har du vanligvis lagt deg om kvelden?
   VANLIG LEGGETID_____

2. I løpet av den siste måneden, hvor lang tid (i minutter) har det vanligvis tatt deg å sovne om kvelden?
   ANTALL MINUTTER_____

3. I løpet av den siste måneden, når har du vanligvis stått opp om morgenen?
   VANLIGVIS STÅTT OPP KL_____

4. I løpet av den siste måneden, hvor mange timer søvn har du faktisk fått om natten? (Dette kan være forskjellig fra hvor mange timer du oppholdt deg i sengen.)
   ANTALL TIMER SØVN HVER NATT _____

For hvert av de følgende spørsmål, kryss av for det beste svar. Vennligst svar på alle spørsmålene.

5. I løpet av den siste måneden, hvor ofte har du hatt problemer med søvnen ***fordi du***…

		Ikke i løpet av den siste måneden	Mindre enn en gang i uken	En eller to ganger i uken	Tre eller flere ganger i uken
A	Ikke klarer å sovne i løpet av 30 minutter				
B	Våkner opp midt på natten eller tidlig om morgenen				
C	Må opp for å gå på toalettet				
D	Ikke klarer å puste ordentlig				
E	Hoster eller snorker høyt				
F	Føler deg for kald				

Fortsetter på baksida!

	(Spørsmål 5 forts.)	Ikke i løpet av den siste måneden	Mindre enn en gang i uken	En eller to ganger i uken	Tre eller flere ganger i uken
G	Føler deg for varm				
H	Har vonde drømmer				
I	Har smerter				
J	Andre grunner, vennligst beskriv:				

6.	Veldig bra	Ganske bra	Ganske dårlig	Veldig dårlig
I løpet av den siste måneden, hvordan vil du bedømme søvnkvaliteten din totalt sett?				

7.	Ikke i løpet av den siste måneden	Mindre enn en gang i uken	En eller to ganger i uken	Tre eller flere ganger i uken
I løpet av den siste måneden, hvor ofte har du tatt medisin (med eller uten resept) som hjelp til å sove?				

8.	Ikke i løpet av den siste måneden	Mindre enn en gang i uken	En eller to ganger i uken	Tre eller flere ganger i uken
I løpet av den siste måneden, hvor ofte har du hatt problemer med å holde deg våken under bilkjøring, måltider eller når du holder på med sosiale aktiviteter?				

9.	Ikke noe problem i det hele tatt	Bare et lite problem	Et visst problem	Et stort problem
I løpet av den siste måneden, hvor stort problem har det vært for deg å ha overskudd nok til å få ting gjort?				

10.	Deler ikke seng eller rom med noen	Partner/ romkamerat i annet rom	Partner i samme rom men ikke i samme seng	Partner i samme seng
Deler du seng eller rom med noen?				

Fortsetter på neste side!

Hvis du har en partner eller romkamerat, ***spør han/henne*** hvor ofte i løpet av den siste måneden du har hatt…

	11.	Ikke i løpet av den siste måneden	Mindre enn en gang i uken	En eller to ganger i uken	Tre eller flere ganger i uken
A	Høy snorking				
B	Lange pustestopp under søvnen				
C	Rykninger eller sammentrekninger i beina under søvnen				
D	Episoder med desorientering eller forvirring under søvnen				
E	Annen type uro under søvnen; vennligst beskriv				

Sent on behalf of Dr. Buysse

Dear Lars Martin Berg,

You have my permission to use the PSQI for your research study (both retrospective and prospective). You can find the instrument, scoring instructions, the original article, links to available translations, and other useful information at www.sleep.pitt.edu under the Measures/Instruments tab. Please ensure that the PSQI is accurately reproduced in any on-line version (including copyright information). We request that you do cite the 1989 paper in any publications that result.

Note that Question 10 is not used in scoring the PSQI. This question is for informational purposes only, and may be omitted during data collection per requirements of the particular study.

Good luck with your research.

Sincerely,

Daniel J. Buysse, M.D.
Professor of Psychiatry and Clinical and Translational Science
University of Pittsburgh School of Medicine
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Pittsburgh, PA 15213
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HELSERELATERT LIVSKVALITET (SF-36)

En studie om søvnapnébehandling, livskvalitet og etterlevelse

ID nr.
Dato:

Dette spørreskjemaet handler om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å utføre dine daglige gjøremål. *Takk for at du fyller ut dette spørreskjemaet!*

1.	Utmerket	Meget god	God	Nokså god	Dårlig
	1	2	3	4	5
Stort sett, vil du si at din helse er:					

2.	Mye bedre nå enn for ett år siden	Litt bedre nå enn for ett år siden	Omtrent den samme som for ett år siden	Litt dårligere nå enn for ett år siden	Mye dårligere nå enn for ett år siden
	1	2	3	4	5
Sammenlignet med for ett år siden, hvordan vil du si at din helse stort sett er **nå**?					

De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig dag. Er din helse slik at den begrenser deg i utførelsen av disse aktivitetene **nå**? Hvis ja, hvor mye?

3.		Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
		1	2	3
A	Anstrengende aktiviteter som å løpe, løfte tunge gjenstander, delta i anstrengende idrett			
B	Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid			
C	Løfte eller bære en handlekurv			
D	Gå opp trappen flere etasjer			
E	Gå opp trappen én etasje			

Fortsetter på baksida!

(Spørsmål 3 fortsetter)		Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
F	Bøye deg eller sitte på huk			
G	Gå mer enn to kilometer			
H	Gå noen hundre meter			
I	Gå hundre meter			
J	Vaske eller kle på deg			

I løpet av **de siste 4 ukene**, hvor ofte har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av din fysiske helse?

4.		Hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
		1	2	3	4	5
A	Du har måttet redusere tiden du har brukt på arbeid eller på andre gjøremål					
B	Du har utrettet mindre enn du hadde ønsket					
C	Du har vært hindret i å utføre visse typer arbeid eller gjøremål					
D	Du har hatt problemer med å gjennomføre arbeidet eller andre gjøremål (f.eks. det krevde ekstra anstrengelser)					

I løpet av **de siste 4 ukene**, hvor ofte har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål på grunn av følelsesmessige problemer (som f.eks. å være deprimert eller engstelig)?

5.		Hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
		1	2	3	4	5
A	Du har måttet redusere tiden du har brukt på arbeid eller på andre gjøremål					
B	Du har utrettet mindre enn du hadde ønsket					
C	Du har utførte arbeidet eller andre gjøremål mindre grundig enn vanlig					

Fortsetter på neste side!

6.	Ikke i det hele tatt	Litt	En del	Mye	Svært mye
	1	2	3	4	5
I løpet av **de siste 4 ukene**, i hvilken grad har din fysiske helse eller følelsesmessige problemer hatt innvirkning på din vanlige sosiale omgang med familie, venner, naboer eller foreninger?					

7.	Ingen	Meget svake	Svake	Moderate	Sterke	Meget sterke
	1	2	3	4	5	6
Hvor sterke kroppslige smerter har du hatt i løpet av **de siste 4 ukene**?						

8.	Ikke i det hele tatt	Litt	En del	Mye	Svært mye
	1	2	3	4	5
I løpet av **de siste 4 ukene**, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?					

Disse spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det **de siste 4 ukene**. For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det. Hvor ofte i løpet av **de siste 4 ukene** har du…

9.		Hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
		1	2	3	4	5
A	Følt deg full av liv?					
B	Følt deg veldig nervøs?					
C	Vært så langt nede at ingenting har kunnet muntre deg opp?					
D	Følt deg rolig og harmonisk?					

Fortsetter på baksida!

E	Hatt mye overskudd?					
F	Følt deg nedfor og deprimert?					
G	Følt deg sliten?					
H	Følt deg glad?					
I	Følt deg trett?					

10.	Hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
	1	2	3	4	5
I løpet av **de siste 4 ukene**, hvor ofte har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektninger osv.)?					

Hvor RIKTIG eller GAL er hver av de følgende påstander for deg?

11.		Helt riktig	Delvis riktig	Vet ikke	Delvis gal	Helt gal
		1	2	3	4	5
A	Det virker som om jeg blir syk litt lettere enn andre					
B	Jeg er like frisk som de fleste jeg kjenner					
C	Jeg tror at helsen min vil forverres					
D	Jeg har utmerket helse					

Takk for at du fylte ut dette spørreskjemaet!

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License Number: QM034949

Licensee Name: Arctic University of Norway (UiT)

Licensee Address: Department of Community Medicine, Faculty of Health Sciences, Tromso N-9037 NO

Approved Purpose: Treatment of mild and moderate obstructive sleep apnea syndrome (OSA) by continuous positive airway pressure (CPAP) or mandibular advancing splint (MAS) - a randomized controlled trial on patient factors, success rate and compliance

Study Name: University Academic Research
Study Type: Non-commercial academic research and/or thesis – Unfunded University
Data Collection Method: Paper

Therapeutic Area: Wellness & Lifestyle

Royalty Fee: None, because this License is granted in support of the non-commercial Approved Purpose

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Signature:_____	Signature:_____
Name:_____	Name: _____
Title:_____	Title:_____
Date:_____	Date:_____

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APPENDIX B

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Tordis A Trovik
Department of Community Medicine
Faculty of Health Sciences
N-9037 Tromso
Norway

License Number: QM034949
Amendment to: N/A
Study Term: 08/01/14 to 12/31/17
Master License Term: N/A

Approved Purpose
Treatment of mild and moderate obstructive sleep apnea syndrome (OSA) by continuous positive airway pressure (CPAP) or mandibular advancing s

Study Name: University Academic Research
Protocol: Wellness & Lifestyle
Govt. ID:
Study Type: UNIVERSITY - FREE
Clients Reference: BACKDATED LICENSE

Licensed Surveys (Modes) and Services:

Item	Description	Mode of Admin	Quantity	Fees
	BACKDATED LICENSE APPROVED.			
	(Please refer to paragraph 2 of Appendix A			
	"Copyright Protection")			
	**SOLUTION PKG: Paper SF36v2 with			
	Desktop Scoring Software.			
PROJ01	License Fee	Paper	1	
ADM012	Patients Enrolled		130	
ADMINS	Administrations @1 each*		200	
	*Rounded up in increments of 100.			
ES0220	SF-36v2, Standard Recall	Paper	1	

Approved Languages:
Norway (Norwegian)

SS100	Scoring Software v5		1	
SS108	SS v5 Key: SF-36v2 Scoring		200	
SS996	DQE: Data Quality Evaluation w/ report		200	
SS997	MSE: Missing Score Estimator		200	

SS998	UI: Utility Index (QALYs)	200
SS999	RCI: Response Consistency Index	200
EM125	SF-36v2 User's Manual 3rd Ed.	1

Approved Languages:
United States (English)

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program.

To accept offer, please sign and return

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26-MAY2016.

TOTAL FEES: 0.00 USD

Payment Terms: Due on Receipt

NOTICE TO INVESTIGATIONAL SITES - APPENDIX C

Effective Date:	April 26, 2016
License:	QM034949
Licensee Name:	Arctic University of Norway (UiT)
Study Term:	Beginning on 01-August 2014 and ending on 31-December 2017
Licensed Surveys:	SF-36v2, Standard Recall, Norway (Norwegian)
Approved Purpose:	Treatment of mild and moderate obstructive sleep apnea syndrome (OSA) by continuous positive airway pressure (CPAP) or mandibular advancing splint (MAS) - a randomized controlled trial on patient factors, success rate and compliance

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HOSPITAL ANXIETY & DEPRESSION SCALE (HADS)

En studie om søvnapnébehandling, livskvalitet og etterlevelse

ID nr.
Dato:

Rettledning: Her kommer noen spørsmål om hvorledes du føler seg. For hvert spørsmål setter du kryss for ett av de fire svarene **som best beskriver** dine følelser den siste uken.
Ikke tenk for lenge på svaret – de spontane svarene er best.

1. Jeg føler meg nervøs og urolig

3 ☐ Mesteparten av tiden
2 ☐ Mye av tiden
1 ☐ Fra tid til annen
0 ☐ Ikke i det hele tatt

2. Jeg gleder meg fortsatt over tingene slik jeg pleide før

0 ☐ Avgjort like mye
1 ☐ Ikke fullt så mye
2 ☐ Bare lite grann
3 ☐ Ikke i det hele tatt

3. Jeg har en urofølelse som om noe forferdelig vil skje

3 ☐ Ja, og noe svært ille
2 ☐ Ja, ikke så veldig ille
1 ☐ Litt, bekymrer meg lite
0 ☐ Ikke i det hele tatt

4. Jeg kan le og se det morsomme i situasjoner

0 ☐ Like mye nå som før
1 ☐ Ikke like mye nå som før
2 ☐ Avgjort ikke som før
3 ☐ Ikke i det hele tatt

5. Jeg har hodet fullt av bekymringer

3 ☐ Veldig ofte
2 ☐ Ganske ofte
1 ☐ Av og til
0 ☐ En gang i blant eller aldri

6. Jeg er i godt humør

3 ☐ Aldri
2 ☐ Noen ganger
1 ☐ Ganske ofte
0 ☐ For det meste

7. Jeg kan sitte i fred og ro og kjenne meg avslappet

0 ☐ Ja, helt klart
1 ☐ Vanligvis
2 ☐ Ikke så ofte
3 ☐ Ikke i det hele tatt

8. Jeg føler meg som om alt går langsommere

3 ☐ Nesten hele tiden
2 ☐ Svært ofte
1 ☐ Fra tid til annen
0 ☐ Ikke i det hele tatt

Fortsetter på baksida!

9. Jeg føler meg urolig som om jeg har sommerfugler i magen

0 ☐ Ikke i det hele tatt
1 ☐ Fra tid til annen
2 ☐ Ganske ofte
3 ☐ Svært ofte

10. Jeg bryr meg ikke lenger om hvordan jeg ser ut

3 ☐ Ja, jeg har sluttet å bry meg
2 ☐ Ikke som jeg burde
1 ☐ Kan hende ikke nok
0 ☐ Bryr meg som før

11. Jeg er rastløs som om jeg stadig må være aktiv

3 ☐ Uten tvil svært mye
2 ☐ Ganske mye
1 ☐ Ikke så veldig mye
0 ☐ Ikke i det hele tatt

12. Jeg ser med glede frem til hendelser og ting

0 ☐ Like mye som før
1 ☐ Heller mindre enn før
2 ☐ Avgjort mindre enn før
3 ☐ Nesten ikke i det hele tatt

13. Jeg kan plutselig få en følelse av panikk

3 ☐ Uten tvil svært ofte
2 ☐ Ganske ofte
1 ☐ Ikke så veldig ofte
0 ☐ Ikke i det hele tatt

14. Jeg kan glede meg over gode bøker, radio og TV

0 ☐ Ofte
1 ☐ Fra tid til annen
2 ☐ Ikke så ofte
3 ☐ Svært sjelden eller aldri

GL Assessment

GL Assessment Ltd

Hospital Anxiety and Depression Scale© (HADS)

PERMISSIONS REGISTRATION FORM AND USER AGREEMENT

Please note that the Terms and Conditions of this agreement are non-negotiable. Modifications to the agreement will not be accepted unless approved in writing by GL Assessment. Please read this agreement in full before completion, especially the notes section starting on Page 8.
Note: This agreement can be completed and returned electronically. **Please provide all details and return as a Word doc attachment**. Once all details are completed, please sign the agreement on page 7 and scan in the entire document and return to GL Assessment for countersignature.

Agreement Dated 01/06/2021

Section 1 – Licensee's contact details & full invoice address

LICENSEE: : Lars Martin Berg……..***(note 1)***

Address : UiT The Arctic University of Norway .....

Ladeveien 21 .....

Country : Norway .....]

Postcode/Zip [7066 Trondheim……..]

VAT Number (if applicable):: …… ***(note 2)***

Contact Details:

Name : Lars Martin Berg……..

Title : ……..

Phone : +47 955 53 693…….. Fax :……..

Email : lars.m.berg@uit.no……..

Invoice Address if Different from above: ***note 3)***

……

……

……

Section 2 – Health, Social Care and Specialist Resources

Which of these bests describes your current organisation or institution's area/s of activity?

☐ NHS Trust
☒ Other Hospital
☒ University/College
☐ Health Authority
☐ Pharmaceutical
☐ Child Psychology and Mental Health
☐ Personal and Social Development
☐ Speech and Language
☐ Special Educational Needs (SEN)
☐ Neuropsychology

Section 3– Membership /Qualifications/ Training /Experience (if registering for the first time)

***Professional Membership**
Please list membership of professional bodies, including your registration or membership number

None

***Academic Qualifications**

Please give full details of qualification and subject. If none, please write 'none'. Note that the information you give here will determine which services you will be able to take advantage of, so please provide as much detail as possible.

Qualification	**Subject**	**Institution**	**Date**	**Certificate encl.**
None				

*Relevant Further Training

e.g. Postgraduate Certificate in Education, psychology qualification. Please give full details of qualification and subject. If none, please write 'none'. **Please include a photocopy of your certificate or diploma with this form. Your registration cannot be processed without it.**

Previous experience:

Please give details of any health and psychology test instruments and/or health questionnaires you have used and whether you administered directly or under supervision. Again, please provide as much detail as possible.

None

Section 4 – GL registration details (to be completed by GL if these details have not already previously been provided)

Note: If you have already received your account details (Reader and Qualification Codes), please skip section 3 and go straight to section 4

GL ACCOUNT NUMBER – […131101……]

GL READER CODE (Mandatory- *note 4)* 306500…….....

GL QUALIFICATION CODE (Mandatory – *note 4*) …PER……..……

*For student licensees the following details are also required- (**note 5**):*

University Course and supervisor's name: ..... ……....

……

Supervisor's GL Reader Code .....

Supervisor's GL Qualification Code .....

Section 5 – Context of HADS use

- **PROJECT/STUDY NAME AND DETAILS (*note 6*):** Treatment success with continuous positive airway pressure or mandibular advancement splints in non-severe obstructive sleep apnea.

A randomized controlled clinical trial on sleep quality, health-related quality of life and clinical predictors of treatment success

- **Number of expected study participants/subjects:** 107
- **Number of administrations of the questionnaire per participant/subject:** 2.5
- **TOTAL NUMBER OF ADMINISTRATIONS (*note 7*):** 268
- **Planned study dates**: *start* 10 | 2014 (month/year) *end* 02 | 2019 (month/year)

Section 6 – Project/Study financing

Please indicate here if your use of HADS will be for commercial use, healthcare or academic research/non-commercial use.

For commercial use: ☐ Qty of administrations

Use by a registered company, an organisation, establishment or individual that enables them to, or is part of them benefitting monetarily by their research with the questionnaire, or the application of the questionnaire, CRO, pharmaceutical and any for-profit companies.

For Healthcare organisations/institutions: ☐ Qty of administrations

Classified as hospitals, General Practitioners, healthcare centres, sports and rehabilitation centres, research organisations, scientific societies and charities.

For academic research/non-commercial use: ☒ Qty of administrations 268

Classified as use by an individual or organisation that is using the questionnaire purely for research or study purposes without financial gain or use by an individual.

Fee for commercial use: *Price shown is per administration/use*	0-1000 @ £1.50 each 1001-2500 @ £1.40 each 2501 + @ £1.25 each
Fee for Healthcare organisations/institutions: *Price shown is per administration/use*	0-1000 @ £1.20 each 1001-2500 @ £1.10 each 2501 + @ £1.00 each
Fee for academic research/non-commercial use: *Price shown is per administration/use*	0-1000 @ £1.00 each 1001-2500 @ £0.95 each 2501 + @ £0.90 each

*Please include cost of Manual at **£55.00 per copy (plus shipping)** in any quote:* *Yes* ☐ *No* ☒

Quantity required: ……0……

TOTAL ADMINISTRATIONS/COPYRIGHT FEE COSTS: £ ……**268**……..]

TOTAL MANUAL/S COSTS: £ [……0……]

TOTAL MANUALS SHIPPING COSTS (GL to add): £

ADMINISTRATION FEE (if applicable): £ [……**0**……..]

Please Note: An additional administration fee of £75.00 will be applicable to orders totalling under £100.00 net in value.

TOTAL INVOICE VALUE: £……..…268……...

Section 7 – HADS versions and translations (note 8)
(These will be sent to you as a PDF file)

DO YOU REQUIRE THE HADS IN UK ENGLISH? YES ☐ NO ☒

PLEASE INDICATE HERE IF YOU WILL REQUIRE TRANSLATIONS ☐ (A separate translation agreement will be required between the LICENSEE and the Mapi Research Trust and is not part of this Agreement). If appropriate, please indicate in which language(s) and for which country(ies) the **HADS** is needed. See **Note 8** for Mapi contact details to obtain a list of available translations.

Do **NOT** include German for Germany, Austria or Switzerland. See **note 8** for further details of how to obtain this translation.

Please enter the required languages into the following table. If you require more fields than currently shown, place your cursor to the right of the last cell and press return.

Languages:

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    (c) If the Licensee is declared insolvent or bankrupt or goes into liquidation (other than voluntary liquidation for the purpose of reconstruction only) or if a Receiver is appointed or if the Licensee is subject to any similar event anywhere in the world.

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16. Counterparts; Electronic Signatures: Where permitted according to applicable law, this Agreement may be executed in two or more counterparts, each of which shall be deemed an original, and all such counterparts together shall constitute one and the same instrument. Where counterparts are not permitted according to applicable law, this Agreement must be executed (i) either in paper form, in as many original copies as there are parties to the agreement, each copy to be signed in full by each party on the same instrument, or (ii) in electronic form through a validated electronic signing software, where the electronic version is signed in full by each party on the same electronic instrument. Electronically executed or electronically transmitted (including via fax) signatures shall have the full force and effect of original signatures.

17. This Agreement constitutes the entire agreement between the parties in respect of the Material and supersedes all prior oral or written proposals, agreements or undertakings concerning the same.

18. This Agreement shall not be amended or modified in any way other than by an agreement in writing and signed by both parties or their duly authorised representatives and shall come into effect on receipt of the payment in full as specified above and a counter-signed copy of this Agreement.

19. This Agreement shall be governed by and construed in all respects in accordance with English Law and the courts of England and Wales shall have exclusive jurisdiction to settle any dispute arising out of or in connection with this Agreement, its subject matter and formation, including non-contractual disputes or claims.

20. Data Protection: your personal data will be processed by GL Assessment which is part of the GL Education Group Ltd. in accordance with any applicable law relating to the processing, privacy and use of personal data, as applicable to you and/or the Services, including the Data Protection Act 1998, the General Data Protection Regulation (EU) 2016/679 and any subsequent UK data protection legislation and our Privacy Policy. We will only process the data provided by you for the purposes stated.

21. The permission comes into effect on receipt by GL Assessment of the payment in full within thirty days of invoicing and the return from GL of a counter-signed copy of the permission agreement.

AS WITNESS THE HANDS OF THE PARTIES hereto the day and year first above written

Signed for and on behalf of:
GL Education Group Limited
Unit 28 Bramble Road
Swindon
SN2 8HB
United Kingdom
Company number: 02603456

Signed on behalf of GL Assessment Limited

M. A Pritchard 07/06/2021

.....

Rights & Permissions Department

Signed by the Licensee: ***Please print this page, sign, and attach this signature page as a scanned document along with your typed User Agreement form, sent as a Word document. Electronic signatures are acceptable.***

User's Signature (handwritten):	**Company/Organisation Stamp (if applicable):**
Title: Ph.d.-candidate.	

Company/Organisation: UiT The Arctic University of Norway _____ _____ Date: June 1st 2021 _____	

PLEASE READ THE FOLLOWING NOTES BEFORE YOU COMPLETE THIS AGREEMENT

Note 1. Licensee's Name	This is the contracting party for the permissions agreement. Please ensure the Licensee is authorised to sign legally binding documents on behalf of the contracting organisation.
Note 2. Vat Number	This is only applicable to EU countries. If you do not include your VAT number and are based in the EU, you will be charged VAT at 20% on your invoice.
Note 3. Details of where invoice should be sent.	If the invoice needs to be sent to someone other than the Licensee whose details have been provided on this form already, you must provide the full details of where and to whom the invoice should be sent. Please include the FULL name and address, contact telephone number and **email address**. If you require a purchase order number, study number or any other specific detail to appear on the invoice in order to have it processed, please include this information in section 5 above. The invoice cannot be sent elsewhere/changed once it has been created. All payments must be made in £ sterling by credit card or cheque drawn on a UK bank or sterling funds transferred directly to the GL Assessment bank account – details of which will be included on the invoice. **To make a payment:** **Proforma invoices**: to pay by credit card, please contact the permissions department on (UK) 0800 6521019 (Int) +44 800 652 1019 If you are unable to call to make a payment, please contact permissions@gl-assessment.co.uk for alternative arrangements. **Sales invoices:** please contact credit control on 01793 516347 int +44 1793 516347 If you are unable to call to make a payment, please contact permissions@gl-assessment.co.uk or credit.control@gl-assessment.co.uk for alternative arrangements.
Note 4. GL Reader Code GL Qualification Code	GL Assessment products are restricted to qualified and registered users. You will be issued with a Reader Code and Qualification Number once your application has been processed.

	If the Licensee for the study is different to that of the registered user, please provide the name of the registered user along with the reader code and qualification number in section 4 above.
Note 5. University Course and Supervisor's Name/Supervisor's GL Reader Code. / qualification code	Complete only if you are an undergraduate student and not qualified to register with GL Assessment yourself. Your supervisor must register and sign an agreement on your behalf.
Note 6. Details of project	Ensure you include study title, project title, name of study group.
Note 7. Total number of Administrations	Administrations mean the number of times the scale is to be used not the number of participants/subjects in the study i.e. test to be administered 3 times to 50 participants/subjects = 150 administrations. If the study is international it should include the total number of administrations, whatever number of countries/languages involved (**excluding** those administered in the German language; see below).
Note 8. Translations of the HADS/GHQ	The HADS questionnaire is distributed in its translated forms by the MAPI Research Trust. **For all queries re. availability and status of translations, please contact Mapi Research Trust in France at** eprovide@mapi-trust.org Tel: +33 472 13 65 75 Please note that further costs, in addition to those charged by GL Assessment for the use of the scale(s), may be charged by the MAPI Research Trust when obtaining the translations of the scale. You must liaise directly with the MAPI Research Trust regarding translations and any additional associated fees. Each new translation must undergo a full linguistic validation process by Mapi Research Institute, according to standard recognized methodology of translation, as described in Acquadro C, Conway K; Giroudet C, Mear I. Linguistic Validation Manual for Patient-Reported Outcomes (PRO) Instruments. Mapi Research Institute, 2004. **Please note that GL Assessment do not hold the rights to the GERMAN translation of the HADS, therefore you will be unable to obtain the German translation of the scale either through ourselves or the MAPI Research Trust. If you require the German translation of the HADS you should contact Sylvia.Schlutius@hogrefe.ch at Hogrefe AG, Bern, Switzerland. Please do not include any number of administrations that are intended for German usage on this form as you may be charged twice.**

Ends.

Appendix 3

Ethical approvals

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Tone Natland Fagerhaug	73597506	07.07.2014	2014/956/REK midt
			Deres dato:	**Deres referanse:**
			13.05.2014	

Vår referanse må oppgis ved alle henvendelser

Lars Martin Berg
Universitetet i Tromsø

2014/956 Obstruktiv søvnapnésyndrom – behandlingsstrategi, behandlingsetterlevelse og livskvalitet

Forskningsansvarlig: Universitetet i Tromsø
Prosjektleder: Lars Martin Berg

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK midt) i møtet 13.06.2014. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Prosjektomtale
Obstruktiv søvnapné (OSAS) er en sykdomstilstand der personen får pustestopp under søvn på grunn av kollaps av gane- og svelgvegg. Dette fører til dårlig søvnkvalitet og øker risikoen for bl.a. hjerte-karsykdommer og ulykker som følge av tretthet/søvnighet. OSAS er en lidelse som anslås å ramme opptil 16 % av nordmenn mellom 30 og 65 år. I Norge er CPAP førstevalg ved behandling av OSAS, men mange opplever ubehag ved bruk og avslutter behandlingen. Et alternativ til CPAP er apnéskinner. Gjennom å kartlegge pasientkarateristika for OSAS-pasienter kan en finne ut hvilke pasienter som har mest nytte av hvilken type behandling. Prosjektet har som mål å finne ut hvordan en moderne apnéskinne skiller seg fra CPAP mht. behandlingseffekt, behandlingsetterlevelse og innvirkning på livskvalitet hos pasienter med mild til moderat OSAS.

Vurdering
Komiteen har vurdert søknad, forskningsprotokoll, målsetting og plan for gjennomføring. Under forutsetning av at vilkårene under oppfylles, framstår prosjektet som forsvarlig, og hensynet til deltakernes velferd og integritet er ivaretatt.

Vilkår for godkjenningen

1. Randomiseringen og informasjonen til deltakerne
Studien legger opp til at deltakerne får informasjon om studien etter at randomiseringen er foretatt. Komiteen ber om at dette endres, slik at deltakerne får informasjon om studien før randomiseringen gjøres. Det skal være ett informasjonsskriv som gis til alle potensielle deltakere, og dette informasjonsskrivet skal beskrive begge studiegruppene og at man blir tilfeldig fordelt til én av gruppene.

2. Informasjonsskrivet
Komiteen ber om at informasjonsskrivet utover påpekningene i punkt 1 også:

- dateres
- opplyser hvorvidt deltakerne får dekket sine kostnader forbundet med å delta i studien eller ikke

- inkluderer e-postadresse og postadresse i tillegg til prosjektleders telefonnummer, slik at deltakeren også har mulighet til å ta kontakt skriftlig
- opplyser at studien er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk

Det reviderte informasjonsskrivet skal sendes komiteen til orientering før studien igangsettes. Vennligst benytt e-postadressen post@helseforskning.etikkom.no og "REK midt 2014/956" i emnefeltet.

3. Melding til Helsedirektoratet
Ved klinisk utprøving av medisinsk utstyr må det sendes en melding til Helsedirektoratet senest 60 dager før utprøvingen begynner, jf. Lov om medisinsk utstyr. Prosjektleder er selv ansvarlig for å avklare med Helsedirektoratet om slik melding er nødvendig for denne studien.

4. Forsikring for deltakerne
Sponsor må avklare med norsk pasientskadeerstatningsordning om denne studien faller inn under erstatningsreglene i pasientskadeloven. Hvis så ikke er tilfelle, må det tegnes egen forsikring.

5. Registeret www.clinicaltrials.gov
De aller fleste kliniske studier skal registreres i det offentlig tilgjengelige registeret www.clinicaltrials.gov. Prosjektleder er ansvarlig for å avklare om forskningsstudien omfattes av kravet til registrering.

6. Gjennomføring i tråd med søknad og helseforskningslovens bestemmelser
Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og protokollen, og etter de bestemmelser som følger av helseforskningsloven med forskrifter.

7. Dataoppbevaring
Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren». Av kontrollhensyn skal prosjektdata oppbevares i 5 år etter prosjektslutt. Prosjektslutt er angitt til 31.12.2019. Data skal derfor oppbevares til 31.12.2024, for deretter å slettes eller anonymiseres.

8. Publisering
Komiteen forutsetter at ingen personopplysninger kan framkomme i personidentifiserbar form ved publisering eller annen offentliggjøring.

9. *Sluttmelding og søknad om prosjektendring*
Prosjektleder skal sende sluttmelding til REK midt på eget skjema senest 30.06.2020, jf. hfl. 12.
Prosjektleder skal sende søknad om prosjektendring til REK midt dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Vedtak
Regional komité for medisinsk og helsefaglig forskningsetikk Midt-Norge godkjenner prosjektet med de vilkår som er gitt. Før prosjektet kan igangsettes må det sendes inn revidert informasjonsskriv i tråd med komiteens vilkår.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK midt. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK midt, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Sven Erik Gisvold
Dr.med.
Leder, REK midt

Tone Natland Fagerhaug
Sekretariatsleder

Emne: Revidert informasjonsskriv tas til orientering
Fra: post@helseforskning.etikkom.no
Dato: 29.08.2014 16:53
Til: lars.martin.berg@hotmail.com
Kopi: claes.crossner@uit.no; rek-midt@medisin.ntnu.no

Vår ref. nr.: 2014/956
Prosjekttittel: "Obstruktiv søvnapnésyndrom – behandlingsstrategi, behandlingsetterlevelse og livskvalitet"
Prosjektleder: Lars Martin Berg

Kjære Lars Martin Berg.

Vi viser til e-post innsendt 22.08.2014 med revidert informasjonskriv vedlagt. Informasjonsskrivet er revidert i tråd med vilkår satt i brev datert 07.07.2014, og vilkåret anses dermed som oppfylt. Studien kan igangsettes.

Med vennlig hilsen
Tone Natland Fagerhaug
Sekretariatsleder
post@helseforskning.etikkom.no
T: 73597506

Regional komité for medisinsk og helsefaglig forskningsetikk REK midt-Norge (REK midt)
http://helseforskning.etikkom.no

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK midt	Marit Hovdal Moan	73597504	28.02.2017	2014/956/REK midt
			Deres dato:	Deres referanse:
			21.02.2017	

Vår referanse må oppgis ved alle henvendelser

Lars Martin Berg
UiT

2014/956 Obstruktiv søvnapnésyndrom – behandlingsstrategi, behandlingsetterlevelse og livskvalitet

Forskningsansvarlig: Universitetet i Tromsø
Prosjektleder: Lars Martin Berg

Vi viser til søknad om prosjektendring datert 21.02.2017 for ovennevnte forskningsprosjekt. Søknaden om prosjektendring er behandlet på fullmakt av REK midts sekretariat, med hjemmel i helseforskningsloven § 11 og forskrift om behandling av etikk og redelighet i forskning § 10.

Prosjektleder søkte om følgende endringer:

1. Ny prosjektleder: Tordis A Torvik
2. Ny forskningsansvarlig: UiT - Norges Arktiske Universitet (Kontaktperson: Tordis Trovik)
3. Nye prosjektmedarbeidere (Anders Sjögren, Lars Martin Berg, Vegard Bugten)
4. Ny dato for prosjektslutt: 31.12.2019
5. Ny rekrutteringskanal: Øre-nese-hals-kjeve-avdelingen ved St.Olavs Hospital, hvor man ønsker å rekruttere 60-70 deltakere. Totalt antall deltakere i studien forblir uendret (112-140 pasienter).

Vurdering
REK midt har vurdert søknad om prosjektendring. Komiteen har ingen forskningsetiske innvendinger mot endringen av prosjektet beskrevet under punkt 1, 3, 4 og 5 ovenfor.

Angående søknad om ny forskningsansvarlig: Komiteen ber prosjektleder avklare navn på kontaktperson for UiT som forskningsansvarlig institusjon. UiT som institusjon er overordnet forskningsansvarlig for prosjekt som utgår fra institusjonen. Kontaktperson for forskningsansvarlig vil vanligvis være instituttleder ved instituttet prosjektet er knyttet til. Prosjektleder kan ikke stå som kontaktperson. Vi ber prosjektleder avklare navn på kontaktperson ved UiT.

Endringen beskrevet i punkt 5. ovenfor innebærer at deler av forskningen i dette prosjektet skal foregår ved Øre-nese-hals-kjeve-avdelingen ved St.Olavs Hospital; St.Olavs Hospital vil derfor være forskningsansvarlig for den delen av prosjektet som utføres der. Komiteen viser til interne retningslinjer ved St Olavs Hospital og at klinikksjef for avdelingen hvor forskningen foregår skal oppgis som kontaktperson for forskningsansvarlig institusjon. Komiteen forutsetter derfor at klinikksjef Mette Bratt er kontaktperson ved St.Olavs Hospital. Vi ber prosjektleder bekrefte dette.

Vennligst send etterspurt informasjon til vår e-postadresse post@helseforskning.etikkom.no, med "REK Midt – 2014/956" i emnefeltet.

Under forutsetning av at vilkårene nedenfor tas til følge, er hensynet til deltakernes velferd og integritet fremdeles godt ivaretatt.

Vilkår for godkjenning

1. Godkjenningen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, protokollen og prosjektendringene datert 21.2.2017 . Prosjektet må også gjennomføres i henhold til tidligere vedtak i saken og de bestemmelser som følger av helseforskningsloven (hfl.) med forskrifter.
2. Prosjektleder skal sende inn oppdatert informasjon om navn på forskningsansvarlige institusjoner, samt navn på kontaktperson for hver forskningsansvarlige institusjon.
3. Prosjektleder skal sende søknad om prosjektendring til REK midt dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.
4. Prosjektleder skal sende sluttmelding til REK midt på eget skjema senest 6 måneder etter prosjektslutt), jf. hfl. § 12. I sluttmeldingen skal resultatene presenteres på en objektiv og etterrettelig måte, som sikrer at både positive og negative funn fremgår, jf. helseforskningsloven § 12.
5. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren». Av kontrollhensyn skal prosjektdata oppbevares i 5 år etter sluttmelding er sendt REK. Data skal derfor oppbevares til denne datoen, for deretter å slettes eller anonymiseres, jf. hfl. § 38.

Vedtak

Regional komité for medisinsk og helsefaglig forskningsetikk Midt-Norge godkjenner søknad om prosjektendring med de vilkår som er gitt, med hjemmel i § 11 i helseforskningsloven.

Klageadgang

Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK midt. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK midt, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

Hilde Eikemo
Sekretariatsleder, REK midt

Marit Hovdal Moan
seniorrådgiver

Kopi til: *claes.crossner@uit.no; tordis.a.trovik@uit.no;*