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Nocturnal sweating—a common symptom of obstructive sleep apnoea: the Icelandic sleep apnoea cohort

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ABSTRACT

Objectives: To estimate the prevalence and characteristics of frequent nocturnal sweating in obstructive sleep apnoea (OSA) patients compared with the general population and evaluate the possible changes with positive airway pressure (PAP) treatment. Nocturnal sweating can be very bothersome to the patient and bed partner.

Design: Case–control and longitudinal cohort study.

Setting: Landspitali—The National University Hospital, Iceland.

Participants: The Icelandic Sleep Apnea Cohort consisted of 822 untreated patients with OSA, referred for treatment with PAP. Of these, 700 patients were also assessed at a 2-year follow-up. The control group consisted of 703 randomly selected subjects from the general population.

Intervention: PAP therapy in the OSA cohort.

Main outcome measures: Subjective reporting of nocturnal sweating on a frequency scale of 1–5: (1) never or very seldom, (2) less than once a week, (3) once to twice a week, (4) 3–5 times a week and (5) every night or almost every night. Full PAP treatment was defined objectively as the use for ≥4 h/day and ≥5 days/week.

Results: Frequent nocturnal sweating (≥3× a week) was reported by 30.6% of male and 33.3% of female OSA patients compared with 9.3% of men and 12.4% of women in the general population ($p<0.001$). This difference remained significant after adjustment for demographic factors. Nocturnal sweating was related to younger age, cardiovascular disease, hypertension, sleepiness and insomnia symptoms. The prevalence of frequent nocturnal sweating decreased with full PAP treatment (from 33.2% to 11.5%, $p<0.003$ compared with the change in non-users).

Conclusions: The prevalence of frequent nocturnal sweating was threefold higher in untreated OSA patients than in the general population and decreased to general population levels with successful PAP therapy. Practitioners should consider the possibility of OSA in their patients who complain of nocturnal sweating.

ARTICLE SUMMARY

Article focus

- Previous studies have suggested a possible relationship between obstructive sleep apnoea and frequent nocturnal sweating. However until now, studies comparing the prevalence of frequent nocturnal sweating in untreated sleep apnoea patients compared with the general population as well as changes with sleep apnoea treatment have been lacking. Our study focuses on the role of nocturnal sweating in sleep apnoea.

Key messages

- Our study indicates a possible role of frequent nocturnal sweating as a marker for untreated sleep apnoea. One-third of adults with sleep apnoea experience this symptom and they are three times more likely to report it compared with adults in the general population. The symptom is responsive to treatment in the majority of sleep apnoea patients.
- Clinicians should include sleep apnoea in the differential diagnosis of patients presenting with a complaint of nocturnal sweating and further investigate that possibility.

Strengths and limitations of this study

- The strengths of this study include the detailed assessment of a large number of sleep apnea patients studied with a two year follow-up and the comparison with a general population cohort.
- Our study was an observational study, not a randomised controlled trial, which may be considered a limitation. Other limitations include the use of subjective measures of sweating and the smaller number of women with sleep apnea than men, due to lower prevalence.

INTRODUCTION

Nocturnal sweating is a symptom commonly encountered in clinical medicine (reviewed by[1]), but has only been evaluated to a limited

degree. Nocturnal sweating can be very bothersome to the patient and the bed partner, often causing the drenching of bed clothes, and is associated with a reduced quality of life.[2–4] However, only a minority of patients report this symptom to their physician.[3 4] The possible causes of nocturnal sweating include, but are not limited to, malignancy, infections, endocrine and neurological disorders, menopause, gastroesophageal reflux (GER), medications (mainly antidepressants and antipyretics), substance abuse, panic attacks as well as sleep disorders, such as obstructive sleep apnoea (OSA) and insomnia (refs. [4–6] and reviewed by the authors of refs. [1 7–9]). Other causes can be as simple as an overheated room or too thick bed clothes (reviewed by Smetana[1]). Nocturnal sweating has been associated with increased daytime tiredness and sleep problems in a general population cohort[3 4] as well as in patients referred to a sleep laboratory.[10] A recent review article by Mold *et al*[9] stated that much is still unknown about the causes, evaluation and management of nocturnal sweating.

OSA is characterised by the repetitive closure of the pharyngeal airway during sleep that is associated with oxygen desaturations and/or arousals. Patients with OSA have disturbed sleep and excessive daytime sleepiness.[11] It has been reported that half of OSA patients report nocturnal sweating, usually around the neck and upper body area.[12] A recently published study of 98 men with untreated OSA found that 34% reported nocturnal sweating which was reduced to 12% with positive airway pressure (PAP) treatment.[13] Those OSA patients who still reported sweating on PAP treatment were younger and had higher OSA severity. However, in another study, sweating complaints were not related to the OSA severity.[10] A study by our group[14] found that untreated OSA patients with a higher electrodermal activity index, an objective measurement of sweating, could reliably estimate the self-report of sweating. These patients also had higher blood pressure and both sweating and blood pressure decreased objectively with PAP treatment.[14] However, larger studies comparing the prevalence of nocturnal sweating in OSA patients before and after treatment, as well as comparisons with randomly selected subjects from the general population, are needed to confirm the association between nocturnal sweating and OSA.

The aim of this study was to evaluate the prevalence and characteristics of nocturnal sweating in patients diagnosed with OSA, both before and following PAP treatment, compared with the general population. The primary a priori hypothesis for this study was that OSA patients have an increased prevalence of nocturnal sweating that normalises with PAP treatment.

MATERIAL AND METHODS

OSA cohort

All patients with moderate-to-severe OSA (apnoea hypopnoea index (AHI)≥15 events/h) who were referred to the Pulmonary Department, Landspitali—The National University Hospital of Iceland for treatment with PAP from September 2005 to December 2009, were invited to participate in the Icelandic Sleep Apnea Cohort (ISAC) study,[15–17] also referred to hereafter as the OSA cohort. No other inclusion or exclusion criteria were used. Briefly, over 90% of eligible and approached patients agreed to participate in the study, a total of 826 patients. Four patients withdrew from the study, leaving 822 in the baseline cohort (666 men and 156 women). The patients in ISAC were also invited to a 2-year follow-up visit, performed in the same manner as the initial visit. This follow-up was completed in 741 (90.1%) patients from October 2007 to January 2012.

General population cohort

The general population cohort was primarily invited to participate in the Burden of Obstructive Lung Diseases initiative in Iceland; a multicentre international study aiming to estimate the burden of chronic obstructive pulmonary disorder worldwide.[18]

The general population sample was a random sample of Icelandic citizens, ≥40 years of age living in the capital area of Reykjavik.[15 19–21] At the end of November 2004, of the 73 391 subjects ≥ 40 years of age living in the area, 939 subjects were randomly selected to participate (for details, see ref. 19). Altogether, 762 of the 939 eligible subjects (81.2%) responded. No significant differences were found with regard to age or smoking status between responders and non-responders in this cohort. However, there was a significant difference in gender with proportionally more men participating ($p<0.01$).

Questionnaires and measurements

The OSA patient cohort and the general population subjects were evaluated at the outpatient clinic of the Pulmonary Department, Landspitali—The National University Hospital of Iceland. They answered the same core questionnaire on general health status, current smoking (smoking or tobacco use during the past month) and whether they had hypertension and/or diabetes (doctor diagnosis and medication), cardiovascular disease (CVD) which was defined as a doctor diagnosis of coronary artery occlusion (myocardial infarction or heart attack), heart failure and/or stroke. Participants in both studies listed their medication use for hypertension and diabetes (pharmacological treatment was coded according to the Anatomical Therapeutic Chemical drug classification system http://www.whocc.no/atcddd), but participants in ISAC also gave a detailed list of all other medications they used. The Basic Nordic Sleep Questionnaire[22] was administered to all participants (includes questions on sleep quality, insomnia symptoms, snoring, nocturnal sweating and GER). The response alternatives for those questions were on a frequency scale of 1–5: (1) never or very seldom, (2) less than once a week, (3) once to twice a week, (4) 3–5 times a week and (5) every day or almost every day of the week. Frequent nocturnal sweating was defined as a score of 4 or 5 for the following question "I perspire heavily

during the night", that is, reporting nocturnal sweating ≥3× week. Insomnia symptoms were defined as difficulties initiating sleep or maintaining sleep ≥3× week.[15] Daytime and nocturnal GER symptoms were defined, respectively, as reporting heartburn during the daytime and after going to bed ≥1× week.[23 24] Other questionnaires included the Epworth Sleepiness Scale,[25] a 12-item Short-Form Health Survey (SF-12) for physical and mental quality of life[26] and questions on symptoms of restless legs syndrome (RLS) based on recommendations from the International Restless Legs Syndrome Study Group[27] (same definition as in our previous paper[21]). Additionally, we defined subjects in the general population as high or low risk for OSA based on the Multivariable Apnea Prediction (MAP) index.[28] The MAP score is based on a self-reported frequency of occurrence of apnoea symptoms (snoring or gasping, breathing stops, choking or struggling for breath during the night) as well as body mass index (BMI), age and gender. The MAP index ranges from 0 to 1 where subjects with a score of 0 are least likely to have OSA. A MAP index cut-off of 0.75 was used to define high risk OSA similar to our previous publication.[15] All questionnaires were translated from English into Icelandic and back-translated to assure accuracy. Height and weight were measured in the same manner for all participants. Participants were asked to remove their shoes and heavy outer garments for the measurements.

The consent of the National Bioethics Committee and the Data Protection Authority of Iceland as well as the Institutional Review Board of the University of Pennsylvania was granted for both studies and written consent obtained from the research participants.

Sleep recording in ISAC cohort

Prior to referral for PAP treatment, all ISAC patients had a type 3 sleep study with an Embletta type 3 portable monitor, an Embla 12 channel system (Natus Medical Inc, Ontario, Canada) or a T3 device (Nox Medical, Reykjavik, Iceland). The same signals were recorded in all studies. To test for systematic differences in the measurement of OSA severity by Embletta versus T3, 13 patients slept with both devices simultaneously during their laboratory diagnostic OSA study. Their AHI ranged from 0 to 58 events/h. The intraclass correlation coefficient for AHI was 0.99 ($p<0.001$) and for oxygen desaturation index (ODI) 0.97 ($p<0.001$) between the devices, showing no significant differences in the measured OSA severity.

All sleep studies were scored by trained sleep technologists based on the following criteria: studies had to have ≥4 h of a scorable O_2 saturation signal. A total of 15 sleep studies did not meet this criterion and were excluded from all analysis of OSA severity. The apnoea–hypopnoea index was calculated as the mean number of apnoeas and hypopnoeas/h of recording (excluding upright time). The ODI was calculated as the number of drops in oxygen of ≥4%/h of recording (for a more detailed methodology, see refs.[16] and [17]).

PAP use

All PAP treatments in Iceland are administered by the Department of Respiratory Medicine and Sleep at Landspitali—The National University Hospital of Iceland, the sole provider of ventilator treatment in Iceland. All patients with OSA were treated with autoPAP or continuous PAP (CPAP) units (ResMed Corp., San Diego, California, USA) and treatment was only changed to bilevel PAP (BiPAP) or adaptive servoventilation if treatment efficacy on autoPAP or CPAP was inadequate (defined by AHI≥15 using PAP and/or persistent patient complaints or based on clinical judgement). In those patients on ResMed S8 machines, PAP adherence at follow-up was objectively measured by downloading the mask on-time stored by the PAP unit in the previous 4 weeks (available for 357 of 469 PAP users). Patients recruited at the beginning of the study period had older models of PAP devices which did not provide this type of information. Self-report data from all patients were also collected at the follow-up visit, based on three multiple-choice questions about average PAP use: (1) Do you use PAP for your sleep apnoea? (Yes, no or do not know), (2) How many nights per week do you use PAP? (Response alternatives: 1, 2, 3, 4, 5, 6 or 7 nights/week), (3) How much of the sleeping time each night do you use PAP? (Response alternatives: all the sleeping time (100%); almost all the sleeping time (80–99%); most of the sleeping time (60–79%); about half of the sleeping time (40–59%); about one-third of the sleeping time (20–39%); almost none of the sleeping time (1–19%); none of the sleeping time (0%); do not know).

Statistical analysis

For bivariate analysis, the χ^2 and t tests were used for nominal and continuous variables, respectively, whereas logistic regression was used for multivariable analyses and assessment of adjusted OR with 95% CI. The significance of change in the prevalence of symptoms with PAP treatment was assessed using population-averaged generalised estimating equations for a binomial outcome. The Wald test was used to examine the differences in the change of prevalence by the level of PAP use. A p value of ≤0.05 was determined as statistically significant. Means are given as ±SD unless otherwise indicated. STATA V.11.0 was used for all statistical analyses. Statistical analysis using the original five-point scale for nocturnal sweating frequency showed the same findings as using the binomial distribution for frequent sweating of ≥3× week (data not shown).

RESULTS

Characteristics of the study population

The characteristics of the study cohorts are shown in table 1. The baseline OSA cohort included 822 patients, n=666 men and n=156 women with an age range 21–83 years. The general population cohort included in the analysis was 703, of whom 374 were men and 329 women (see figure 1 for exclusion criteria).

Table 1 Characteristics of the males and females in the general population and OSA cohorts

	Males			Females		
	General population (n=374)	OSA cohort (n=666)	p Value	General population (n=329)	OSA cohort (n=156)	p Value
Age (years)	55.9±10.6	53.6±10.7	*0.0008*	56.9±11.6	58.4±9.1	0.16
BMI (kg/m^2)	28.4±4.3	33.4±5.6	*<0.0001*	27.6±5.3	34.1±6.2	*<0.0001*
Epworth sleepiness scale	6.4±3.9	11.8±5.0	*<0.0001*	5.7±4.0	11.2±5.3	*<0.0001*
Current smokers (%)	15.6	21.6	*0.02*	20.7	19.2	0.71
Hypertension (%)	21.6	44.5	*<0.0001*	28.1	50.6	*<0.0001*
CVD (%)	14.7	20.0	*0.03*	14.0	11.6	0.47
Diabetes (%)	2.7	8.8	*<0.0001*	3.1	8.4	*0.01*

Significant findings (p<0.05) are shown in italics.
BMI, body mass index; CVD, cardiovascular disease, defined as a doctor diagnosis of coronary artery occlusion (myocardial infarction or heart attack), heart failure and/or stroke. Hypertension and diabetes were defined as a doctor diagnosis and treatment with medication.

Patients in the OSA cohort had a higher BMI on average than the general population subjects (see table 1), but the range was similar (ISAC: 20.1–58.6 kg/m^2, controls: 20–55 kg/m^2). Patients in the OSA cohort had a higher prevalence of treated hypertension and diabetes than subjects from the general population (table 1) and reported more sleepiness on the Epworth Sleepiness Scale. Additionally, men in the OSA cohort were 2 years younger on average, more likely to be current smokers and have a diagnosis of CVD than the men from the general population. These differences were not found in women.

Prevalence and characteristics of nocturnal sweating

Frequent nocturnal sweating (≥3 × a week) was reported by 30.6% of men in the OSA cohort, while men in the general population had a prevalence of 9.6% (p<0.0001). A total of 33% of women in the OSA cohort had frequent nocturnal sweating compared with 12.8% of women in the general population (p<0.0001). Hence, the OSA cohort had a threefold higher prevalence of frequent nocturnal sweating than the general population cohort (figure 2). Patients in the OSA cohort had a higher prevalence of frequent nocturnal sweating within all comparable gender and age groups (40–49, 50–59, 60–69 and ≥70 years) except in women ≥70 years, likely due to power issues (n=20 OSA women and n=55 general population women; see figure 2). The distribution of sweating on the original five-point scale was also much more skewed to the left in the general population than in the untreated OSA cohort, where more subjects report some degree of nocturnal sweating (see figure 3).

The demographic characteristics of subjects with and without frequent nocturnal sweating are shown in table 2

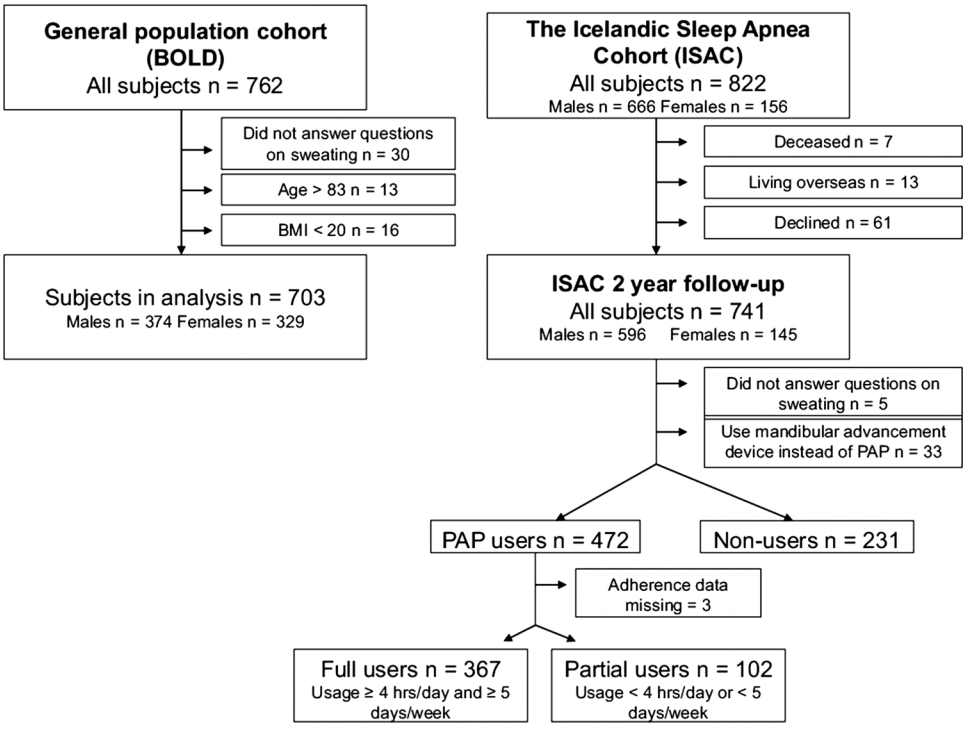

Figure 1 The study cohorts.

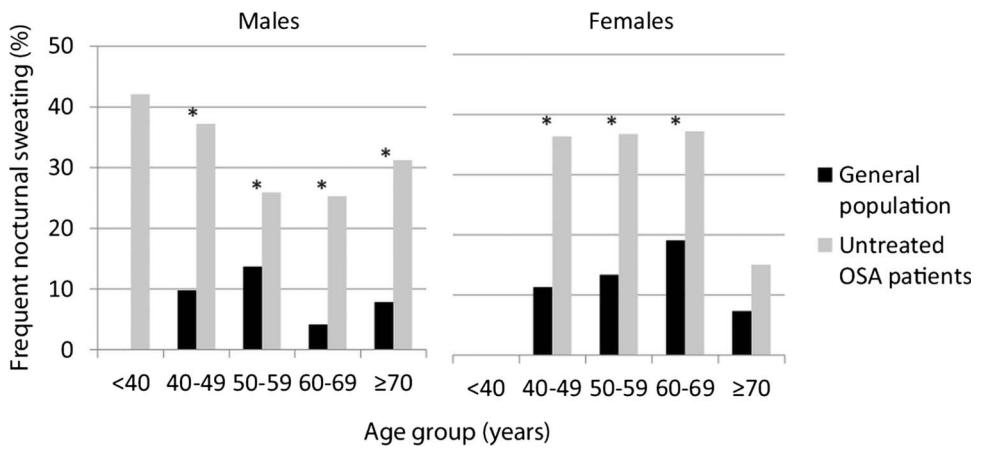

Figure 2 The prevalence of frequent nocturnal sweating (≥3× week) for subjects in the general population and the untreated obstructive sleep apnoea (OSA) patient cohort, divided by gender and age groups. Significant differences (p<0.05) are shown by an asterisk (*).

(univariate analysis). Younger age was significantly related to nocturnal sweating among OSA patients (p=0.003), but not in the general population (p=0.44). Only in the general population cohort, subjects with medically treated diabetes (n=20) were more likely to report frequent nocturnal sweating (p<0.05). No relationship was found with gender, current smoking, diagnosed hypertension or CVD in either cohort in unadjusted analyses (data not shown). However, those reporting frequent nocturnal sweating reported lower mental and physical quality of life, both the general population and the OSA cohort (table 2).

To understand better which factors were associated with frequent nocturnal sweating after adjustment for other covariates, a multilogistic regression model was created. OSA patients and general population subjects were assessed separately. Variables tested in the model were gender, age, BMI, current smoking, diagnosed hypertension, CVD and diabetes. For both cohorts, lower age was a significant predictor of nocturnal sweating (see online supplementary Table S1). For the general population subjects only, diagnosed CVD was an additional significant factor, and for the OSA cohort only, hypertension was an additional significant factor. The effect of β-blockers and calcium-channel blockers was tested specifically by multivariate analysis and was not significantly related to frequent nocturnal sweating (data not shown). The role of antidepressants was tested for the OSA cohort only (data not available in the general population cohort). The use of antidepressants was significantly associated with frequent nocturnal sweating, but did not change the significance of other findings within the OSA cohort.

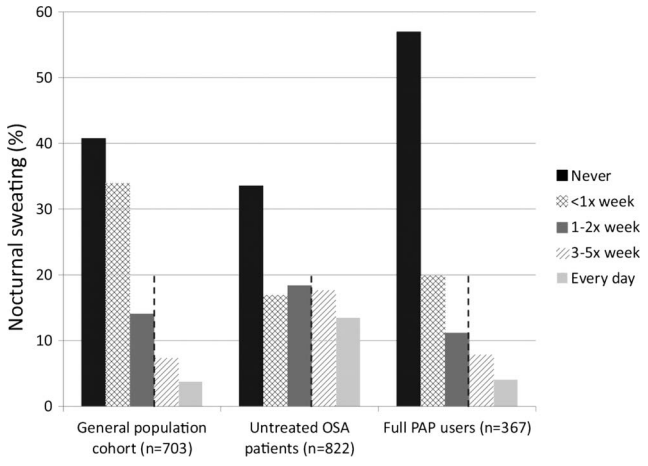

Figure 3 The distribution of reported nocturnal sweating (%) on a 1–5 frequency scale for the general population and untreated obstructive sleep apnoea (OSA) cohort. Additionally, the full positive airway pressure (PAP) users at the 2-year follow-up in the OSA cohort are shown. Subjects with frequent nocturnal sweating were defined by a prevalence ≥3× a week, as shown by the broken line.

When we combined both cohorts into one analysis and adjusted for demographic factors, being a part of the OSA cohort was still significantly related to higher prevalence of nocturnal sweating, with an OR of 3.11 (95% CI 2.25 to 4.30). No interaction with gender was found for any of the tested demographic variables, neither within the OSA cohort, general population cohort or all subjects combined. Decreased mental and physical quality of life remained significantly lower in those reporting frequent nocturnal sweating after adjustment for demographic factors, both in the OSA and general population cohorts (p<0.01).

Symptoms related to nocturnal sweating

Many sleep and respiratory symptoms were significantly related to nocturnal sweating in univariate analysis (table 2). After adjustment for demographic factors, in both the OSA cohort and the general population cohort, nocturnal sweating was associated with insomnia symptoms, excessive daytime sleepiness and RLS symptoms (see online supplementary Table S2). However, only participants in the OSA cohort showed a

Table 2 Characteristics of those reporting frequent nocturnal sweating (≥3× week) versus those reporting less frequent sweating (≤2× week) in the general population and OSA cohorts

	General population cohort			OSA cohort		
	Frequent sweating (n=78)	Seldom sweating (n=625)	p Value	Frequent sweating (n=256)	Seldom sweating (n=566)	p Value
Age (years)	55.5±9.9	56.5±11.2	0.44	52.8±10.9	55.2±10.4	*0.003*
BMI (kg/m^2)	28.9±4.8	27.9±4.8	0.09	34.0±4.9	33.3±6.0	0.08
Diabetes (%)	6.4	2.4	*0.046*	7.1	9.4	0.27
Physical quality of life (SF-12)	48.1±9.1	51.4±7.5	*0.0004*	37.6±10.4	41.5±10.8	*<0.0001*
Mental quality of life (SF-12)	49.9±5.5	51.6±4.6	*0.003*	45.9±11.8	49.4±10.3	*<0.0001*
Snoring ≥3 days/week (%)	39.0	24.6	*0.02*	98.0	94.2	*0.02*
Difficulties initiating sleep ≥3× week (%)	37.3	11.1	*<0.0001*	21.1	13.1	*0.003*
Difficulties maintaining sleep ≥3× week (%)	52.0	29.0	*<0.0001*	68.4	53.7	*<0.0001*
Epworth sleepiness scale	6.6±4.3	6.0±3.9	0.16	12.5±5.0	11.3±5.1	*0.002*
Feeling sleepy or drowsy 6–7× week (%)	16.7	7.2	*0.004*	78.8	60.1	*<0.0001*
Restless legs syndrome symptoms (%)	31.2	17.2	*0.003*	43.4	33.8	*0.009*
Nocturnal GER symptoms ≥1× week	9.0	5.5	0.22	21.9	10.5	*<0.0001*
Daytime GER symptoms ≥1× week	5.8	4.3	0.58	34.5	21.3	*<0.0001*

Significant findings (p<0.05) are shown in italics.
BMI, body mass index; GER, gastroesophageal reflux; OSA, obstructive sleep apnoea. Diabetes was defined as a doctor diagnosis and treatment with medication.

relationship between daytime and nocturnal GER and nocturnal sweating. Subjects in the general population reporting frequent nocturnal sweating were more likely to report snoring. Also those with an increased risk of OSA as calculated by the MAP score (n=46, 6.5%) were borderline twice as likely to report frequent nocturnal sweating (adjusted OR 2.08, 95% CI 0.94 to 4.59).

Fully adjusted models taking into account the effect of other sleep and respiratory complaints were also performed. Difficulty initiating sleep was most strongly related to nocturnal sweating in the general population (OR 4.05, 95% CI 1.72 to 9.54). For the OSA patients, however, difficulties maintaining sleep, daytime sleepiness and GER symptoms were most strongly associated with frequent nocturnal sweating (see online supplementary Table S2). Additional adjustment for antidepressant use in the OSA cohort did not affect the findings for the role of sleep or respiratory complaints.

No association was found between frequent nocturnal sweating and sleep apnoea severity in the OSA group on continuous or categorical comparison with AHI and ODI (categories: <20, 20–40, 40–60 and >60 events/h.).

Two year ISAC follow-up

A total of 741 (90.1%) participants in the OSA cohort returned for a 2-year follow-up visit after starting PAP treatment. No significant differences were found in age, BMI, OSA severity (as assessed by AHI or ODI) or gender between non-responders (n=81) and responders (n=741). At follow-up, five patients did not complete the questions on nocturnal sweating, 33 patients were using a mandibular advancement device instead of PAP and 3 had missing adherence data on PAP, leaving 700 patients in follow-up analysis of whom 469 were PAP users and 231 non-users (figure 1).

PAP usage

At the 2-year follow-up, objective PAP data were available for 357 of 469 PAP users (76.1%) with average (±SD) PAP use per day for the last 4 weeks of 6.2 (±1.9) hours. Of the PAP users, 53% were on autoPAP, 43% on CPAP, 3% on BiPAP and 1% on adaptive servoventilation. Participants with objective data, who used PAP for ≥20 days and ≥4 h/day on average for the previous 4 weeks, were considered full users (n=285 of 357 with objective data). Full users used their device on average 26.7±2.0 days in the previous 4 weeks and 6.8±1.2 h/day. Patients with objective PAP data who did not fulfil objective criteria for full users were classified as partial users (n=72). On average, partial users used their device for 14.5±7.1 days in the previous 4 weeks and 3.6±2.1 h/day based on objective data. Non-users were defined as those who had returned their PAP device, had no objective use in the last 4 weeks or reported no current use of PAP.

In those OSA patients for whom objective PAP data were not available (n=112), the self-reported data were used to define patients as full or partial PAP users. To validate this approach, among the 355 patients with both objective (memory cards) and self-reported data on frequency of PAP use, we compared the cut-off for objective full use (≥20 days and ≥4 h/day) versus partial use to a comparable subjective cut-off for full use (≥5 nights/week and ≥60% of the sleeping time) versus partial use. Self-report had 98.6% sensitivity and 45.1% specificity in distinguishing full versus partial users.

Table 3 Frequent nocturnal sweating at 2-year follow-up for the different PAP adherence groups in the OSA cohort

Frequent nocturnal sweating (≥3× week)	Baseline (%)	Follow-up (%)	p_{change}	p compared with non-PAP use
Non-users (n=231)	31.6	20.4	*<0.001*	–
Partial PAP users (n=102)	31.4	26.5	0.33	0.28
Full PAP users (n=367)	33.5	12.0	*<0.001*	*0.01*

Significant findings (p<0.05) are shown in italics.
OSA, obstructive sleep apnoea; PAP, positive airway pressure treatment.

Primary data analysis did not exclude patients with self-report PAP data only and patients on BiPAP or adaptive servoventilation (n=125). However, similar findings were obtained when these patients were excluded from follow-up analysis.

Non-users

Among the non-PAP users (n=231) in the OSA cohort, 56.7% (n=129) had a repeat sleep study when followed after 2 years. On average, the AHI increased from 37.8 ±15.0 events/h at baseline to 48.4±18.6 events/h at follow-up, p<0.0001 and there was no weight change on average. Altogether, 98% of the 129 patients still had AHI ≥15 events/h at the 2-year follow-up. A total of 17 non-users underwent upper airway surgery on the uvula and/or soft palate between baseline and follow-up and 13 patients had >10% weight loss. Of these, 18 patients had a repeat sleep study at follow-up. No significant change was found in their AHI between baseline and follow-up on average and all patients still had AHI ≥15 despite their alternative treatment for OSA. Primary data analysis did not exclude these patients from the non-user group. However, similar findings were obtained when these patients were excluded from follow-up analysis (n=30).

Change in nocturnal sweating with treatment

The change in the prevalence of frequent nocturnal sweating with PAP treatment in the OSA cohort was tested by comparing full PAP users, partial PAP users and non-users. A significant decrease in the prevalence of frequent nocturnal sweating was found in the full PAP users as well as non-users at the 2-year follow-up (p<0.001), but no significant change was found in partial PAP users. The full PAP users had a significantly greater decrease in frequent nocturnal sweating than non-users (33.5% to 12% vs 31.6% to 20.4%, p=0.01; table 3). A borderline significant but small linear correlation was found between decreased sweating at follow-up and higher average daily use of PAP (r=−0.09, p=0.08) in the 357 patients with objective data. Therefore, while full PAP users were more likely to have a decrease in nocturnal sweating than partial users, this effect was not strongly linear.

The distribution of nocturnal sweating on the 1–5 frequency scale for full PAP users was similar to the distribution of the general population (figure 3). Non-users and partial PAP users were also more likely than full PAP users to report the continuation or development of frequent sweating (≥3× week) at follow-up (p<0.01, figure 4). However, frequent nocturnal sweating at baseline did not predict whether a participant with OSA became a full PAP user, partial PAP user or non-user as all groups had similar prevalence of sweating at baseline.

Patients with decreased sweating had less development and persistence of difficulties maintaining sleep ≥3× week compared with those with persistent sweating. This was found both for full PAP users and non-users (p<0.01 for both groups), but no difference was found for

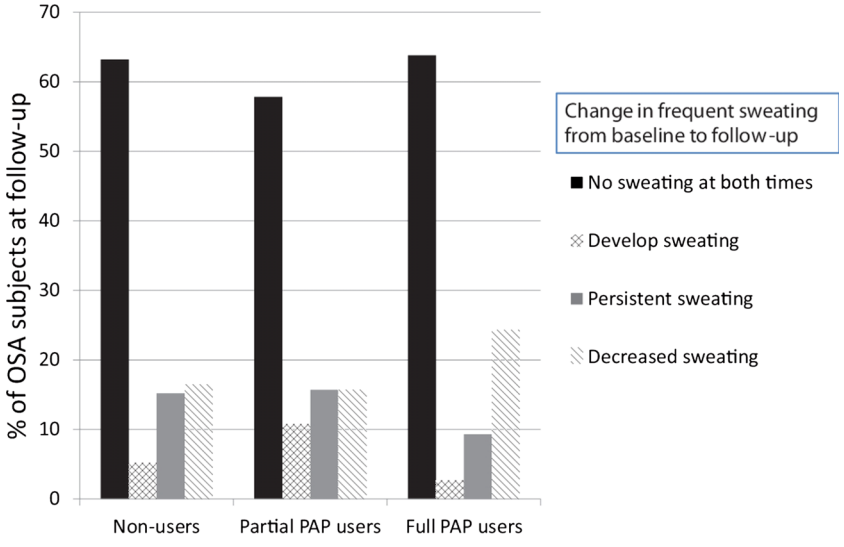

Figure 4 The percentage of obstructive sleep apnoea (OSA) patients who reported no frequent sweating (≥3× week) at both baseline and follow-up, those who developed sweating and had persistent sweating between baseline and follow-up, as well as those with decreased sweating (≤2× a week). The results are shown separately for non-users, partial positive airway pressure (PAP) users and full PAP users. The change in reported frequent nocturnal sweating was significantly different between the three PAP groups (p<0.001).

partial PAP users. Similarly, full PAP users that developed frequent nocturnal sweating at follow-up had more difficulties maintaining sleep (p=0.003) than patients with no frequent sweating at both baseline and follow-up.

Only in non-users, patients with decreased sweating also had decreased daytime sleepiness as assessed by the Epworth Sleepiness Scale compared with those with persistent frequent sweating (decrease by −3.5±4.4 vs, −0.6±4.1 points, p=0.006). Also, full PAP users were more likely to remain feeling sleepy/drowsy (p=0.003) at follow-up if they developed frequent sweating, comparing to patients with no frequent sweating.

No significant changes were found in reported difficulties initiating sleep, GER symptoms or RLS symptoms. No significant changes were found in mental or physical quality of life for any of the PAP groups. No significant differences were found in the prevalence or change in antidepressant use between full PAP users, partial users or nonusers, indicating that this did not affect the changes in nocturnal sweating found with PAP treatment.

DISCUSSION

The prevalence of frequent nocturnal sweating was threefold higher in untreated OSA patients than in the general population and decreased to general population levels with successful PAP therapy. Nocturnal sweating was more common among younger subjects. Subjects with nocturnal sweating had an increased prevalence of other sleep complaints, specifically, daytime sleepiness and symptoms of insomnia. In the general population, nocturnal sweating may be a marker of increased risk of OSA as well as presence of insomnia.

The strengths of this study include the large number of OSA patients studied and the comparison with a general population cohort, as well as the extensive 2-year follow-up of the ISAC cohort. This study included detailed questionnaire assessments as well as anthropometric measurements and sleep studies in all the OSA patients. Our study was an observational study, not a randomised controlled trial (RCT), which may be considered a limitation. However, an RCT study with such long-term follow-up of untreated symptomatic OSA patients would be difficult to perform due to a lack of clinical equipoise for PAP treatment. Other weaknesses include the use of subjective measures of sweating. The authors, however, recently conducted a study showing that objective measurements of sweating (electrodermal activity) during sleep in patients with OSA decreases with PAP treatment, albeit in a smaller sample than that reported here. Also, a significant correlation was found between reported frequency of nocturnal sweating by the same questions and scale as we used in the present study and the measured objective sweating in untreated OSA patients (r=0.61, p=0.01).[14] The OSA patients in the current study were more obese and had a higher prevalence of hypertension, CVD and diabetes than the subjects from the general population. Therefore, we adjusted for these comorbidities as covariates. Also, the number of women was substantially lower in the OSA cohort, a consequence of patients in Iceland in whom OSA has been diagnosed and the lower prevalence of OSA in women than men.[29 30] However, no gender differences were found in the prevalence of sweating and no statistical interactions were found between gender and the other tested variables related to nocturnal sweating (see online supplementary Tables S1 and S2). Also, a sleep study was not performed in the general population cohort. Therefore, we do not know how many subjects in the general population cohort had treated or untreated OSA and how much effect undiagnosed OSA had on the prevalence of nocturnal sweating in the general population. However, we assessed their OSA risk by calculating their MAP index,[28] a widely used and validated tool for OSA risk assessment.[31] Finally, some patients in the OSA cohort reported an improvement in frequent nocturnal sweating despite receiving no PAP treatment at follow-up. These patients also described less sleepiness. This may be related to other life style changes during the 2-year interim between baseline and follow-up, demand characteristics, the Hawthorne effect (improvement due to observation alone[32]) or regression to the mean as most patients described severe symptoms at baseline. Also, other treatment use may be a factor. We did, however, remove all patients using a mandibular advancement device from our follow-up analysis in the OSA cohort and repeated the analyses excluding all non-PAP users with significant weight loss and upper airway surgery (uvula/soft palate) between the baseline and follow-up assessments, and this did not affect the results. Finally, we would like to mention that heating in Icelandic houses is relatively cheap and year-round outdoor temperatures in Reykjavik rather low (monthly average of −1°C to 11°C). Therefore, ambient temperatures in houses should be stable across the year and should not affect the current findings. Also, data collection was year-round, both for baseline and follow-up data.

Our study confirms the findings of Cruz *et al*[13] and Kiely *et al*[33] who showed a decrease of subjective sweating with PAP treatment in smaller cohorts of OSA patients (n=98 and 56, respectively). We have extended their findings by showing that the prevalence in nocturnal sweating in untreated OSA is three times larger than in a general population cohort and that it is reduced to general population levels with full PAP treatment. Also, our findings show that partial PAP treatment is not sufficient to reduce nocturnal sweating. This relationship was not strongly linear in nature, but rather required a minimum of 4 h of usage and 5 days a week on average similar to the Crawford *et al*[34] study on the effects of CPAP therapy on sleepiness. In the present study, we did not find a relationship between OSA severity and subjective nocturnal sweating, in agreement with Mold *et al*,[10] but in disagreement with Cruz *et al*[13] However, most of the participants in our OSA cohort had moderate-to-severe OSA, limiting our ability to assess

relationships with OSA severity. The results of the current study that nocturnal sweating is related to daytime sleepiness are in agreement with Mold *et al*.[10] Even in non-treated OSA patients, decreased complaints of nocturnal sweating were related to decreased sleepiness, possibly indicating a relationship with nocturnal sweating beyond the presence of OSA per se. A possible relationship may be found between nocturnal sweating and decreased sleep quality as subjects reporting nocturnal sweating are sleepier and report poorer quality of life in this study. In our earlier study, an association was found between high objective sweating and low REM sleep percentage in untreated OSA patients.[14] However, no association was found between objective sweating and arousals or awakenings.[14] Unlike the Mold *et al* study, we did not find a relationship with RLS symptoms. However, they used a less strict definition of RLS than we did. Interestingly, our findings are in agreement with a study of a general cohort of children (n=6381) in whom their parents reported more sleep-related sweating in relation to both OSA and insomnia symptoms.[35] Nocturnal sweating has also previously been found to be related to GER symptoms[36] and younger age,[13] as found in this study. For the general population cohort, we found indications that having OSA symptoms (both snoring and higher MAP index) is related to reporting frequent nocturnal sweating, unlike Mold *et al*[10] in their sleep laboratory sample. Our study also showed a relationship between decreased quality of life and frequent nocturnal sweating, both in the general population and OSA cohort, as has been shown previously in elderly primary care patients.[2] However, decreased sweating at the follow-up of OSA patients was not related to any improvement in quality of life. Similar to our earlier study with objective measurements of sweating,[14] we found a possible relationship between reported sweating and hypertension in OSA patients in this study.

Taken together, the results show that reported nocturnal sweating is common in patients with OSA and is related to lower sleep quality and more daytime sleepiness in this patient group. After successful PAP treatment, the prevalence of nocturnal sweating decreases to the same level as in the general population. Therefore, clinicians should include OSA in the differential diagnosis of patients presenting with a complaint of nocturnal sweating and further evaluate that possibility by performing a more complete sleep evaluation.

Future research that increases the understanding of the link between OSA and nocturnal sweating is important. Studies assessing whether the subgroup of OSA patients reporting nocturnal sweating have a different risk profile and/or different consequences such as increased blood pressure would also be of interest.

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Contributors ESA drafted the paper, participated in data collection and performed the statistical analysis. CJ contributed to the statistical analysis plan and manuscript preparation. EB participated in data collection, the statistical analysis plan and revising of paper. BB participated in data collection, the design of the study and manuscript preparation. SJ participated in data collection and manuscript preparation, STK participated in the manuscript preparation. AIP participated in the design of the study and manuscript preparation. TG was the main person who designed the study and participated in manuscript preparation. He is the guarantor of the study. SG, LG and KAK, Reykjavik, Iceland, implemented the study. BS, GM, MOS, OFL, RH, BK and NJ participated in data analysis and database construction. TGL proofread the manuscript.

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Table S1: Demographic factors associated with frequent nocturnal sweating (≥3x a week) in the general population and OSA cohorts. The associations are expressed as adjusted odds ratio with a 95% confidence interval (OR (95% CI)). Significant findings (p<0.05) are shown in bold.

	General population only		**OSA cohort only**	
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*	Unadjusted OR (95% CI)	Adjusted OR (95% CI)*
Female gender	1.37 (0.86 - 2.2)	1.38 (0.85 - 2.24)	1.13 (0.78 – 1.64)	1.24 (0.84 - 1.82)
Age per 10 year	0.92 (0.74 - 1.14)	**0.75 (0.57 – 0.99)**	**0.81 (0.70 – 0.93)**	**0.79 (0.67 – 0.93)**
BMI per 5 units	1.22 (0.97 - 1.52)	1.21 (0.96 - 1.52)	1.12 (0.99 - 1.28)	1.05 (0.92 - 1.21)
Current smoker	1.56 (0.89 - 2.72)	1.77 (0.98 - 3.19)	1.27 (0.89 – 1.81)	1.22 (0.85 – 1.76)
Hypertension	1.32 (0.79 – 2.23)	1.37 (0.75 – 2.51)	1.20 (0.89 – 1.62)	**1.48 (1.06 – 2.08)**
CVD	1.64 (0.90 -2.97)	**2.38 (1.14 – 4.95)**	0.69 (0.46 – 1.04)	0.68 (0.38 – 1.23)
Diabetes	2.77 (0.98 – 7.8)	2.66 (0.87 – 8.16)	0.73 (0.42 – 1.27)	0.83 (0.54 – 1.28)

Abbreviations: BMI, body mass index; CVD, cardiovascular disease, defined as a doctor diagnosis of coronary artery occlusion (myocardial infarction or heart attack), heart failure and/or stroke. Hypertension and diabetes were defined as a doctor diagnosis and treatment with medication. *Adjusted for all other variables in table.

Table S2: Independent associations between reported symptoms with nocturnal sweating in the general population and OSA cohorts. Odds ratios (OR) are shown with 95% confidence intervals (CI) and significant findings ($p < 0.05$) are shown in bold.

	General population only		**OSA patients only**	
	OR (95% CI) Partially adjusted *	OR (95% CI) Fully adjusted**	OR (95% CI) Partially adjusted *	OR (95% CI) Fully adjusted**
Reported snoring ≥3d/w	**1.92 (1.04 – 3.54)**	1.00 (0.47 – 2.11)	2.47 (0.94 – 6.53)	1.77 (0.62 – 5.02)
Difficulties initiating sleep ≥3d/w	**4.70 (2.66 – 8.32)**	**4.31 (1.84 – 10.10)**	**1.64 (1.09 – 2.46)**	1.49 (0.88 – 2.52)
Difficulties maintaining sleep ≥3d/w	**2.68 (1.63 - 4.41)**	1.12 (0.53 - 2.37)	**2.01 (1.46 – 2.78)**	**1.71 (1.15- 2.55)**
Feeling sleepy or drowsy during the day (6-7d/w)	**2.31 (1.16 - 4.58)**	2.28 (0.81 – 6.48)	**2.34 (1.57 – 3.49)**	**1.96 (1.28 – 3.01)**
Epworth Sleepiness Scale per 5 unit[$]	1.24 (0.91 - 1.68)	1.26 (0.83 – 1.91)	**1.24 (1.07 - 1.45)**	**1.19 (1.01 - 1.40)**
Restless legs syndrome symptoms	**2.00 (1.15 - 3.46)**	1.27 (0.57 – 2.87)	**1.47 (1.07 – 2.00)**	1.24 (0.84 – 1.82)
Nocturnal GER symptoms ≥1d/w	1.75 (0.74 – 4.17)	0.97 (0.12 - 7.78)	**2.21 (1.46 – 3.33)**	**1.84 (1.06 – 3.20)**
Daytime GER symptoms ≥1d/w	1.19 (0.39 - 3.66)	0.66 (0.08 – 5.37)	**1.99 (1.41 – 2.80)**	1.76 (0.95 – 2.42)
High risk OSA (MAP score ≥0.75)[#]	2.08 (0.94 – 4.59)	1.43 (0.54 – 3.79)		

Abbreviations: d/w, day per week; GER, gastroesophageal reflux.
*Partially adjusted odds ratios are adjusted for the demographics shown in Table S1.

**Fully adjusted odds ratios are adjusted for demographics as well as snoring, difficulties initiating and maintaining sleep, feeling sleepy/drowsy, restless legs syndrome, daytime and nocturnal GER.
[$]The fully adjusted Epworth score is not adjusted for feeling sleepy/drowsy during the day.
[#]The partial MAP score is not adjusted for gender, age and BMI, as it forms a part of the MAP score itself. Additionally the fully adjusted MAP score is not adjusted for snoring.