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

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SUMMARY

Obstructive sleep apnea (OSA) leads to recurrent arousals from sleep, oxygen desaturations, daytime sleepiness and fatigue. This can have an adverse impact on quality of life. The aims of this study were to compare: 1) quality of life between the general population and untreated OSA patients; and 2) changes of quality of life among OSA patients after two years of positive airway pressure (PAP) treatment between adherent patients and non-users. Propensity score

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Declaration of contribution:

Erla Björnsdóttir designed the study with Thorarinn Gislason, Bryndis Benediktsdóttir, Erna Sif Arnardóttir and Allan I Pack. Erla performed the literature search, statistical analyses with the help of Brendan Keenan and Christer Janson. Erla drafted the paper and participated in all revisions of the paper with the co-authors

Brendan Keenan performed the propensity matching analyses and participated in data interpretation and all revisions of the manuscript.

Björg Eysteinsdóttir participated in the data collection, the literature review and in all revisions of the manuscript.

Erna Sif Arnardóttir participated in the study design, data collection and all revisions of the manuscript.

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methodologies were used in order to minimize selection bias and strengthen causal inferences. The enrolled OSA subjects (n=822) were newly diagnosed with moderate to severe OSA who were starting PAP treatment and the general population subjects (n=742) were randomly selected Icelanders. The Short Form 12 was used to measure quality of life. Untreated OSA patients had worse quality of life when compared to the general population. This effect remained significant after using propensity scores to select samples, balanced with regard to age, body mass index, gender, smoking, diabetes, hypertension and cardiovascular disease. We did not find significant overall differences between full and non-users of PAP in improvement of quality of life from baseline to follow up. However, there was a trend towards more improvement in physical quality of life for PAP adherent patients and the most obese subjects improved their physical quality of life more. The results suggest that co-morbidities of OSA such as obesity, insomnia and daytime sleepiness have a great effect on life qualities and need to be taken into account and addressed with additional interventions.

Keywords

Mental and physical health; improvement; treatment adherence; general population comparison

INTRODUCTION

Obstructive sleep apnea (OSA) is a disorder characterized by recurrent apneas and hypopneas during sleep associated with oxygen desaturation and arousals (Punjabi, 2008). OSA affects almost every system in the body, resulting in an increased incidence of hypertension, cardiovascular disease, stroke, pulmonary hypertension, cardiac arrhythmias, and systemic inflammation (McNicholas and Bonsignore, 2007). Sleep fragmentation due to OSA may also result in decreased energy, impaired cognition and altered mood (Soldatos and Paparrigopoulos, 2005) and OSA increases the risk of traffic and work accidents (Sassani et al., 2004). However, symptoms and the presence of co-morbidities vary among OSA patients (McNicholas and Bonsignore, 2007).

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

The most effective treatment of OSA is positive airway pressure (PAP), which has been shown to decrease sleepiness and improve neurocognitive function and vigilance (Gay et al., 2006). PAP treatment is mostly beneficial for patients who use PAP for at least 4 hours per night (Kohler et al., 2010). Studies have shown that untreated patients with severe OSA have reduced quality of life compared to normal controls (Bjornsdottir et al., 2012; Yang et al., 2000) and a few weeks of PAP treatment improves daytime function and quality of life (D'Ambrosio et al., 1999; Jenkinson et al., 1999; Ballester et al., 1999; Terri et al., 2012). A

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

Despite the evidence discussed above, there are few large studies with long-term follow-up periods that have assessed: 1) the difference in quality of life among OSA patients and the general population, and 2) how quality of life changes with long term PAP treatment between adherent patients and non-users. Given this, the aims of this study were two-fold. First, we compared health-related quality of life between the general population and a large group of patients with moderate to severe OSA prior to PAP treatment initiation. Second, we examined differences in the changes of quality of life after two years of PAP treatment between adherent patients and non-users.

MATERIALS AND METHODS

OSA cohort

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

General population cohort

The general population cohort was primarily invited to participate in the Burden of Obstructive Lung Diseases (BOLD) initiative; a multi-center international study aiming to estimate the burden of chronic obstructive pulmonary disorder worldwide (Buist et al., 2007). This was a random sample of Icelanders, 40 years living in the capital area of Reykjavik. Altogether 762 (404 males and 358 females) of the 939 eligible subjects (81.2%) responded. The mean age in this cohort was 57.0 ± 11.8 years and the mean BMI was 27.9 ± 4.9 kg/m².

General health questionnaire

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

Quality of life

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

Excessive daytime sleepiness

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

Symptoms of sleep disorders

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

Sleep recording in ISAC cohort

Prior to referral for PAP treatment, all OSA patients had a sleep study with an Embletta type 3 portable monitor or an Embla 12 channel system (Natus Medical Inc., Ontario, Canada) or a T3 device (Nox Medical, Reykjavik, Iceland). The same signals were recorded on all

studies; nasal airflow by cannula, oxygen saturation, heart rate, respiratory movements by respiratory inductance plethysmography (RIP) belts, body position and activity by accelerometer. Trained sleep technologists scored all sleep studies and the studies had to have 4 hours of a scorable O₂ saturation signal. Scoring of a hypopnea required a 30% decrease in airflow for 10 sec with 4% oxygen desaturation or 50% decrease in airflow for 10 sec with a sudden increase in flow at the end of the event. Scoring of an apnea required 80% decrease in flow for 10 sec. The AHI was calculated as the mean number of apneas and hypopneas per hour of recording (excluding upright time). The oxygen desaturation index (ODI) was calculated as the number of transient drops in oxygen saturation 4% per hour of recording. For further details, see our previous publications (Bjornsdottir et al., 2013; Arnardottir et al., 2013).

PAP use

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

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

Participants who used PAP for 20 days and 4 hrs/day on average for the previous four weeks based on objective data or 5 nights/week for 60% of the night by questionnaire were considered full users. PAP users not meeting criteria for full users were classified as partial users; these patients were excluded from the propensity score sample estimating the effect of PAP treatment on changes in quality of life to allow propensity score matching between the 2 primary groups of interest — full users and non-users. Non-users were defined as those who had returned their PAP device within one year of therapy initiation and did not undergo upper airway surgery and were not using mandibular device.

Statistical analyses

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

Propensity score sub-classification analyses

Sub-classification using propensity score (PS) quintiles, following an established sequential heuristic described in detail by Maislin and Rubin (2010), was used in two separate analyses: 1) to obtain a comparable sample of OSA patients and subjects from the general population with respect to relevant covariates; and 2) to minimize selection bias due to measured covariate imbalance in our non-randomized treatment group comparison between PAP adherent patients and non-users, thereby allowing for causal inference (Keenan et al., 2014). The importance of using PS and related methodologies within the context of observational studies has been highlighted by a recent working group from the National Heart, Lung and Blood Institute (Lieu et al., 2011). For further details, see supplement.

In order to obtain a comparable sample of OSA patients and subjects from the general population, we first restricted both populations to participants aged 40–75 years and with BMIs between 25–40 kg/m², based on the obvious distributional differences in age and BMI between the two samples. This restriction resulted in an initial sample of 611 (74.3%) OSA patients and 471 (61.7%) general population subjects. Within this restricted sample, we used sub-classification by PS quintiles to further match samples on relevant covariates, including age, gender, BMI, smoking status, hypertension, cardiovascular disease, and diabetes. The PS heuristic identified 494 (80.9%) OSA patients and 418 (88.7%) general population participants from this restricted sample that were included in the final PS designed sample (referred to as the ‘*OSA-general population PS Sample*’).

Within the OSA cohort only, we then used PS sub-classification to construct a sample of PAP full and non-users in which to obtain an unbiased assessment of the effect of PAP adherence on changes in quality of life. Full and non-users were balanced within subclass with respect to relevant measured covariates at baseline, including: age, gender, BMI, smoking status, hypertension, cardiovascular disease, diabetes, insomnia symptoms (early, middle and late), sleep medication use, antidepressant use, ESS, OSA severity (AHI, ODI, SaO₂ nadir, and hypoxia time [% of sleep time with SaO₂ below 90%]) and baseline levels of PCS and MCS. Of the 348 full and 214 non-users, a total of 308 (89%) and 200 (93%) were included in the PS designed sample (referred to as the ‘*PAP Treatment PS Sample*’). Comparisons of subjects included and excluded from the PS sample are presented in the online supplement.

RESULTS

Results in all subjects

Baseline characteristics in the overall sample—Overall, OSA patients were slightly younger, with a higher BMI, more daytime sleepiness, as well as a higher prevalence of hypertension, diabetes and middle insomnia when compared to subjects from the general population (Table 1). OSA subjects were also more likely to be males, have a smoking history and reported significantly lower mental and physical quality of life. Both MCS and PCS remained significantly lower among OSA patients after adjusting for age, BMI, gender, smoking and the co-morbidities listed in table 1; on average, OSA patients had PCS scores

9.48 points lower (95% CI: -10.53, -8.44; $p < 0.0001$) and MCS scores 3.35 points lower (95% CI: -4.35, -2.35; $p < 0.0001$) than the general population.

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

When examining sleep symptoms (Table 3), symptoms of initial and middle insomnia were both associated with lower MCS and PCS among general population subjects. Among OSA patients, we found no significant relationships between severity of OSA, based on AHI and ODI, and either PCS or MCS. Among OSA patients, initial insomnia was associated with lower PCS and MCS, and late insomnia was associated with lower MCS. More subjective sleepiness was associated with decreased quality of life among OSA patients; no such relationship was seen among controls. Sleep medication and antidepressant use was associated with poorer PCS and MCS in OSA subjects. These data were not available in the general population sample (Table 3).

OSA and general population cohorts: Results in the PS sample—The covariate balance achieved by applying our PS methodology to the OSA patients and general population subjects is shown in a modified version of a Love plot (Ahmed et al., 2006). Prior to implementing the PS heuristic, there were significant differences between OSA patients and controls for BMI ($p < 0.0001$), gender ($p < 0.0001$), past smoking status ($p = 0.001$), never smoker status ($p < 0.0001$), hypertension ($p < 0.0001$), diabetes ($p = 0.0001$) and cardiovascular disease ($p = 0.010$). However, after sub-classification and controlling for PS quintile, there were no differences between OSA cases and general population subjects (all $p > 0.686$). See Figure 1 in supplement.

When comparing PCS and MCS within this PS designed sample of OSA cases and general population subjects (Table 4), OSA patients had significantly lower quality of life in both measures; with a PCS score 9.5 points lower than controls ($p < 0.0001$) and an MCS score 3.0 points lower ($p < 0.0001$).

Change in quality of life among OSA patients in OSA-general population PS sample 2 years after initiating PAP treatment—When looking at OSA patients in the OSA-general population PS sample, both PCS (mean \pm SE change: 2.6 ± 0.4 ; $p < 0.0001$) and MCS (1.9 ± 0.5 ; $p < 0.001$) increased significantly two years after treatment initiation. Despite these significant increases, PCS values in OSA patients at the 2-year follow-up remained significantly lower than the values seen in the general population at baseline (mean \pm SE after 2 years: 43.9 ± 0.5 vs. 50.9 ± 0.5 , $p < 0.0001$). MCS values were borderline non-significantly lower in the OSA group after 2 years of therapy than the general population at baseline (50.3 ± 0.40 vs. 51.3 ± 0.42 , $p = 0.072$). In the current PS sample, full

PAP users had an average increase in BMI of 0.9 kg/m², compared to a non-significant increase of 0.09 kg/m² in non-users (p<0.001 comparing full vs. non-users). Within the overall observational sample, we observed a significant negative correlation ($\rho=-0.18$, p<0.0001) between BMI change and PCS change, controlling for baseline BMI and PCS; thus, patients with more weight loss had more positive PCS changes.

Positive airway pressure full vs. non-users: Results in the PAP treatment PS sample—Prior to implementing the PS heuristic, there were significant differences between full and non-users in terms of BMI (p=0.01), gender (p=0.04), hypertension (p=0.001), initial (p=0.004) and late (p=0.001) insomnia, sleep medication use (p=0.02) and all OSA severity measures (all p<0.0001). After sub-classification and controlling for PS quintile, there were no differences between full and non-users (all p>0.677). See Figure 2 in supplement.

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

Given our previously reported co-morbidity of OSA and insomnia (Bjornsdottir et al., 2012; Bjornsdottir et al., 2013), we also examined the effect of PAP treatment within strata defined by baseline subjective sleepiness or insomnia. We did not observe any significant difference in quality of life changes between PAP groups when comparing patients based on ESS at baseline. When looking within patients with and without insomnia at baseline, we observed a significant difference in PCS change between full users and PAP non-users for those who did not have initial (p=0.02), middle (p=0.01) or late (p=0.02) insomnia at baseline; full users had greater increases in PCS (Table 3 in supplement).

While we observed statistically significant results within these strata, we note that we did not observe significant interactions between PAP group and any of these cut points; thus, results should be considered suggestive and replicated within independent populations. Given the established relationship between quality of life and depression, we also examined the effect of PAP in patients stratified by antidepressant use at baseline was analyzed. We did not observe a significant interaction between PAP adherence and antidepressant medication use for either PCS (p=0.498) or MCS (p=0.327) and there were no significant differences between PAP groups in PCS or MCS change within strata (Table 4 in supplement).

DISCUSSION

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

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

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

Reduced quality of life among OSA patients

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

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

to changes in OSA severity, but rather to worsening of difficulties initiating and maintaining sleep, as well as daytime sleepiness. Akashiba et al., (2002) found that mood or depression has more effect on quality of life than OSA severity and excessive daytime sleepiness. Others have reported similar results regarding the association of depression and quality of life (Kawahara et al., 2005; Diamanti et al., 2013). Unfortunately, measures of depression were unavailable in our study, but we did ask about antidepressant use and found a strong relationship with worse quality of life. Furthermore, we controlled for insomnia symptoms in our analysis, which are highly correlated to symptoms of depression (Lustberg and Reynolds 2000).

The effect of PAP treatment

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

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

A randomized controlled study by Montserrat et al. (2001) of the effectiveness of CPAP treatment, using a sham CPAP as a placebo for the control group, found positive effects of

CPAP on daytime sleepiness and vitality. In this study, there was, however, no difference found in quality of life scores, measured by the SF-36, between those who were treated with CPAP as compared to placebo. Similar results were found in another randomized controlled trial using sham CPAP, with no significant benefits of CPAP over placebo on quality of life measured by the SF-36 (Barnes et al., 2000). Jenkinson et al (1999) did, however, find a positive effect on quality of life when comparing therapeutic CPAP to sub therapeutic CPAP in a randomized study and Ballester et al. (1999) reported similar results when comparing conservative treatment (sleep hygiene and weight loss therapy) alone to conservative treatment plus CPAP.

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

Even though quality of life is significantly improved from baseline to follow up for all OSA patients (both PAP users and nonusers) in our study, these patients still have much poorer physical health than subjects from the general population even after 2 years of therapy. OSA patients have various co-morbidities, such as obesity, high blood pressure and disturbed sleep, and these symptoms are often still apparent even though the OSA is well treated. In our observational sample, full users showed a higher increase in BMI from baseline to follow-up as compared to non-users. This increase in BMI while on PAP is likely to limit the benefit that would have occurred had patients who were adherent to PAP not gained weight. This indicates a need for more personalized medicine including broader therapeutic interventions that target co-morbidities such as obesity and sleep difficulties. In our previous study (Bjornsdottir et al., 2013) we found that symptoms of initial insomnia tend to persist in spite of successful PAP treatment. Therefore, it may well be that some of these patients have another untreated disorder and/or health condition besides OSA that impacts their quality of life. The existence of these underlying comorbidities could help explain why quality of life is still significantly impaired, despite successful PAP treatment. Long term follow up studies are needed to explore how PAP treatment affects co-morbid symptoms related to quality of life and well-being of OSA patients. Particularly, there is a need for studies on more personalized treatment interventions for these patients, for example additional interventions for those suffering from co-morbid insomnia.

The major strengths of this study include the large clinical cohort of OSA patients, the comparison with a general population cohort using propensity matching and the comparison between OSA patients with different degree of PAP use, as well as the extensive two-year follow-up with a high response rate (>90%). Furthermore, this study included detailed questionnaire assessments of co-morbid conditions as well as sleep studies in all OSA subjects. The major limitations were that we did not have measures of depression, which is an important indicator of quality of life. We did, however, control for insomnia symptoms and the use of antidepressants. Although a majority of patients (75%) using PAP had objective adherence information, a subset of patients included in this manuscript were classified based on subjective data only. As described in previous publications (Bjornsdottir et al., 2013; Arnardottir et al., 2013), our subjective criteria has high sensitivity (98.6%) and

moderate specificity (45.1%) for classifying full vs. partial users. This combination of high sensitivity and low specificity means that full users are likely to be correctly classified, but also that a proportion of patients meeting our subjective criteria of full usage are actually partial users. While not ideal, the misclassification of partial users as full users in this minority of patients is expected to bias us towards the null, i.e., against observing a strong PAP effect. Moreover, we observed no significant changes in our estimates or results when restricting to only the subset of PAP users that had objective data. Furthermore, we did not have short-term follow-up results to evaluate the acute effects of PAP treatment on mental and physical health and we used the SF-12 to measure quality of life whereas using SF-36 could have potentially provided better discrimination. PS methodologies create balance with respect to measured covariates included in the matching, however, we cannot rule out the potential for unknown or unrecognized confounding. Moreover, we note that in order to obtain a well-matched sample of OSA patients and general population subjects, we necessarily excluded patients with higher obesity and the most co-morbidities, while simultaneously including less healthy and more obese general population subjects. While this restriction may reduce the scope of our inference, we note that our sample is more inclusive of “real-world” patients than typical randomized trials. Finally, while we recognize that there is likely a subset of the general population with undiagnosed OSA, including these patients as controls is expected to bias our results towards the null, suggesting that the significant differences observed in this study may be even greater.

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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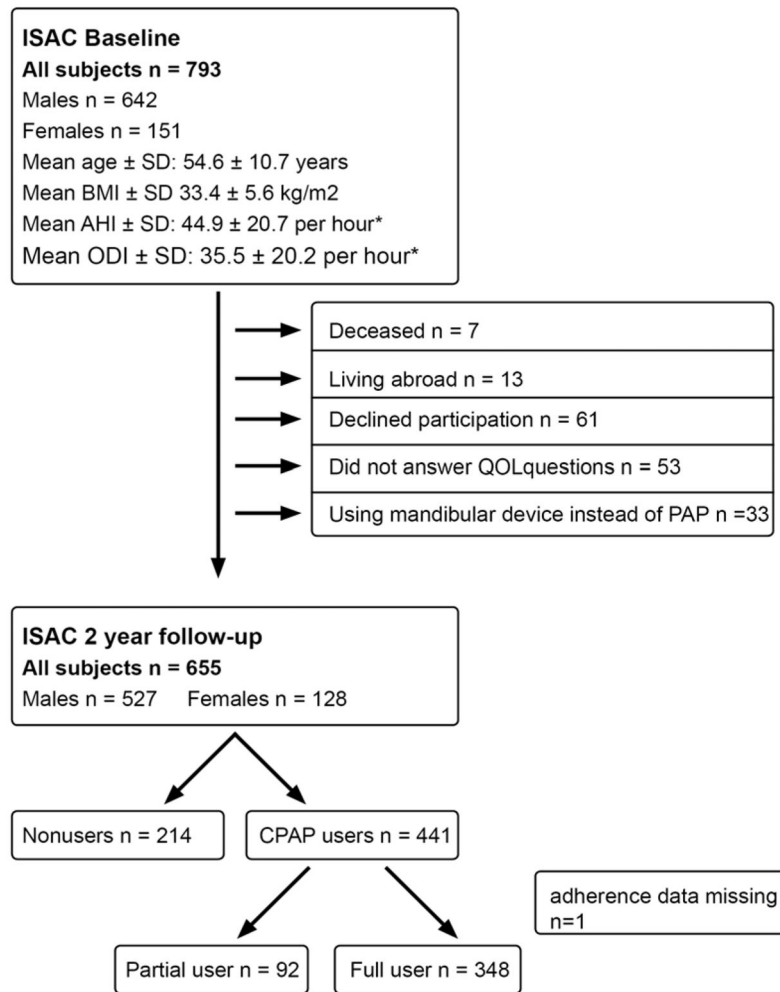


Figure 1.
Flow chart of the study population

Table 1

Baseline characteristics of all OSA patients and the general population cohort

	General population (n=762)	OSA (n=793)	P
Age (years)	57.0 ± 11.8	54.6 ± 10.7	<0.0001
BMI (kg/m ²)	27.9 ± 4.9	33.4 ± 5.6	<0.0001
Male (%)	53.0	81.0	<0.0001
Smoking history			<0.0001
Never smoker (%)	39.2	27.3	
Previous smoker (%)	42.6	51.0	
Current smoker (%)	18.2	21.7	
Hypertension (%)	25.1	45.3	<0.0001
Cardiovascular disease (%)	15.1	18.4	0.0781
Diabetes (%)	2.9	8.7	<0.0001
Epworth Sleepiness Scale (ESS)	6.0 ± 3.9	11.7 ± 5.1	<0.0001
Early insomnia (%)	14.1	15.3	0.5200
Middle insomnia (%)	17.3	34.8	<0.0001
Late insomnia (%)	—	27.9	—
Mental quality of life (MCS)	51.4 ± 4.7	48.3 ± 10.9	<0.0001
Physical quality of life (PCS)	50.9 ± 7.8	40.3 ± 10.9	<0.0001

Values are given as mean ± standard deviation for continuous variables and percentages for nominal variables. Abbreviations: BMI, body mass index.

Table 2

Independent association with physical (PCS) and mental (MCS) component scores in the general population cohort and OSA patients.

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

Values are given as adjusted beta-values (95% CI); estimates are adjusted for all other variables in the table.

Table 3

Independent associations of sleep symptoms with physical (PCS) and mental (MCS) component scores in general population subjects and OSA patients.

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

Values are given as adjusted beta-values (95% CI). The beta estimates are adjusted for all variables in the table and for gender, age and BMI.

Table 4Comparison of baseline quality of life measures in the *OSA-general population propensity score sample*

	LS Mean \pm SE		Difference (95% CI)	p*
	OSA patients	General population		
Physical Quality of Life	41.4 \pm 0.45	50.9 \pm 0.48	-9.48 (-10.81, -8.14)	<0.0001
Mental Quality of Life	48.3 \pm 0.40	51.3 \pm 0.43	-2.95 (-4.15, -1.75)	<0.0001

* p-value adjusted for propensity score subclass

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Table 5Comparison of Change in Quality of Life in PAP Treatment *propensity score* sample

	BMI Group ^{*,†}	<i>LS Mean±SE Change</i>		<i>p</i> [‡]
		<i>Adherent</i>	<i>Non-Users</i>	
Physical Quality of Life	<i>Overall</i>	3.42 ± 0.53 [§]	1.79 ± 0.66 [§]	0.0631
	<30	2.91 ± 0.97 [§]	1.73 ± 1.15	0.4511
	30–35	2.50 ± 0.89 [§]	2.49 ± 1.08 [§]	0.9959
	35	4.64 ± 0.88[§]	1.05 ± 1.22	0.0216
Mental Quality of Life	<i>Overall</i>	2.13 ± 0.54 [§]	2.35 ± 0.68 [§]	0.7988
	<30	2.60 ± 0.97 [§]	4.06 ± 1.15 [§]	0.3525
	30–35	0.98 ± 0.96	1.32 ± 1.17	0.8313
	35	2.80 ± 0.88 [§]	1.96 ± 1.22	0.5892

[‡] p-value from ANCOVA model, adjusted for PS subclass and baseline PCS or MCS;

[§] within group estimate of quality of life change significantly (p<0.05) different from zero;

** p-value for PAP x BMI group interaction: 0.5266 for PCS and 0.4579 for MCS