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Real-world impact of continuous positive airway pressure on sleepiness in patients with obstructive sleep apnea in a national registry

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ABSTRACT

Objective: Excessive daytime sleepiness (EDS) persists in some patients with obstructive sleep apnea (OSA) despite continuous positive airway pressure (CPAP) treatment. This study characterized response to CPAP and factors associated with residual EDS.

Methods: Danish National Patient Registry data were analyzed. Patients with OSA diagnosis (1994–2016), Epworth Sleepiness Scale (ESS) scores and apnea-hypopnea index recorded before beginning CPAP (baseline) and after 1–13 months of CPAP use, and CPAP adherence were included. Odds ratios (OR) for residual EDS after CPAP treatment were estimated using multivariate logistic regression.

Results: Of 1174 patients (mean age, 57 years; 75.5% male), 41.1% had baseline EDS (mild, 13.2%; moderate, 14.0%; severe, 13.9%); 58.9% did not. After CPAP treatment, follow-up mean ESS scores were normal (≤10) for all baseline EDS subgroups; however, 15.6% (n = 183) of patients had residual EDS (mild, 6.7%; moderate, 5.5%; severe, 3.4%). Odds of residual EDS were higher for patients with mild (OR, 5.2; 95% confidence interval [CI], 3.2–8.6), moderate (OR, 4.5; 95% CI, 2.7–7.4), and severe (OR, 13.0; 95% CI, 8.0–21.2) EDS at baseline compared with those with normal daytime sleepiness at baseline. Patients adherent with CPAP use were 38.2% less likely to have residual EDS compared with nonadherent patients (OR, 0.62; 95% CI, 0.43–0.88).

Conclusions: EDS was common in this cohort of Danish patients with OSA. Baseline EDS severity predicted higher odds of residual EDS. After CPAP treatment, adherence was associated with reduced odds of residual EDS, but EDS persisted in a subgroup of patients.

1. Introduction

Excessive daytime sleepiness (EDS) is a debilitating symptom of many sleep disorders that is characterized by the inability to stay awake or alert during the day [1]. EDS is associated with numerous consequences that can impact quality of life, health, and safety. Specifically, EDS is associated with reduced cognitive function, mood, and daily functioning, including impairments in social interactions, work productivity, time management, and work quantity and quality [2–5]. In addition, individuals with EDS are at increased risk for motor vehicle crashes and workplace injuries [6–8]. Furthermore, EDS can lead to complications with cardiovascular health, increased mortality, and overall greater healthcare resource utilization [9,10].

EDS is a key presenting symptom among patients with obstructive sleep apnea (OSA) [1]. An estimated 56%–79% of patients with OSA report EDS prior to initiating airway therapy (the primary treatment for OSA) [11–13]. Some patients continue to experience EDS even after breathing, oxygenation, and sleep quality have been normalized with the use of airway therapy—known as residual EDS. Approximately 9%–28% of patients treated with continuous positive airway pressure (CPAP) have residual EDS [5,14].

It is unclear why some patients experience residual EDS while others do not, and risk factors for residual EDS have not been well defined. The prevalence of residual EDS has been shown to decrease with longer durations of nightly CPAP use, such that significantly more patients who

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Abbreviations

AHI	apnea-hypopnea index
ATC	Anatomical Therapeutic Chemical
CI	confidence interval
CPAP	continuous positive airway pressure
DS	daytime sleepiness
EDS	excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
OSA	obstructive sleep apnea
SD	standard deviation

use CPAP for ≤5 h per night experience residual EDS compared with those who use CPAP for >6 h per night [15]. Most studies suggest that patients with severe EDS at OSA diagnosis are more likely to experience residual EDS after CPAP treatment [5,12,14,16,17]; however, others have found that the likelihood of improving sleepiness levels into the normal range after CPAP is not dependent on how close to the "threshold" patients were prior to treatment [15]. Some data suggest that depression may be a possible risk factor for residual EDS in patients with OSA, and whether comorbid diabetes and hypertension increase risk is unclear [5,12,14]. There is also evidence that patients' quality of life may be more greatly impacted at higher levels of EDS [18].

Insufficient evidence regarding the characteristics of patients with residual EDS limits a clinician's ability to identify patients at risk. Therefore, this real-world study was conducted to characterize patients' response to CPAP treatment, in terms of sleepiness and breathing, and to identify risk factors for residual EDS in patients with OSA.

2. Materials and methods

2.1. Registry design and patient population

Data from the Danish National Patient Registry (DNPR) were analyzed [19]. To determine the response to CPAP treatment, a study design that investigated the change in Epworth Sleepiness Scale (ESS) scores for patients who started CPAP treatment between 2 ESS measurements was employed (Fig. 1). Key inclusion criteria were OSA diagnosis between 1994 and 2016, ESS score and apnea-hypopnea index (AHI) recorded before starting CPAP and after 1–13 months of CPAP intervention, and registered CPAP adherence status on the same day as follow-up ESS measurement. As this study was registry-based, ethics committee approval was not required. In accordance with the ethics committee in Denmark, only projects that incorporate biological material require ethical approval [20]. Therefore, the registry-based data presented in this study did not require approval from an ethics committee.

2.2. Assessments

The primary outcome was change in sleepiness, as assessed with the ESS, and breathing, as assessed by AHI, from baseline (≤12 months before starting CPAP) to follow-up (1–13 months after starting CPAP). Mean (SD) changes in ESS and AHI and percentages of residual EDS by severity subgroup were estimated. Information on medications used to treat EDS (central nervous system stimulants and sedatives) and comorbidities within 1 year prior to baseline (diabetes medication and cardiovascular medication) were based on Anatomical Therapeutic Chemical (ATC) codes collected from the Danish National Prescription Registry. CPAP adherence data were obtained from the CPAP machine (auto-CPAP) on the same date as the follow-up ESS assessment. Adherence was based on the US Centers for Medicare & Medicaid Services threshold and defined as CPAP use for ≥4 h per night on ≥70% of nights [21].

2.3. Statistical analysis

Patients were categorized by baseline EDS severity (defined by ESS score): normal daytime sleepiness (ESS ≤10), mild EDS (ESS 11–12), moderate EDS (ESS 13–15), severe EDS (ESS ≥16) [22]. AHI severity was categorized as normal (<5 events per hour), light (5–14 events per hour), moderate (15–29 events per hour), and severe (≥30 events per hour) [23]. Baseline demographic and clinical characteristics were tabulated. A logistic regression analyzing the relationship between CPAP adherence and EDS group was conducted to determine if improving adherence has a greater impact on some baseline AHI groups versus others. Odds ratios (OR) were calculated to identify factors associated with improvement in EDS after CPAP treatment using a multivariate logistic regression model. Improvement in EDS was defined as a >3-point change in ESS score from baseline to follow-up (indicator variable: yes = 1), whereas no improvement in EDS was defined as a ≤3-point change in ESS score from baseline to follow-up (indicator variable: no = 0). This definition of EDS improvement was based on established criteria from previously published studies that assessed changes in EDS [24,25]. A second model calculated the odds of residual EDS after CPAP treatment, with residual EDS defined as ESS scores above the normal range (>10). Variables included in both models were predictor variables (CPAP adherence, ESS group at baseline, baseline AHI, comorbidities, sedative use) and control variables (sex, age, spouse status, depression, education level). In untreated individuals, ESS scores can change markedly over time [26,27]. To test the validity of our baseline (≤12 months before CPAP initiation) ESS measure, we performed a sensitivity analysis restricted to baseline ESS scores measured within 4 weeks (ie, 28 days) of starting CPAP.

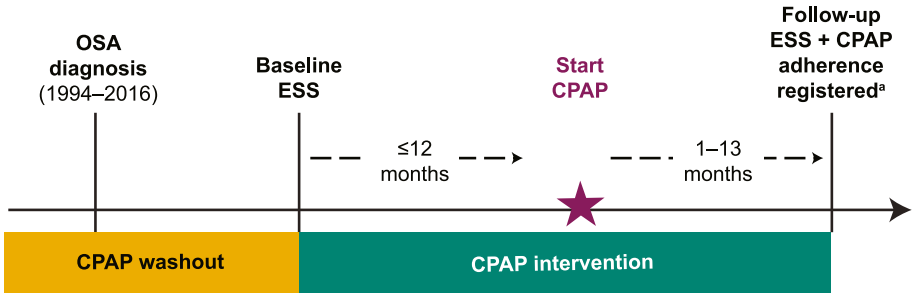


Fig. 1. Study design
CPAP, continuous positive airway pressure; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea.
[a]CPAP adherence data were obtained from the CPAP apparatus on the same date as the follow-up ESS assessment; adherence was defined as CPAP use for ≥4 h on ≥70% of nights.

3. Results

3.1. Patient disposition and baseline demographic/clinical characteristics

Of 12,453 patients, 1423 started CPAP between 2 ESS measurements. Of these, 1174 also had CPAP adherence information registered at the follow-up ESS assessment and were included in this analysis.

At baseline, 41.1% (n = 482) of patients had EDS (mild, 13.2% [n = 155]; moderate, 14.0% [n = 164]; severe, 13.9% [n = 163]), whereas 58.9% (n = 692) did not (Table 1). Most patients had severe AHI at baseline (normal, 36.0% [n = 249]; mild, 47.1% [n = 73]; moderate, 47.0% [n = 77]; severe, 54.6% [n = 89]). Patients with severe EDS had more severe mean AHI compared with those with normal daytime sleepiness, mild EDS, or moderate EDS (Table 1). Comparisons between patients included in the analysis and patients in the registry are provided in Supplementary Tables S1 and S2.

Education level and marital status were similar among EDS severity subgroups (Table 1). However, there were differences in the distribution of sex, age, and employment subgroups, such that the group of patients with severe EDS had a larger percentage of females, were generally younger (larger percentages of individuals aged 40–49 years or 50–59 years; lower percentages of individuals aged 60–69 years or ≥70 years), and had a larger percentage who were employed (with smaller percentages of individuals who indicated early retirement or age pension) compared with the groups with normal daytime sleepiness, mild EDS, or moderate EDS.

Overall, 12.9% (n = 152) of patients used sedatives before CPAP treatment (normal daytime sleepiness, 13.0% [n = 90]; mild EDS, 11.0% [n = 17]; moderate EDS, 15.9% [n = 26]; severe EDS, 11.7% [n = 19]), and 9.5% (n = 112) used sedatives during CPAP treatment (normal daytime sleepiness, 9.5% [n = 66]; mild EDS, 5.8% [n = 9]; moderate EDS, 12.8% [n = 21]; severe EDS, 9.8% [n = 16]). Few patients (<1.0%) used stimulants during either period (Table 1).

3.2. Changes in ESS and AHI after starting CPAP treatment

3.2.1. CPAP use

Overall, patients used CPAP for a mean (SD) of 146 (108) days (median [range]: 102 [30–394] days) before the follow-up assessment (normal daytime sleepiness, 163 [117] days; mild EDS, 135 [100] days; moderate EDS, 130 [91] days; severe EDS, 101 [70] days). More than half of patients were adherent with CPAP, using CPAP for ≥4 h per night on ≥70% of nights (Fig. 2).

3.2.2. ESS scores

After starting CPAP treatment, the overall median (IQR) ESS score decreased (improved) by 2 (6) points from baseline to follow-up, and mean ESS scores decreased into the normal range (≤10) for all EDS severity subgroups (Fig. 3). However, 15.6% (n = 183) of patients continued to experience EDS at the follow-up assessment (mild residual EDS, 6.7% [n = 79]; moderate residual EDS, 5.5% [n = 64]; severe residual EDS, 3.4% [n = 40]) (Fig. 4). Specifically, 23.9% (n = 37), 20.0% (n = 32), and 39.9% (n = 65) of patients who had mild, moderate, and severe EDS at baseline, respectively, had residual EDS (Fig. 5). Notably, after CPAP treatment, 17.2% and 12.9% of patients who had severe EDS at baseline remained severely and moderately sleepy, respectively, while only 60 patients had increased EDS at follow-up (Fig. 5). After CPAP treatment, 87.0% of patients adherent to CPAP had normal daytime sleepiness and 13.0% of patients showed above normal daytime sleepiness levels. Among those nonadherent to CPAP, 81.5% of patients showed normal daytime sleepiness after CPAP treatment. The percentage of patients with normal daytime sleepiness after CPAP treatment among those nonadherent to CPAP treatment decreased with increasing severity of daytime sleepiness (Table 2). Statistical testing of the interaction between CPAP adherence and EDS group showed a significant, positive estimate among the severe EDS group ($P = 0.011$) compared

Table 1
Baseline demographic and clinical characteristics, by ESS group.

Characteristic	ESS Group				
	Normal DS (n = 692)	Mild EDS (n = 155)	Moderate EDS (n = 164)	Severe EDS (n = 163)	Total (N = 1174)
Sex, n (%)					
Male	540 (78.0)	123 (79.4)	115 (70.1)	108 (66.3)	886 (75.5)
Female	152 (22.0)	32 (20.6)	49 (29.9)	55 (33.7)	288 (24.5)
Age, years, mean (SD)	59 (12.0)	57 (11.6)	54 (12.0)	53 (11.3)	57 (12.0)
Age group, n (%)					
0–39 years	50 (7.2)	15 (9.7)	19 (11.6)	16 (9.8)	100 (8.5)
40–49 years	100 (14.5)	28 (18.1)	33 (20.1)	39 (23.9)	200 (17.0)
50–59 years	182 (26.3)	40 (25.8)	54 (32.9)	66 (40.5)	342 (29.1)
60–69 years	224 (32.4)	55 (35.5)	38 (23.2)	28 (17.2)	345 (29.4)
≥70 years	136 (19.7)	17 (11.0)	20 (12.2)	14 (8.6)	187 (15.9)
Region, n (%)					
Capital region of Denmark	504 (72.8)	102 (65.8)	119 (72.6)	118 (72.4)	843 (71.8)
South Denmark region	168 (24.3)	45 (29.0)	42 (25.6)	39 (23.9)	294 (25.0)
Zealand region	20 (2.9)	8 (5.2)	<5 (<1)	6 (3.7)	37 (3.2)
Employment status, n (%)					
Employed	363 (52.5)	90 (58.1)	97 (59.1)	111 (68.1)	661 (56.3)
Unemployed	33 (4.8)	9 (5.8)	9 (5.5)	13 (8.0)	64 (5.5)
Sick leave or other leave	10 (1.4)	<3 (<1)	6 (3.7)	6 (3.7)	23 (2.0)
Disability pension	36 (5.2)	15 (9.7)	18 (11.0)	11 (6.7)	80 (6.8)
Early retirement	31 (4.5)	6 (3.9)	5 (3.0)	<3 (<1)	42 (3.6)
Age pension	206 (29.8)	32 (20.6)	25 (15.2)	19 (11.7)	282 (24.0)
Education or other	13 (1.9)	<5 (<1)	<5 (<1)	<5 (<1)	22 (1.9)
Marital status, n (%)					
Married/ cohabitating	502 (72.5)	112 (72.3)	113 (68.9)	103 (63.2)	830 (70.7)
Living alone	190 (27.5)	43 (27.7)	51 (31.1)	60 (36.8)	344 (29.3)
Education, n (%)					
Primary	163 (23.6)	42 (27.1)	43 (26.2)	31 (19.0)	279 (23.8)
Secondary	37 (5.3)	6 (3.9)	16 (9.8)	8 (4.9)	67 (5.7)
Vocational	296 (42.8)	55 (35.5)	58 (35.4)	73 (44.8)	482 (41.1)
College (short)	37 (5.3)	7 (4.5)	7 (4.3)	15 (9.2)	66 (5.6)
College (medium)	87 (12.6)	22 (14.2)	20 (12.2)	24 (14.7)	153 (13.0)
College (long + PhD)	63 (9.1)	19 (12.3)	15 (9.1)	10 (6.1)	107 (9.1)
Unknown	9 (1.3)	<5 (<1)	5 (3.0)	<5 (<1)	20 (1.7)
Days since OSA diagnosis, mean (SD)	24 (54.0)	28 (56.9)	23 (35.0)	19 (47.9)	24 (51.3)
AHI, mean (SD)	25 (22.3)	33 (25.6)	33 (26.7)	37 (26.3)	29 (24.4)
Medication use at baseline, n (%)					
Sedative	90 (13.0)	17 (11.0)	26 (15.9)	19 (11.7)	152 (12.9)
Stimulant	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)
Medication use during follow-up period					

(continued on next page)

Table 1 (*continued*)

Characteristic	ESS Group				
	Normal DS (n = 692)	Mild EDS (n = 155)	Moderate EDS (n = 164)	Severe EDS (n = 163)	Total (N = 1174)
Sedative	66 (9.5)	9 (5.8)	21 (12.8)	16 (9.8)	112 (9.5)
Stimulant	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)	<5 (<1)

AHI, apnea-hypopnea index; DS, daytime sleepiness; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnea; SD, standard deviation.

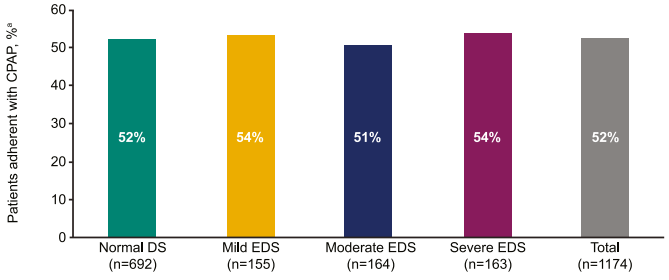


Fig. 2. CPAP adherence after CPAP treatment, by ESS group
CPAP, continuous positive airway pressure; DS, daytime sleepiness; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale.
[a]CPAP adherence was defined as CPAP use for ≥4 h on ≥70% of nights.

with the normal EDS group, suggesting CPAP adherence has a greater effect on ESS for the severe EDS group. However, interactions among the mild and moderate EDS groups did not show statistical significance. These findings should be considered in the context that, while CPAP adherence is most important in the severe EDS group, this group is also the most likely to have residual EDS despite being adherent to CPAP.

3.2.3. AHI

After starting CPAP treatment, the overall mean (SD) AHI decreased (improved) by 25.3 (24.0) events per hour, and mean AHI decreased into the normal range (<5) for all EDS severity subgroups (Fig. 3). At the follow-up assessment, mean (SD) AHI for patients who had mild, moderate, and severe residual EDS was 4.3 (6.7), 3.3 (3.4), and 7.1 (13.9), respectively, compared with 3.6 (4.3) for patients who did not have residual EDS. The majority of patients (75.3%) achieved normal AHI with CPAP treatment (no residual EDS, 75.2% [n = 745]; mild residual EDS, 74.7% [n = 59]; moderate residual EDS, 79.7% [n = 51]; severe residual EDS, 72.5% [n = 29]). Few patients had moderate AHI (28 [2.4%]) or severe AHI (7 [0.6%]) at the follow-up assessment.

3.3. Factors associated with changes in EDS

3.3.1. Factors associated with improvement in EDS

Patients with severe EDS at baseline had the highest odds of showing improvement in EDS (ie, decrease of ≥3 points in ESS score) after starting CPAP treatment (Fig. 6). Patients with mild, moderate, and severe EDS at baseline were 5, 12, and 14 times more likely, respectively, to have improvement in EDS after CPAP compared with those with no EDS. Other factors associated with increased odds of improvement in EDS with CPAP treatment were adherence with CPAP, baseline AHI (as a continuous variable), and being married/cohabitating.

3.3.2. Factors associated with the presence of residual EDS

After adjusting for baseline AHI, adherence with CPAP, sedative medication use, comorbidities (depression), education, being married/cohabitating, age, and sex, patients with mild, moderate, and severe EDS

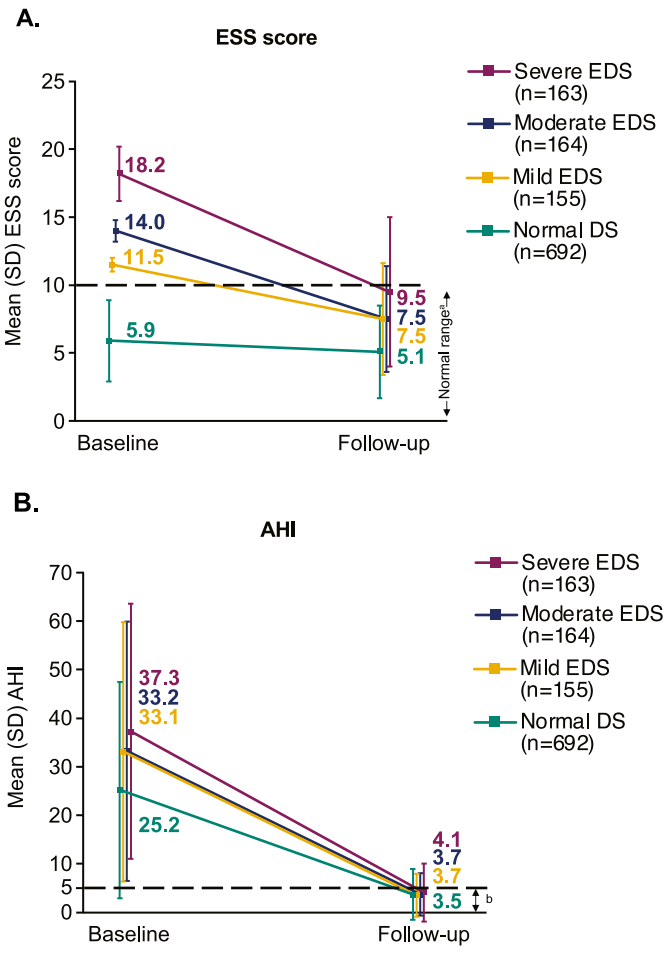


Fig. 3. Changes in mean ESS scores (A) and mean AHI (B) from baseline (before CPAP treatment) to follow-up (after CPAP treatment), by ESS group
AHI, apnea-hypopnea index; DS, daytime sleepiness; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; SD, standard deviation.
[a]Normal range ESS: score ≤10.
[b]Normal range AHI: <5 apneic events per hour.

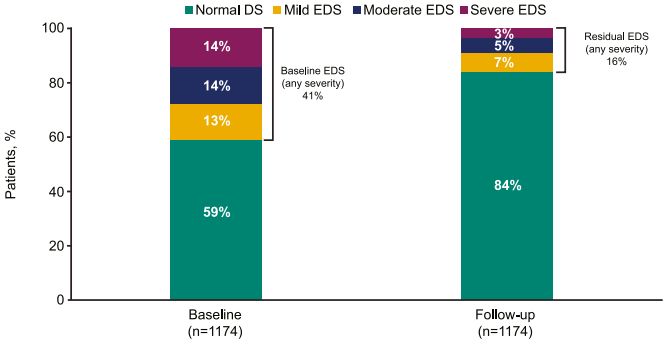


Fig. 4. Prevalence of EDS at baseline (before CPAP treatment) and follow-up (after CPAP treatment), by ESS group
CPAP, continuous positive airway pressure; DS, daytime sleepiness; EDS, excessive daytime sleepiness.

at baseline were 5, 4, and 13 times more likely to have residual EDS compared with those with normal daytime sleepiness at baseline (Fig. 7). Patients who were adherent with CPAP were 38.2% less likely to have residual EDS compared with those who were nonadherent (Fig. 7). CPAP adherence (OR, 0.62; 95% confidence interval [CI], 0.43–0.88; $P = 0.0084$) and AHI at baseline (as a continuous variable;

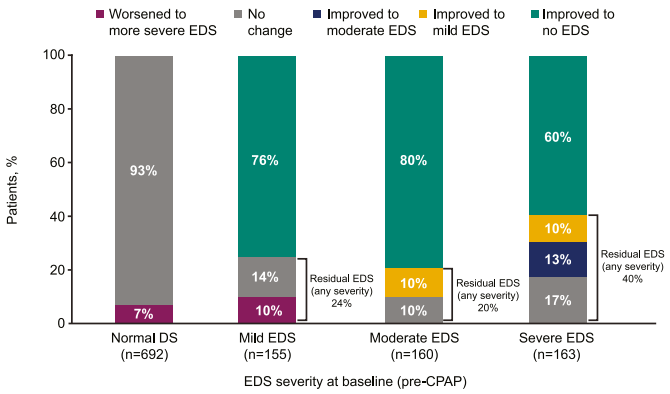


Fig. 5. Change in EDS severity from baseline to follow-up after CPAP treatment,[a] by ESS group
CPAP, continuous positive airway pressure; DS, daytime sleepiness; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale.
[a]Change determined as a shift to a different EDS severity group from baseline to follow-up ESS assessment.

OR, 0.98; 95% CI, 0.98–0.99; $P = 0.0001$) were also significant in this model.

3.4. Sensitivity analysis

A sensitivity analysis was performed to examine a narrower window between baseline ESS score and CPAP initiation. This included 598 patients with baseline ESS scores within 28 days of starting CPAP. These patients represent 50.9% of the original sample, but only 40.5% of patients with severe ESS at baseline start CPAP within 28 days. The resulting model indicated CPAP adherence no longer had a positive significant effect on ESS improvement (OR, 1.31; 95% CI, 0.83–2.05; $P = 0.246$).

4. Discussion

This real-world report provides insight into the prevalence and characteristics of patients with residual EDS and OSA in Danish clinical practice settings. Before starting CPAP, 41.1% of patients had significant EDS. Although most of these patients achieved normal levels of daytime sleepiness after starting CPAP treatment, 1 in 6 patients continued to have pathological levels of EDS. This analysis revealed several factors

Table 2
Daytime sleepiness status after CPAP treatment, by ESS group.

	All		ESS Group							
			Normal DS		Mild EDS		Moderate EDS		Severe EDS	
	CPAP Adherent (≥70%)	CPAP Nonadherent	CPAP Adherent (≥70%)	CPAP Nonadherent	CPAP Adherent (≥70%)	CPAP Nonadherent	CPAP Adherent (≥70%)	CPAP Nonadherent	CPAP Adherent (≥70%)	CPAP Nonadherent
Patients, n	616	558	362	330	83	72	83	81	88	75
Second CPAP measurement, n (%)										
Above normal DS	80 (13.0)	103 (18.5)	17 (4.7)	28 (8.5)	20 (24.1)	17 (23.6)	15 (18.1)	21 (25.9)	28 (31.8)	37 (49.3)
Normal DS	536 (87.0)	455 (81.5)	345 (95.3)	302 (91.5)	63 (75.9)	55 (76.4)	68 (81.9)	60 (74.1)	60 (68.2)	38 (50.7)

CPAP, continuous positive airway pressure; DS, daytime sleepiness; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale.

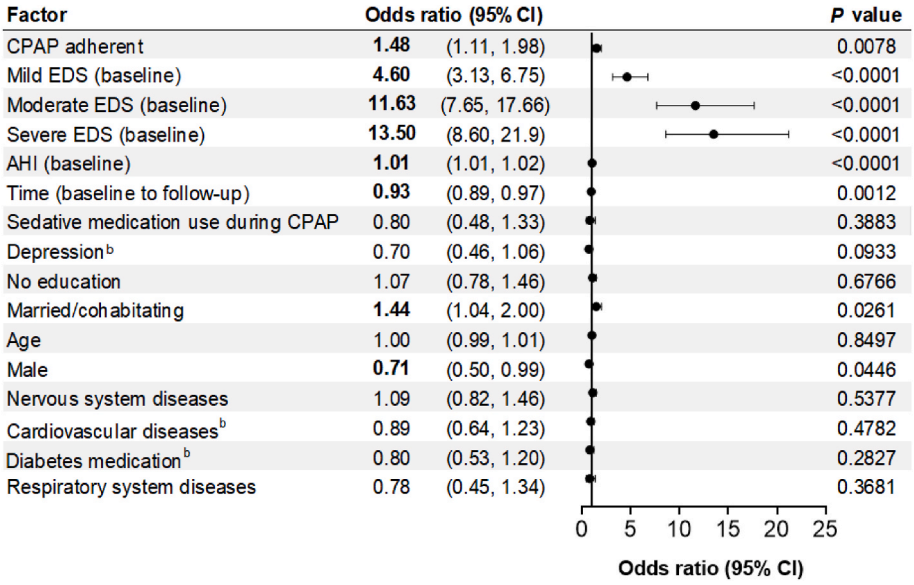


Fig. 6. Odds of improved EDS[a] after starting CPAP treatment
AHI, apnea-hypopnea index; CI, confidence interval; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness.
Odds ratios for factors with $P < 0.05$ indicated in bold font.
[a]Improvement in EDS was defined as a >3-point change in ESS score from baseline to follow-up (indicator variable: yes = 1), whereas no improvement in EDS was defined as a ≤3-point change in ESS score from baseline to follow-up (indicator variable: no = 0).
[b]Within 1 year prior to baseline.

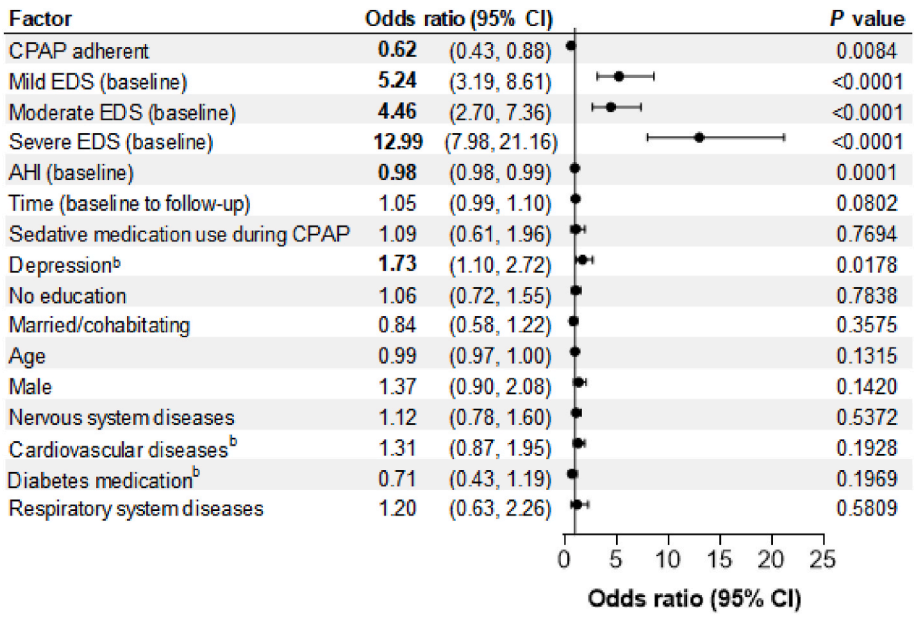


Fig. 7. Odds of residual EDS[a] after starting CPAP treatment[b]
AHI, apnea-hypopnea index; CI, confidence interval; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness.
Odds ratios for factors with $P < 0.05$ indicated in bold font.
[a]ESS scores above the normal range (>10).
[b]Within 1 year prior to baseline.

that were associated with increased odds of improvement in EDS with CPAP treatment, including baseline EDS severity, adherence with CPAP, baseline AHI, and being married/cohabitating. Conversely, EDS at baseline was associated with greater odds of residual EDS (with the highest odds associated with severe baseline EDS), independent of depression, and adherence with CPAP was associated with a reduced odds of residual EDS.

In the current analysis, 15.6% of CPAP-treated patients had residual EDS. This is consistent with what has been reported by other European studies, which have estimated that 8.7%–28.2% of CPAP-treated patients have residual EDS [5,13,14]. Despite having the highest odds of improvement in EDS (≥3 points on the ESS) after CPAP treatment, patients with severe EDS at baseline also had the highest odds of having residual EDS. This is likely since they had higher baseline ESS scores and, therefore, would require a larger degree of improvement (reduction in ESS score) to achieve normal sleepiness levels. Specifically, the current study found that 39.9% of patients who had severe EDS at baseline had residual EDS, compared with 23.9% and 20.0% who had mild and moderate EDS at baseline, respectively. Notably, 17.2% and 12.9% of patients with severe EDS at baseline continued to have severe and moderate EDS, respectively, after CPAP treatment. Consistent with these findings, a recent review concluded that most studies agree that patients with more severe EDS at baseline are more likely to remain sleepy after CPAP treatment [17].

The present analysis also found that patients who were adherent with CPAP were 45.7% more likely to have improved EDS compared with those who were nonadherent. In addition, this analysis found that adherence to CPAP (≥70%) was associated with a 38.2% *reduction* in the likelihood of residual EDS. In the same model, the presence of EDS at baseline significantly *increased* the risk of having residual EDS; individuals with mild or moderate EDS at baseline were 4–5 times as likely and those with severe EDS at baseline were 13 times as likely to experience residual EDS relative to those with normal daytime sleepiness at baseline. Having EDS at baseline has a much greater impact on odds of residual EDS than CPAP adherence does, which suggests EDS at baseline may be a more important predictor of residual EDS than previously thought. These findings imply that treatment should emphasize supporting patients with greatest EDS severity at baseline versus focusing solely on increasing CPAP adherence. The results of our sensitivity analysis also support this hypothesis. When restricting our analysis to a narrower window between baseline ESS and CPAP initiation, we excluded relatively more severe EDS cases and found CPAP adherence no longer had a positive significant effect on ESS improvement. Because patients with more severe ESS have more room for improvement, when they are excluded, CPAP adherence no longer predicts improvement in ESS. Likewise, a recent real-world US study found that 36% of patients who were highly adherent to CPAP had residual EDS, and rates were even higher among those who were intermediately adherent (53%) or nonadherent (52%) to CPAP [28]. Interestingly, in the current study, AHI was within the normal range (<5 events per hour) for the majority of patients after CPAP treatment—even among those who had moderate and severe residual EDS. Together, these data suggest that although adherence to CPAP decreases the risk of residual EDS, some patients will continue to experience EDS even with high levels of CPAP use and normalization of AHI.

This study adds data from a large, real-world sample to the literature to help estimate the prevalence of EDS before and after CPAP treatment among patients with OSA. Further, several factors associated with increased odds of improving EDS with CPAP treatment were identified, thereby providing clinicians with insight into why patients may be more or less likely to experience residual EDS. Finally, CPAP adherence data were obtained from the CPAP apparatus rather than self-reported, likely reducing risk for overestimation. Despite these strengths, there were limitations. For one, patient information, including medication use, was based on ATC codes [19]. As such, the reliability of these data is dependent on the correct use of these codes, and coding practices could vary among clinicians and settings. These limitations, however, were not expected to significantly affect the primary results. Medication coding reflects prescribing patterns rather than actual medication use, and comorbidities are coded based on treatments. Some untreated comorbidities may not be fully recorded, which could introduce noise into the data but would bias the results only if these unrecorded comorbidities were intrinsically linked to the variables of interest. In a similar vein, EDS variables of interest were limited to what was available within the

DNPR data. The DNPR relies on clinical information and results of diagnostic procedures [29]. While these diagnostic procedures are registered, the specific results of these procedures are not recorded [29]. This limits the ability to estimate the presence or absence of a low arousal threshold that is associated with EDS and has the potential to influence adherence. As patients included in the analysis represent <2% of the full OSA population identified during the study period, some selection bias may have occurred. However, a meaningful number of patients remained in the sample, and the analysis remained unhindered. In addition, AHI at follow-up was derived from CPAP device data, which may underestimate sleep-disordered breathing [30].

Although this study's results add to prior data in EDS research, its design and methodology did not allow for investigation of novel factors that could potentially influence EDS outcomes and the causes of residual EDS. To address this limitation and explore novel factors that influence residual EDS in patients treated for OSA, future studies need to take a longitudinal, prospective approach that assesses the evolution of EDS and identifies factors that emerge over time [31]. In addition, data limitations allowed for adjustment of only certain comorbidities, such as depression and diabetes. More comprehensive analyses that consider a broad range of factors, including psychological, lifestyle, and genetic variables, such as stress levels, physical activity, and genetic predispositions, should be performed [32–35]. This would ideally allow for the discovery of new and potentially modifiable determinants of residual EDS.

5. Conclusions

EDS before starting CPAP was common in this real-world cohort of Danish patients with OSA. Baseline EDS severity predicted higher odds of residual EDS. For most patients, EDS, as assessed by the ESS, and breathing, as assessed by AHI, normalized after CPAP therapy; however, 15.6% of patients continued to experience residual EDS after starting treatment. CPAP adherence was associated with lower odds of residual EDS after CPAP treatment. Furthermore, being married or cohabitating was associated with increased odds of EDS improvement with CPAP treatment. Patients with severe EDS improved the most, but EDS persisted in a subgroup of these patients, with 17.2% and 12.9% continuing to have severe and moderate EDS, respectively, independent of age, sex, marital status, and comorbidities.

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CRediT authorship contribution statement

Poul Jennum: Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Jakob Kjellberg:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Conceptualization. **Ginger Carls:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Rikke Ibsen:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Sam Mettam:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization.

Declaration of competing interest

Poul Jennum, Jakob Kjellberg, and Rikke Ibsen have nothing to disclose.

Ginger Carls: Former employee of Jazz Pharmaceuticals who, in the course of this employment, received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc.

Sam Mettam: Employee of Jazz Pharmaceuticals who, in the course of this employment, has received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc.

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Appendix A. Supplementary data

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