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Original Article

Socioeconomic and humanistic burden of illness of excessive daytime sleepiness severity associated with obstructive sleep apnoea in the European Union 5

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ABSTRACT

Objective/Background: Evaluate the impact of excessive daytime sleepiness (EDS) severity on burden of illness among adults with obstructive sleep apnoea (OSA) in European Union 5 (EU5) countries (France, Germany, Italy, Spain, United Kingdom).

Patients/Methods: This retrospective observational study used data from the 2017 EU5 National Health and Wellness Survey, a self-administered, internet-based, non-screening survey. Respondents who self-reported both having experienced OSA in the last 12 months and having had their OSA diagnosed by a physician were considered to have OSA. Respondents completed the Epworth Sleepiness Scale (ESS) and were consequently categorised into 4 groups: OSA-with-EDS (ESS >10) subdivided by EDS severity (mild [ESS = 11–12], moderate [ESS = 13–15], severe [ESS = 16–24]), and OSA-without-EDS (ESS ≤10). Bivariate and multivariable analyses examined group differences in health-related quality of life (HRQoL), work productivity and activity impairment, and health care utilisation.

Results: The analysis included 2008 respondents with OSA: n = 661 (32.9%) with EDS (29.5% mild, 34.5% moderate, 36.0% severe) and n = 1347 without EDS. Compared with the OSA-without-EDS group, the OSA-with-EDS subgroups generally had higher rates of obesity, depression, and other reported comorbidities. Greater severity of EDS was associated with worse self-reported HRQoL (all domains, $P < 0.001$) and work productivity and activity impairment (absenteeism, $P = 0.031$; presenteeism, overall work impairment, and non–work activity impairment, $P < 0.001$), as well as increased numbers of health care provider visits ($P < 0.001$).

Conclusions: Compared to patients with OSA but without EDS, those with EDS had substantially higher socioeconomic and humanistic burden of disease, which was more profound among those reporting greater EDS.

1. Introduction

Obstructive sleep apnoea (OSA) is a sleep disorder marked by recurring episodes of partial or complete collapse of the upper airway during sleep [1]. It is associated with multiple complications, including systemic hypertension and cardiovascular disease, and is a precursor of abnormalities of glucose metabolism [2–4]. In addition, OSA causes significant socioeconomic burden, such as increased rates of health care visits and costs, medication use, and unemployment among patients relative to control subjects [5]. The cardinal symptoms of OSA include excessive daytime sleepiness (EDS), snoring, and ascertainable pauses during sleep [1]. EDS is of particular significance for people with OSA, as it can impact various dimensions of living. A majority of individuals with OSA wake up in

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Abbreviations

AHI	apnoea-hypopnoea index
BMI	body mass index
CCI	Charlson Comorbidity Index
CPAP	continuous positive airway pressure
EDS	excessive daytime sleepiness
ESS	Epworth Sleepiness Scale
EU5	European Union 5
GLM	generalised linear model
GP	general practitioner
HCRU	health care resource utilisation
HRQoL	health-related quality of life
MCID	minimal clinically important difference
MCS	Mental Component Summary
NHWS	National Health and Wellness Survey
OSA	obstructive sleep apnoea
PCS	Physical Component Summary
QoL	quality of life
RES	residual excessive sleepiness
RoW	rest of world
SD	standard deviation
SF-12v2	12-Item Short Form Health Survey version 2
UK	United Kingdom
US	United States
WPAI-GH	Work Productivity and Activity Impairment: General Health questionnaire

the morning feeling tired and unrefreshed, regardless of how much time they spent in bed [6]. In addition, people with OSA often experience extreme EDS at inappropriate times, such as while actively conversing, eating, walking, or driving [6]. EDS in OSA has been linked to impaired cognition, falls, motor vehicle accidents, and increased mortality in the elderly [7–11]. EDS is common among patients with OSA before treatment [12] and may persist after primary therapy, usually continuous positive airway pressure (CPAP). EDS that persists after treatment is commonly referred to as *residual sleepiness* [13].

Historically, the scientific literature has focused on capturing the total impact of OSA, with few evaluating the additional influence of EDS on OSA (especially in a broad European context) [10,11,14] or differentiating burden by sleepiness severity. Pepin et al. [15] assessed the prevalence of residual excessive sleepiness (RES) in CPAP users; predictors of RES; and differences between RES and non-RES CPAP users on quality of life (QoL) measures. Ronksley et al. [16] determined that EDS was independently associated with increased health care resource utilisation (HCRU) among patients referred for assessment of OSA. However, at the present time researchers have not given consideration to EDS severity. On the other hand, in clinical practice OSA severity has been described using the apnoea-hypopnoea index (AHI), a scale with several limitations. AHI does not always accurately quantify disease severity (eg, it does not take into account the duration [mean time] of an apnoea-hypopnoea), or predict whether an individual with OSA experiences EDS, as well as not being associated with OSA-related quality of life [17,18]. Distinctly, the Epworth Sleepiness Scale (ESS) is a well-studied and widely-used instrument [19] that has been employed to evaluate EDS and its relative degree of severity in randomised controlled trials and to measure the impact of various pharmacological and behaviour-based therapies in patients with OSA and/or other sleep disorders [20,21]. This brief questionnaire assesses how likely an individual is to doze off during various daily activities (eg, while driving, reading, or watching television) [19]. Its validity, reliability, and internal consistency have been documented [19], as well as its high sensitivity and specificity (cutoff score, >10) [22,23]. Although the ESS is a self-reported assessment, it does not ask about subjective feelings of sleepiness, but instead asks respondents to retrospectively report their sleep propensity in situations of varying soporific nature [19,24]. The ESS has been used as a barometer of EDS, demarcating the threshold of pathological sleepiness, as well as providing a means to calculate relative improvement. A closer evaluation of the continuum of EDS, a key symptom of OSA, using the ESS may impart further understanding of the implications of pathological sleepiness on health and well-being.

The present study, which evaluated the burden of illness of EDS severity among patients with OSA, analysed European survey data to describe group differences in health-related quality of life (HRQoL), work productivity, and HCRU.

2. Materials and methods

This study used 2017 European Union 5 (EU5) National Health and Wellness Survey (NHWS) data collected from France, Germany, Italy, Spain, and the United Kingdom (N = 62,000) in the context of a cross-sectional analysis. The NHWS is a self-administered, internet-based, non-screening survey for adults (age, ≥18 years). Survey data were collected between May 2017 and September 2017. Participants were identified primarily through their participation in opt-in online survey panels. Stratified random sampling by age and sex within each country was used to ensure national representativeness. The Pearl Institutional Review Board granted the 2017 NHWS exemption from review. The NHWS survey items did not specify type of sleep apnoea (ie, obstructive or central). This study's use of the term *obstructive sleep apnoea* reflects an analytic decision to accept *sleep apnoea* as adequately capturing and representing OSA, based on the significantly higher prevalence of OSA relative to that of central sleep apnoea, with recent analysis of baseline data from a large community-based cohort study (ie, the Sleep Heart Health Study) calculating prevalence of 47.6% and 0.9%, respectively, among adults aged 40 years and over [25].

2.1. OSA diagnosis validation

Comprising the patient population of interest were survey respondents reporting OSA with or without EDS (with subsequent groupings by EDS severity) (Fig. 1). The OSA study population consisted of those respondents who self-reported both having been diagnosed with OSA by a physician, as well as experiencing OSA within the past 12 months. Respondents who self-reported having been diagnosed with narcolepsy by a physician were excluded from the study. The ESS was completed by all OSA respondents as part of the NHWS Sleep Conditions module, and subsequent scores were used to categorise the patients according to their reported EDS status—11–12 (mild EDS), 13–15 (moderate EDS), and 16–24 (severe EDS) [24]—or absence thereof, ≤10 (no EDS) [26]. The threshold separating normal from pathological levels of sleepiness was established in a study of Australian workers [26], whereas the cutoffs used to further subdivide patients by degrees of EDS are the developer's suggested interpretations, empirically informed by the ESS scores reported by patients with narcolepsy. These EDS cutoffs are widely used in the United States (US) and abroad (though not

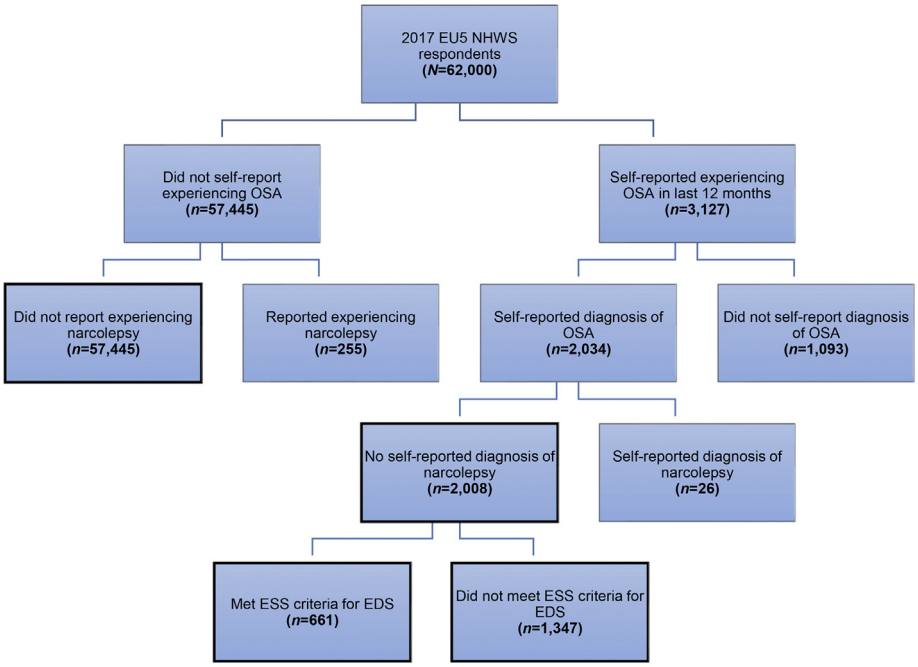

Fig. 1. Study population. Excessive daytime sleepiness was defined by Epworth Sleepiness Scale scores >10. Respondents who self-reported a narcolepsy diagnosis were excluded from the obstructive sleep apnoea analytic groups. EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; EU5, European Union 5; NHWS, National Health and Wellness Survey.

uniformly in all countries, like the United Kingdom) and will be referred to in this study as US/rest of world (RoW) cutoffs [19,24].

2.2. Outcomes of interest

The demographic and personal health information reported by survey respondents included age, sex, country of residence, marital status, education level, labour force participation, employment status, annual household income, health insurance status, medical and psychiatric comorbidities (tabulated individually), a Charlson Comorbidity Index score (CCI; a weighted summary score) [27], body mass index (BMI), smoking status, alcohol use, and exercise activity. HRQoL was assessed with the 12-Item Short Form Health Survey version 2 (SF-12v2) [28] Mental Component Summary (MCS) and Physical Component Summary (PCS) scales, and the Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health subscales. Work productivity was assessed with the Work Productivity and Activity Impairment: General Health (WPAI-GH) questionnaire (version 2.0) [29], which calculates absenteeism (work time missed), presenteeism (reduced on-the-job effectiveness), overall work impairment (work productivity lost), and non–work activity impairment. EDS was assessed with the ESS [30], and HCRU was assessed in terms of number of traditional health care visits, emergency department visits, and hospitalisations. HCRU specific to traditional health care visits was summarised collectively and reported individually for the following provider types: general practitioner, internist, nurse practitioner/physician assistant, pulmonologist, neurologist, and psychiatrist. The entire list of traditional health care provider types captured in the NHWS survey and reported in aggregate includes general practitioner/family practitioner, internist, allergist, cardiologist, dentist, dermatologist, diabetologist, endocrinologist, gastroenterologist, geriatrician, gynaecologist, hepatologist, infectious disease specialist/infectologist, neurologist, nephrologist, nurse practitioner/physician assistant, obstetrician, oncologist, ophthalmologist, orthopaedist, otolaryngologist, plastic surgeon, podiatrist, psychiatrist, psychologist/therapist, pulmonologist, respiratory therapist, rheumatologist, urologist, and other medical specialist.

While the focus of this study is the burden of EDS regardless of underlying treatment/therapy, it is important to note considerations regarding respondents' potential underlying treatment. At the time of data collection, no pharmacological agent was approved for the treatment of EDS associated with OSA. Survey respondents with comorbid insomnia and/or other sleep difficulties (except for narcolepsy, which was cause for exclusion from this analysis) were included in the study population. An artefact of these circumstances was the inability to discern the intended use of medications reported by participants. Treatment or adherence to CPAP—a primary OSA treatment modality that studies have shown may not resolve EDS entirely if at all [13,15]—were also not captured in this survey.

2.3. Statistical analysis

Quantitative methods were used to evaluate the data and illustrate the patterns within and between variables. Descriptive and bivariate analyses examined differences among the 4 OSA groups of interest (OSA-without-EDS; OSA with mild EDS; OSA with moderate EDS, OSA with severe EDS) and informed their subsequent multivariable modeling. The multivariable analyses applied generalised linear models (GLMs; which use maximum likelihood estimation for parameter estimates in the regression model) to adjust for potential confounders, which were set to the average study population values of the entire OSA population included in this analysis. Adjusted means for all outcomes of interest were then calculated for each analytic group to help illustrate the pattern of results. Using the OSA-without-EDS as the reference group, pairwise comparisons were conducted for each tier of EDS severity. Covariates were selected from the results of the bivariate analyses and from medical expert discussions on the theoretical model of causality. Multivariable model covariates included age, CCI, sex, marital status, income, BMI, smoking status, alcohol use, and

exercise activity. GLMs specifying normal distributions and identity link functions were used to predict normally distributed outcomes (eg, SF-12v2 scale and subscale scores). GLMs specifying negative binomial distributions with log link functions were used to predict outcomes for variables with skewed distribution (eg, work productivity, HCRU). Only respondents who reported being employed full-time or part-time provided data on absenteeism, presenteeism, and overall work impairment. All respondents provided data on non–work activity impairment. Trend analysis using a polynomial contrast statement was performed to evaluate the relationship between categorical EDS and the outcomes of interest. Data presented are descriptive, and there were no adjustments for multiplicity, as outcomes variables (for both work productivity and HCRU) are independent measures of burden (ie, not domains of the same scale), and the explanatory variable has only one reference group (OSA-without-EDS). While the SF-12v2 does generate a set of domain and subscale scores, it should be noted that this study is not testing against any predefined hypotheses. However, all *P* values presented are nominal.

There was limited missing data, as respondents were required to answer a question before they could proceed to the next; on sensitive questions, a "prefer not to answer" option was offered and results reported. All respondents completed the ESS, SF-12v2, and HCRU items on the survey; therefore, there were no missing values for those outcomes. For outcomes generated from the WPAI-GH questionnaire, only responses from employed respondents were used to calculate absenteeism and presenteeism. Furthermore, absenteeism and overall work impairment were not calculated for those who worked 0 h and missed 0 h within the past 7 days (total OSA, n = 690; OSA-with-EDS, n = 246; OSA-without-EDS, n = 444). Presenteeism is asked only among those who worked >0 h within the past 7 days (total OSA, n = 643; OSA-with-EDS, n = 224; OSA-without-EDS, n = 419). No imputation was made for missing WPAI-GH data. Of all the study variables, 2 recorded responses of "prefer not to answer" (educational level, n = 12; income level, n = 145) and 1 recorded responses of "unknown" (BMI, n = 74). In multivariable models, the unknown or "prefer not to answer" categories for marital status, household income, and BMI were collapsed with the reference group.

3. Results

Of the 62,000 respondents in the 2017 NHWS EU5 dataset, 2008 were eligible for study inclusion and subsequently defined as patients with OSA. Per the ESS cutoff for pathological sleepiness, 661 (32.9%) reported EDS, and 1347 (67.1%) did not report EDS. Among those with EDS, there was a relatively even number of respondents in each tier of EDS severity: 29.5% with mild EDS (n = 195), 34.5% with moderate EDS (n = 228), and 36.0% with severe EDS (n = 238). Compared with respondents in the OSA-without-EDS group, those in all the OSA-with-EDS groups (mild, moderate, or severe) were on average slightly younger (Table 1) and had a relatively higher mean CCI score. A large proportion of the OSA-with-EDS groups were male (65.8%) and lived in Germany (32.4%). The distribution of EDS in the EU5 countries varied. In France, 74.6% (data not shown) of OSA respondents reported normal levels of sleep propensity, with a relatively even split of remaining respondents in each of the 3 groups of EDS severity (data not shown). A similar pattern was observed in Germany, Italy, and Spain, though greater proportions of respondents had EDS (36.0%, 35.3%, and 37.4%, respectively). In the UK, while 63.3% of OSA respondents reported normal levels of sleep propensity, the distribution of pathological sleepiness was not even: 8.0% with mild EDS, 10.7% with moderate EDS, and 18.0% with severe EDS. Among OSA respondents with some level of EDS, a relatively high proportion were married or living with a partner. Additionally, only a portion of EDS respondents had a university degree (32.4%) and participated in the labour force (39.5%). Obesity (BMI, $\geq$30 kg/m^2) was higher among respondents in 2 of the OSA-with-EDS groups (50.0%, moderate; 59.2%, severe) compared with OSA respondents without EDS (48.9%).

There were visible differences in the frequency of comorbidities among those in the OSA-without-EDS group compared to those with EDS, varying by severity (Table 2), including for depression (26.7% [no EDS] vs 31.8% [mild], 39.5% [moderate], and 50.8% [severe]), insomnia (20.0% vs 24.1%, 28.9%, and 30.7%, respectively), gastroesophageal reflux disease (17.3% vs 22.1%, 25.4%, and 23.1%, respectively), and posttraumatic stress disorder (3.5% vs 6.2%, 5.3%, and 10.1%, respectively). A large proportion of OSA respondents in all groups, regardless of presence or severity of EDS, reported having cardiometabolic-risk factors (specifically, high blood pressure and high cholesterol).

Multivariable analysis described HRQoL outcomes, work productivity, and HCRU by EDS severity among respondents with OSA. Higher levels of sleep propensity on the ESS were linearly associated with lower reported HRQoL outcomes ($P < 0.001$ for the linear trend between increasing EDS severity and all SF-12v2 outcomes; Table 3). The lowest (worst) MCS and PCS scores were reported by respondents in the OSA with severe EDS group—driven in large part by the MCS Social Functioning, Mental Health, and Role-Emotional subscales and the PCS Role-Physical and Bodily Pain subscales, respectively. There were also differences between groups across all MCS subscales (Fig. 2A). For example, compared with respondents in the OSA group without EDS, those with mild EDS scored an average of 1.1 and 0.9 points lower on the Social Functioning and Role-Emotional subscales, respectively. Relative to respondents in the OSA group with mild EDS, those with moderate EDS scored an average of 2.6, 2.4, 2.5, and 2.6 points lower on the MCS scale and its Social Functioning, Role-Emotional, and Mental Health subscales, respectively. Compared with respondents in the OSA group with moderate EDS, those with severe EDS scored an average of 1.6, 1.4, 2.3, and 1.6 points lower on the MCS scale and its Vitality, Role-Emotional, and Mental Health subscales, respectively. Similarly, marked differences in score were observed between groups across all PCS subscales, with an increased impact on PCS as EDS severity increased (Fig. 2B). Relative to respondents in the OSA group without EDS, those with mild EDS scored an average of 1.0 point lower on the PCS Role-Physical subscale. Compared with respondents in the OSA group with mild EDS, those with moderate EDS scored an average of 1.2, 1.4, 1.8, 2.0, and 1.8 points lower on the PCS scale and its Physical Functioning, Role-Physical, Bodily Pain, and General Health subscales, respectively. Finally, relative to respondents in the OSA group with moderate EDS, those with severe EDS scored an average of 1.1, 1.4, 1.3, and 1.8 points lower on the PCS scale and its Physical Functioning, Role-Physical, and Bodily Pain subscales, respectively.

Increased impairment in both work productivity and non–work activity was observed with escalating EDS following a linear trend (Table 4) across all components of the WPAI-GH questionnaire ($P = 0.031$ for absenteeism; $P < 0.001$ for presenteeism, overall work impairment, and non–work activity impairment). WPAI-GH outcomes represent the ratio of impairment to functional potential, with higher numbers indicating greater impairment. Compared with respondents in the OSA group without EDS, those with moderate EDS experienced heightened presenteeism, overall work impairment, and activity impairment, whereas those with severe EDS experienced relatively greater impairment in all aspects of the WPAI-GH, including absenteeism. On a more granular level, there were notable differences between groups with differing levels of severity (Fig. 3). With respect to absenteeism, there was an average percentage point increase of 4.3 (12.0% vs 16.3%) from the

Table 1
OSA respondent demographics by EDS status.

Demographic	OSA/No EDS (ESS, 0–10) n = 1347	OSA/Mild EDS (ESS, 11–12) n = 195	OSA/Moderate EDS (ESS, 13–15) n = 228	OSA/Severe EDS (ESS, 16–24) n = 238
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age, y	60.3 (12.0)	59.2 (14.0)	57.2 (13.1)	57.5 (11.9)
Charlson Comorbidity Index	0.50 (1.11)	0.70 (1.22)	0.74 (1.15)	0.77 (1.21)
	n (%)	n (%)	n (%)	n (%)
Male	970 (72.0%)	130 (66.7%)	152 (66.7%)	153 (64.3%)
Country				
France	462 (34.3%)	46 (23.6%)	65 (28.5%)	46 (19.3%)
Germany	381 (28.3%)	60 (30.8%)	73 (32.0%)	81 (34.0%)
United Kingdom	183 (13.6%)	23 (11.8%)	31 (13.6%)	52 (21.8%)
Italy	145 (10.8%)	31 (15.9%)	24 (10.5%)	24 (10.1%)
Spain	176 (13.1%)	35 (17.9%)	35 (15.4%)	35 (14.7%)
Married/living with partner	949 (70.5%)	127 (65.1%)	157 (68.9%)	165 (69.3%)
College degree	493 (36.6%)	67 (34.4%)	75 (32.9%)	72 (30.3%)
Labour force participation	476 (35.3%)	76 (39.0%)	85 (37.3%)	100 (42.0%)
Obesity (BMI, ≥30 kg/m^2)	659 (48.9%)	87 (44.6%)	114 (50.0%)	141 (59.2%)

BMI, body mass index; EDS, excessive daytime sleepiness; OSA, obstructive sleep apnoea; SD, standard deviation.

mild- to moderate-EDS group and again from the moderate- to severe-EDS group (16.3% vs 20.6%). On the topic of presenteeism, there was an average percentage point increase of 9.3 (25.6% vs 34.9%) from the mild- to moderate-EDS group and of 3.4 from the moderate- to severe-EDS group (34.9% vs 38.3%). As overall work impairment is a composite of absenteeism and presenteeism, the largest increases in overall work impairment were from the mild- to moderate-EDS group (6.7 average percentage point difference; 35.4% vs 42.1%) and from the moderate- to severe-EDS group (6.3 average percentage point difference; 42.1% vs 48.4%). Finally, respondents with moderate EDS experienced more activity impairment than those with mild EDS (6.8 average percentage point difference; 44.8% vs 38.0%).

HCRU within the past 6 months, quantified by number of traditional health care visits, particularly general practitioner (GP), internist, and neurologist visits, increased linearly with EDS severity (Table 5). Compared with respondents in the OSA group without EDS, those with moderate or severe EDS reported a higher number of traditional health care visits, particularly neurologist visits. The steepest change in HCRU with respect to traditional health care visits occurred between the mild- and moderate-EDS groups (average increase, 2.6 visits; 8.3 vs 10.9, respectively). Respondents in the OSA group with severe EDS reported a higher HCRU relative to those without EDS (9.9 vs 8.0 visits, respectively) but not compared with those with moderate EDS. Relative to respondents in the OSA group without EDS, those with moderate EDS reported more GP, internist, neurologist, and psychiatrist visits (3.7 vs 2.8, 0.4 vs 0.2, 0.3 vs 0.2, and 0.4 vs 0.2, respectively), while those with severe EDS reported more hospitalisations and emergency department visits (0.4 vs 0.3 for both, respectively).

The analyses described thus far were performed using the US/RoW EDS cutoffs that are widely used by a variety of stakeholders in the United States and abroad (eg, Australia, China, and certain European organisations) [24,31,32]. However, different sets of sleepiness thresholds are implemented in other regions of the world. For example, in the United Kingdom, the Scottish Intercollegiate Guidelines Network [33] uses sleepiness thresholds of 11–14 (mild), 15–18 (moderate), and 19–24 (severe). These thresholds are endorsed by the British Thoracic Society and are available on patient-accessible portals such as that hosted by the British Snoring

Table 2
Health comorbidities among OSA respondents by EDS status.

Comorbidity (self-reported diagnosis)				
	OSA/No EDS (ESS, 0–10) n = 1347	OSA/Mild EDS (ESS, 11–12) n = 195	OSA/Moderate EDS (ESS, 13–15) n = 228	OSA/Severe EDS (ESS, 16–24) n = 238
	n (%)	n (%)	n (%)	n (%)
Medical				
Insomnia	270 (20.0%)	47 (24.1%)	66 (28.9%)	73 (30.7%)
Other sleep difficulties	126 (9.4%)	25 (12.8%)	41 (18.0%)	46 (19.3%)
Restless legs syndrome	85 (6.3%)	20 (10.3%)	24 (10.5%)	45 (18.9%)
Parkinson disease	4 (0.3%)	3 (1.5%)	1 (0.4%)	1 (0.4%)
Fibromyalgia	47 (3.5%)	6 (3.1%)	10 (4.4%)	24 (10.1%)
High blood pressure	709 (52.6%)	100 (51.3%)	106 (46.5%)	124 (52.1%)
Atrial fibrillation	67 (5.0%)	14 (7.2%)	16 (7.0%)	16 (6.7%)
High cholesterol	521 (38.7%)	73 (37.4%)	92 (40.4%)	104 (43.7%)
Angina	132 (9.8%)	13 (6.7%)	41 (18.0%)	26 (10.9%)
Unstable angina	35 (2.6%)	9 (4.6%)	15 (6.6%)	10 (4.2%)
Asthma	162 (12.0%)	36 (18.5%)	46 (20.2%)	54 (22.7%)
Gastroesophageal reflux disease	233 (17.3%)	43 (22.1%)	58 (25.4%)	55 (23.1%)
Psychiatric				
Depression	359 (26.7%)	62 (31.8%)	90 (39.5%)	121 (50.8%)
Posttraumatic stress disorder	47 (3.5%)	12 (6.2%)	12 (5.3%)	24 (10.1%)

EDS, excessive daytime sleepiness; OSA, obstructive sleep apnoea.

Table 3
Multivariable analysis of quality-of-life outcomes by EDS status using US/RoW cutoffs, adjusting for covariates (N = 2008).[a]

Response Variable (SF-12v2 Scores)	OSA/No EDS (Reference) n = 1347		OSA/Mild EDS (ESS, 11–12) n = 195			OSA/Moderate EDS (ESS, 13–15) n = 228			OSA/Severe EDS (ESS, 16–24) n = 238			*P* (Linear)
	Mean	95% CI	Mean	95% CI	*P* vs No EDS	Mean	95% CI	*P* vs No EDS	Mean	95% CI	*P* vs No EDS	
Mental Component Summary	45.6	45.1 46.2	45.0	43.6 46.4	0.384	42.4	41.1 43.8	<0.001	40.8	39.5 42.1	<0.001	<0.001
Vitality	46.9	46.4 47.4	46.7	45.3 48.0	0.727	45.6	44.4 46.8	0.052	44.2	43.0 45.4	<0.001	<0.001
Social Functioning	44.5	44.0 45.0	43.4	42.0 44.7	0.115	41.0	39.8 42.2	<0.001	40.0	38.8 41.2	<0.001	<0.001
Role-Emotional	42.7	42.1 43.4	41.8	40.2 43.4	0.301	39.3	37.8 40.8	<0.001	37.0	35.5 38.4	<0.001	<0.001
Mental Health	46.6	46.0 47.1	46.3	45.0 47.7	0.743	43.7	42.4 44.9	<0.001	42.1	40.9 43.4	<0.001	<0.001
Physical Component Summary	43.7	43.2 44.2	43.3	42.1 44.6	0.631	42.1	40.9 43.2	0.014	41.0	39.9 42.2	<0.001	<0.001
Physical Functioning	45.4	44.9 45.9	45.0	43.7 46.4	0.575	43.6	42.4 44.9	0.009	42.2	41.0 43.4	<0.001	<0.001
Role-Physical	43.2	42.7 43.7	42.2	41.0 43.5	0.175	40.4	39.3 41.6	<0.001	39.1	37.9 40.2	<0.001	<0.001
Bodily Pain	43.4	42.8 43.9	43.5	42.0 44.9	0.903	41.5	40.1 42.9	0.012	39.7	38.4 41.0	<0.001	<0.001
General Health	42.0	41.5 42.5	41.6	40.4 42.9	0.607	39.8	38.6 40.9	0.001	39.2	38.0 40.3	<0.001	<0.001

CI, confidence interval; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnoea; RoW, rest of world; SF-12v2, 12-Item Short Form Health Survey version 2; US, United States.

[a] Covariates in health-related quality-of-life models included age, Charlson Comorbidity Index, sex, marital status, income level, body mass index category (≥25 [overweight or above] and reference group <25 [underweight, normal weight or unknown]), smoking status, alcohol use, and exercise activity. Covariates were set to the average population values in each generalised linear model.

and Sleep Apnoea Association. Moreover, this set of cutoffs is found on the National Institute for Health and Care Excellence (NICE, the UK's health technology assessment agency) Clinical Knowledge Summaries site [34]. In an effort to evaluate burden using these "UK cutoffs," the multivariable analyses were replicated. The findings remained consistent. HRQoL (SF-12v2) was linearly associated with the level of sleep propensity on the ESS; this association was observed on the MCS and PCS scales and all 8 subscales (Supplementary Table S1). While there were numerical differences in reported SF-12v2 values between the UK and US/RoW OSA group pairings, these differences were not assessed for statistical significance. Compared with the sleepiness groups constructed using the US/RoW ESS cutoffs, the UK cutoff–based sleepiness groups had lower (worse) MCS and PCS scores for all severity tiers (mild, moderate, and severe). A trend analysis using UK cutoffs also demonstrated the linear relationship between severity and all WPAI-GH outcomes (at least $P < 0.05$) except absenteeism (Supplementary Table S2). Nevertheless, compared with their US/RoW counterparts, UK cutoff–derived EDS groups experienced relatively greater (worse) absenteeism, and this was largely observed for the other outcomes of the WPAI-GH questionnaire. Consistent with HCRU reported using US/RoW ESS cutoffs, HCRU defined by UK cutoffs was greater for respondents with EDS (mild, moderate, or severe) than for those without EDS. HCRU increased linearly with EDS severity; this trend was observed for traditional health care, GP, and neurologist visits, but not internist visits (Supplementary Table S3).

4. Discussion

This cross-sectional study utilised real-world data from a large, representative population of survey respondents across 5 European countries to characterise the complex relationship between patient-reported outcomes and one specific pathological aspect of OSA. While sleepiness is frequently reported in the general population, individuals without any evidence of a sleep disorder score between 0 and 10 on the ESS (mean score, 4.6); inversely, those with sleep disorders such as narcolepsy or idiopathic hypersomnia score in the range of 12–24 [26]. Patients diagnosed with OSA may not all manifest or complain of sleepiness [6], and our study focused on survey respondents reporting OSA with or without EDS.

Analysis of demographic characteristics of OSA respondents provided more granular insight into intergroup differences across a multinational European population. Country-specific distribution of EDS suggested that in the EU5, from 25.4% (France) to 37.4% (Spain) of the OSA population experienced some degree of pathological sleepiness. Furthermore, 7.4%–18.0% of OSA respondents reported severe EDS. Geographic differences in OSA-associated EDS morbidity may warrant further investigation and mitigation of the underlying factors contributing to such burden, especially amidst a global pandemic of obesity—a risk factor [35].

Although it was not clear from the data whether EDS was currently treated by medical device or off-label medication, the results of this study do relay that there is an unresolved burden of illness among people with OSA across the EU5. Furthermore, as conveyed by average CCI scores—a weighted sum of multiple comorbid conditions predictive of mortality—OSA patients with EDS reported relatively more health risk factors and disorders, and these frequencies tended to be greatest among those with higher EDS levels. Multiple sources have described overlapping sleep pathologies/diagnoses [36–38]. However, this study of the general population goes further: OSA patients with severe EDS reported more insomnia and other sleep difficulties, as well as restless legs syndrome, fibromyalgia, and depression, than both the non-EDS and mild-EDS OSA groups. While the complex relationship between OSA and depression is still under investigation [39], greater frequencies of psychiatric comorbidities in OSA patients, especially those with more severe levels of EDS, are problematic for the prognosis of various mood disorders [40]. For example, the presence of OSA may inhibit response to pharmacological treatment for depression; undiagnosed OSA may worsen with sedative antidepressant medications, like benzodiazepines [41].

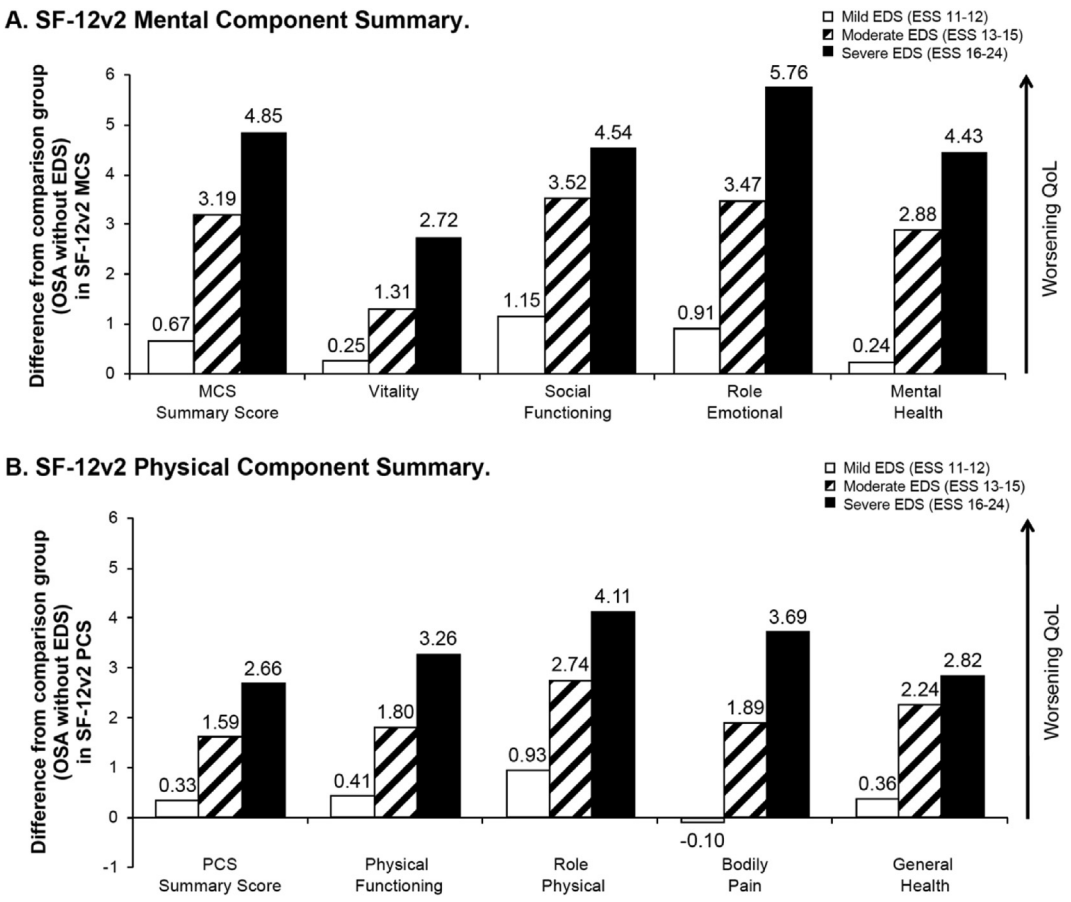

Fig. 2. Health-related quality of life, by severity of excessive daytime sleepiness (EDS) in patients with OSA. Values shown are differences in the mean values between the 3 groups of OSA patients with EDS (severity-specific) and the comparison group of OSA patients without EDS. $P < 0.001$ for the linear trend between increasing EDS severity and all quality-of-life outcomes. EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; MCS, Mental Component Summary; PCS, Physical Component Summary; QoL, quality of life; SF-12v2, 12-Item Short Form Health Survey version 2.

The results of this study also demonstrated that the burden of illness was higher for people with both OSA and EDS than for those with OSA-without-EDS, and that as EDS worsened among patients with OSA, so did HRQoL, work productivity, and HCRU. These data emphasise both the importance of characterising the severity of EDS and the need to manage EDS manifestation among those with

Table 4
Multivariable analysis of WPAI-GH by EDS status using US/RoW cutoffs, adjusting for covariates.[a]

Response Variable	OSA/No EDS (Reference)			OSA/Mild EDS (ESS, 11–12)				OSA/Moderate EDS (ESS, 13–15)				OSA/Severe EDS (ESS, 16–24)				*P* (Linear)
	N	Mean	95% CI	n	Mean	95% CI	*P* vs No EDS	n	Mean	95% CI	*P* vs No EDS	n	Mean	95% CI	*P* vs No EDS	
Absenteeism, % (n = 690)	444	9.7	7.7 12.2	74	12.0	6.7 21.2	0.512	77	16.3	9.4 28.2	0.091	95	20.6	12.5 33.9	0.008	0.031
Hours missed	444	3.9	3.1 4.9	74	4.8	2.7 8.5	0.549	77	6.2	3.5 10.8	0.144	95	7.6	4.6 12.6	0.020	0.054
Presenteeism, % (n = 643)	419	24.5	22.3 26.9	68	25.6	20.3 32.4	0.716	71	34.9	27.9 43.8	0.005	85	38.3	31.1 47.1	<0.001	<0.001
Hours missed due to impairment	419	8.3	7.5 9.2	68	7.4	5.7 9.6	0.431	71	11.1	8.7 14.2	0.033	85	12.3	9.8 15.5	0.002	0.001
Overall work impairment, % (n = 690)	444	30.6	28.0 33.5	74	35.4	28.4 44.1	0.237	77	42.1	33.9 52.2	0.008	95	48.4	39.8 58.8	<0.001	<0.001
Non–work activity impairment, % (n = 2008)	1347	37.4	35.9 39.0	195	38.0	34.1 42.4	0.775	228	44.8	40.6 49.6	0.001	238	48.4	43.9 53.3	<0.001	<0.001

CI, confidence interval; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; OSA, obstructive sleep apnoea; RoW, rest of world; US, United States; WPAI-GH, Work Productivity and Activity Impairment: General Health.

[a] Covariates in absenteeism, overall work impairment, presenteeism, and activity impairment models included age, Charlson Comorbidity Index, sex, marital status, income level, body mass index category (≥25 [overweight or above] and reference group <25 [underweight, normal weight or unknown]), smoking status, alcohol use, and exercise activity. Covariates were set to the average population values in each generalised linear model.

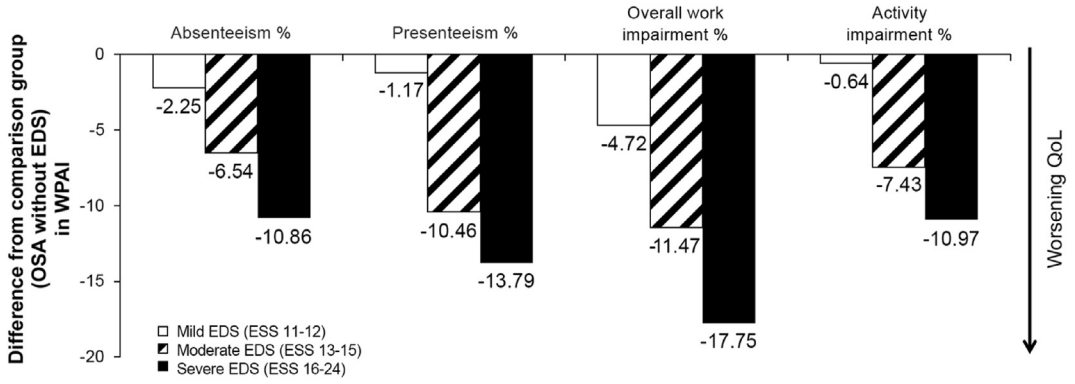

Fig. 3. Work productivity as measured with Work Productivity and Activity Impairment: General Health (WPAI-GH) questionnaire, by severity of excessive daytime sleepiness (EDS) in patients with OSA. Values shown are differences in the mean WPAI-GH values between the 3 groups of OSA patients with EDS (severity-specific) and the comparison group of OSA patients without EDS. Linear trend between increasing EDS severity and WPAI-GH ($P = 0.031$ for absenteeism and $P < 0.001$ for presenteeism, overall work impairment, and non–work activity impairment). EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; QoL, quality of life; WPAI-GH, Work Productivity and Activity Impairment: General Health.

OSA. Improving EDS by one tier of severity has the potential to significantly impact an individual's burden of disease; clinical treatment to improve a patient's EDS, either via their primary airway therapy or, if needed, pharmacological treatment, has the potential to provide a meaningful impact on the patient's quality of life. In addition, as EDS severity is associated with the frequency of other comorbidities, a reduction in EDS may also be associated with overall health improvement.

Findings from this study resonate with those of an experimental nature. For example, results from a phase 2b clinical trial of a wake-promoting agent suggested that a 25% reduction from baseline in ESS score among patients with narcolepsy represents an initial optimal threshold for potentially defining clinically meaningful change [42]. A broader analysis from 5 clinical trials of the same wake-promoting agent among patients with OSA or narcolepsy further suggested that clinically meaningful patient- or clinician-rated improvements—defined as at least minimally or much improved changes—were associated with decreases of 4–6 points (~25%–~38%) on the ESS [43]. A prospective study of patients with OSA treated with CPAP determined that the minimal clinically important improvement (decrease) in ESS was between 2 and 3 points [44]. Collectively, these results support the premise that a relative or absolute clinically meaningful improvement is a feasible goal. Furthermore, quantifying burden along the ESS can provide further details of the discreet impact of manifestations of sleep disorders. Such evidence can be leveraged to inform treatment options, strategies, and priorities for patients, health care providers, managed care/payer entities, public health departments, and other government agencies.

The current study used validated outcome measures to evaluate HRQoL and work/activity impairment. Contextualisation of study results relative to clinical meaningfulness may allow for practical application of the findings. One way of defining clinically meaningful change in HRQoL is to use cross-sectional data to compare

Table 5
Multivariable analysis of HCRU (past 6 months) by EDS status using US/RoW cutoffs, adjusting for covariates (N = 2008).[a]

Response Variable (Number of Visits)	OSA/No EDS (Reference) n = 1347		OSA/Mild EDS (ESS, 11–12) n = 195			OSA/Moderate EDS (ESS, 13–15) n = 228			OSA/Severe EDS (ESS, 16–24) n = 238			Trend *P* (Linear)
	Mean	95% CI	Mean	95% CI	*P* vs No EDS	Mean	95% CI	*P* vs No EDS	Mean	95% CI	*P* vs No EDS	
Traditional health care	8.0	7.6 8.4	8.3	7.3 9.5	0.604	10.9	9.7 12.3	<0.001	9.9	8.8 11.2	0.001	<0.001
General practitioner	2.8	2.7 3.0	2.7	2.3 3.1	0.444	3.7	3.2 4.2	<0.001	3.0	2.7 3.5	0.334	0.025
Internist	0.2	0.1 0.2	0.2	0.1 0.3	0.683	0.4	0.3 0.6	<0.001	0.2	0.2 0.4	0.158	0.042
Nurse practitioner or physician assistant	0.3	0.2 0.4	0.2	0.1 0.4	0.423	0.4	0.2 0.9	0.205	0.4	0.2 0.9	0.200	0.140
Pulmonologist	0.2	0.2 0.3	0.2	0.2 0.3	0.690	0.3	0.2 0.4	0.077	0.2	0.2 0.3	0.860	0.551
Neurologist	0.2	0.1 0.2	0.2	0.1 0.3	0.804	0.3	0.2 0.5	0.012	0.4	0.3 0.7	<0.001	0.001
Psychiatrist	0.2	0.1 0.3	0.2	0.1 0.4	0.870	0.4	0.2 0.6	0.039	0.3	0.2 0.5	0.390	0.209
Emergency department	0.3	0.2 0.3	0.4	0.3 0.5	0.062	0.4	0.3 0.5	0.103	0.4	0.3 0.5	0.014	0.067
Hospitalisations	0.3	0.2 0.3	0.3	0.2 0.4	0.823	0.3	0.2 0.4	0.727	0.4	0.3 0.6	0.022	0.087

CI, confidence interval; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; HCRU, health care resource utilisation; OSA, obstructive sleep apnoea; RoW, rest of world; US, United States.

[a] Covariates in HCRU models included age, Charlson Comorbidity Index, sex, marital status, income level, body mass index category (≥25 [overweight or above] and reference group <25 [underweight, normal weight or unknown]), smoking status, alcohol use, and exercise activity. Covariates were set to the average population values in each generalised linear model. For number of internist visits and number of psychiatrist visits, Poisson distribution was used instead of negative binomial distribution.

groups differing on disease-related criteria, and then taking differences in mean HRQoL values across groups to estimate a minimal clinically important difference (MCID) [45]. This anchor-based approach (so called because it uses other measures that have clinical relevance to compare HRQoL) has been used with the 36-Item Short Form Health Survey [46]. Another more commonly used method utilises longitudinal data—in the form of global ratings of change and/or distribution-based measures, including statistical significance, sample variation, and measurement precision—to derive a threshold of clinically meaningful change [45]. Ultimately, the values derived from these efforts allow qualification of health states both horizontally and vertically. For example, a term related to the MCID, the *minimal important difference (MID),* operationalises the smallest difference that patients perceive as beneficial [47] and has the versatility to inform decision making at individual and group levels [48]. As there are various methods for calculating MCID, which is subsequently contingent on the study population and context, a wide selection of MCID estimates exists [49]. An amalgam or range of values may provide a more comprehensive threshold for assessing meaningful change [50], especially in cases in which disease-specific values are unavailable. Since MCID values for the outcomes assessed in this study have not previously been generated for OSA, this study's cross-sectional dataset enabled us to calculate the difference in mean values between OSA groups, to serve as a point of reference for disease-specific MCIDs on the SF-12v2.

As one of the largest, representative, population-based OSA studies, this analysis demonstrated markedly distinct outcomes among EDS severity groups. Specifically, the differences in PCS and MCS scores between EDS groups (mild, moderate, and severe) were as large as the MCIDs among patients receiving treatment in other therapeutic areas [49–51], suggesting that differences are potentially clinically significant. Similarly, differences in WPAI-GH impairment between OSA groups in this study were similar to the minimally important differences (MIDs; a related but distinct variation of MCIDs) calculated using clinical trial data in an unrelated therapeutic area [52]. A comparison of HCRU in the 3 EDS tiers provides further evidence of the association between expenditures and pathological sleepiness severity. The number of traditional health care visits, and the subset of GP visits, increased as EDS severity worsened, illustrating the serious impact of sleep propensity on patients' lives and on the health care system. Results reported herein demonstrate that patients with OSA and greater EDS severity use health care resources to a greater extent than patients with OSA having normal or mild levels of sleepiness. Given that the safety and efficacy of various pharmacological agents and medical devices for the treatment of OSA and other sleep disorders have been demonstrated in clinical settings, their discernible global impact on patient-reported outcomes in the real world is essential to understanding the patient journey. While comparisons were made at the group level and at a single point in time, these data suggest that ordinal-level improvements in EDS in patients with OSA may lead to corresponding improvements in resource use, quality of life, and work productivity.

This study had several limitations. The NHWS data are collected through direct patient reporting, and therefore external or objective validation of the participant-reported medical (eg, OSA) diagnoses or EDS status could not be performed. In addition, other relevant disease and treatment information, such as sleep apnoea type and OSA treatment utilisation, are not captured in the survey. Further, the study's cross-sectional design did not allow for temporality to be established, and therefore causal inference is not possible. Although the multivariable models adjusted for CCI, other factors contributing to sleepiness, such as insomnia and other sleep disorders, were not included as covariates. This study also evaluated the impact of sleepiness on patient burden regardless of therapy/treatment (pharmacological or medical device); the absence of data regarding underlying treatment may have been a source of confounding. Despite these limitations, this large European study showed the increased burden of OSA, specifically as it pertains to the incremental impact of EDS along the ESS continuum. While previous research has captured the negative consequences of EDS among OSA patients, data have been specific to the United States or Nordic countries. Our current study, in addition to evaluating data from a representative sample of EU5 respondents, adds to the literature by applying an EDS segmentation approach to differentiate the OSA patient burden at each tier of EDS severity—mild, moderate, severe, and none.

5. Conclusions

Patients with OSA and EDS had greater HCRU (more health care provider interactions and emergency department visits), were less productive in and outside of the workplace, and reported worse health-related quality of life (on both the physical and mental health components) compared with patients with OSA-without-EDS. These impairments were associated with EDS severity such that patients reporting worse EDS severity also reported greater HCRU, work and non–work activity impairment, and quality-of-life impairment. These results suggest that patients with both OSA and EDS have a higher socioeconomic and humanistic burden of disease than patients with OSA but no EDS, with the impact of burden contingent on degree of EDS severity.

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Credit author statement

All authors were involved in the concept, data analysis, and writing for this manuscript.

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Ethics statement

The 2017 National Health and Wellness Survey (NHWS) was granted exemption from review by Pearl Institutional Review Board (Indianapolis, IN, USA).

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Conflict of interest

P.J. reports no conflicting interests.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.05.010.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2021.05.010.

References

[1] Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc 2008;5(2):136–43.
[2] Peppard PE, Young T, Palta M, et al. Prospective study of the association between sleep-disordered breathing and hypertension. N Engl J Med 2000;342(19):1378–84.
[3] Peker Y, Carlson J, Hedner J. Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up. Eur Respir J 2006;28(3):596–602.
[4] Punjabi NM, Polotsky VY. Disorders of glucose metabolism in sleep apnea. J Appl Physiol (1985) 2005;99(5):1998–2007.
[5] Jennum P, Ibsen R, Kjellberg J. Social consequences of sleep disordered breathing on patients and their partners: a controlled national study. Eur Respir J 2014;43(1):134–44.
[6] American Academy of Sleep Medicine. Obstructive sleep apnea, adult. In: International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014. p. 53–62.
[7] Engleman HM, Douglas NJ. Sleep. 4: sleepiness, cognitive function, and quality of life in obstructive sleep apnoea/hypopnoea syndrome. Thorax 2004;59(7):618–22.
[8] Onen F, Higgins S, Onen SH. Falling-asleep-related injured falls in the elderly. J Am Med Dir Assoc 2009;10(3):207–10.
[9] de Mello MT, Narciso FV, Tufik S, et al. Sleep disorders as a cause of motor vehicle collisions. Int J Prev Med 2013;4(3):246–57.
[10] Gooneratne NS, Richards KC, Joffe M, et al. Sleep disordered breathing with excessive daytime sleepiness is a risk factor for mortality in older adults. Sleep 2011;34(4):435–42.
[11] Jennum P, Kjellberg J. Health, social and economical consequences of sleep-disordered breathing: a controlled national study. Thorax 2011;66(7):560–6.
[12] Seneviratne U, Puvanendran K. Excessive daytime sleepiness in obstructive sleep apnea: prevalence, severity, and predictors. Sleep Med 2004;5(4):339–43.
[13] Gasa M, Tamisier R, Launois SH, et al. Residual sleepiness in sleep apnea patients treated by continuous positive airway pressure. J Sleep Res 2013;22(4):389–97.
[14] Stepnowsky C, Sarmiento KF, Bujanover S, et al. Comorbidities, health-related quality of life, and work productivity among people with obstructive sleep apnea with excessive sleepiness: findings from the 2016 US National Health and Wellness Survey. J Clin Sleep Med 2019;15(2):235–43.
[15] Pepin JL, Viot-Blanc V, Escourrou P, et al. Prevalence of residual excessive sleepiness in CPAP-treated sleep apnoea patients: the French multicentre study. Eur Respir J 2009;33(5):1062–7.
[16] Ronksley PE, Hemmelgarn BR, Heitman SJ, et al. Excessive daytime sleepiness is associated with increased health care utilization among patients referred for assessment of OSA. Sleep 2011;34(3):363–70.
[17] Asghari A, Mohammadi F. Is apnea-hypopnea index a proper measure for obstructive sleep apnea severity? Med J Islam Repub Iran 2013;27(3):161–2.
[18] Dündar Y, Saylam G, Tatar E, et al. Does AHI value enough for evaluating the obstructive sleep apnea severity? Indian J Otolaryngol Head Neck Surg 2015;67(suppl 1):S16–20.
[19] Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14(6):540–5.
[20] Sweetman A, McEvoy RD, Smith S, et al. The effect of cognitive and behavioral therapy for insomnia on week-to-week changes in sleepiness and sleep parameters in patients with comorbid insomnia and sleep apnea: a randomized controlled trial. Sleep 2020;43(7):zsaa002.
[21] Schweitzer PK, Rosenberg R, Zammit GK, et al. Solriamfetol for excessive sleepiness in obstructive sleep apnea (TONES 3): a randomized controlled trial. Am J Respir Crit Care Med 2019;199(11):1421–31.
[22] Johns MW. Reliability and factor analysis of the Epworth Sleepiness Scale. Sleep 1992;15(4):376–81.
[23] Johns MW. Sensitivity and specificity of the Multiple Sleep Latency Test (MSLT), the Maintenance of Wakefulness Test and the Epworth Sleepiness Scale: failure of the MSLT as a gold standard. J Sleep Res 2000;9(1):5–11.
[24] About the ESS. 2020. Available at: https://epworthsleepinessscale.com/about-the-ess/. [Accessed 9 June 2020].
[25] Donovan LM, Kapur VK. Prevalence and characteristics of central compared to obstructive sleep apnea: analyses from the Sleep Heart Health Study cohort. Sleep 2016;39(7):1353–9.
[26] Johns M, Hocking B. Daytime sleepiness and sleep habits of Australian workers. Sleep 1997;20(10):844–9.
[27] Quan H, Li B, Couris CM, et al. Updating and validating the Charlson Comorbidity Index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol 2011;173(6):676–82.
[28] Cheak-Zamora NC, Wyrwich KW, McBride TD. Reliability and validity of the SF-12v2 in the Medical Expenditure Panel Survey. Qual Life Res 2009;18(6):727–35.
[29] Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics 1993;4(5):353–65.
[30] Kallweit U, Schmidt M, Bassetti CL. Patient-reported measures of narcolepsy: the need for better assessment. J Clin Sleep Med 2017;13(5):737–44.
[31] Guo Q, Song WD, Li W, et al. Weighted Epworth Sleepiness Scale predicted the apnea-hypopnea index better. Respir Res 2020;21(1):147.
[32] Epworth Sleepiness Scale. 2019. Available at: https://www.blf.org.uk/support-for-you/obstructive-sleep-apnoea-osa/diagnosis/epworth-sleepiness-scale. [Accessed 18 February 2021].
[33] Management of obstructive sleep apnoea/hypopnoea syndrome in adults. In: A national clinical guideline 73. Edinburgh, Scotland: Scottish Intercollegiate Guidelines Network; 2003.
[34] Obstructive sleep apnoea syndrome: how should I assess a person with suspected obstructive sleep apnoea syndrome? 2015. Available at: https://cks.nice.org.uk/topics/obstructive-sleep-apnoea-syndrome/diagnosis/assessment/. [Accessed 18 February 2021].
[35] Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet 2014;383(9918):736–47.
[36] Luyster FS, Buysse DJ, Strollo Jr PJ. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. J Clin Sleep Med 2010;6(2):196–204.
[37] Smith S, Sullivan K, Hopkins W, et al. Frequency of insomnia report in patients with obstructive sleep apnoea hypopnea syndrome (OSAHS). Sleep Med 2004;5(5):449–56.
[38] Ohayon M, Thorpy M, Black J, et al. Misdiagnoses and comorbidities among participants in the Nexus Narcolepsy Registry [abstract]. Neurology 2019;92(15 suppl):P3. 6-037.
[39] Ejaz SM, Khawaja IS, Bhatia S, et al. Obstructive sleep apnea and depression: a review. Innov Clin Neurosci 2011;8(8):17–25.
[40] Fleming JA, Fleetham JA, Taylor DR, et al. A case report of obstructive sleep apnea in a patient with bipolar affective disorder. Can J Psychiatr 1985;30(6):437–9.
[41] Schröder CM, O'Hara R. Depression and obstructive sleep apnea (OSA). Ann Gen Psychiatr 2005;4:13.
[42] Scrima L, Emsellem HA, Becker PM, et al. Identifying clinically important difference on the Epworth Sleepiness Scale: results from a narcolepsy clinical trial of JZP-110. Sleep Med 2017;38:108–12.
[43] Lammers GJ, Bogan R, Schweitzer PK, et al. Thresholds for clinically meaningful changes on the Epworth Sleepiness Scale and Maintenance of Wakefulness Test sleep latency [abstract]. Sleep Med 2019;64(suppl 1):S210.
[44] Patel S, Kon SSC, Nolan CM, et al. The Epworth Sleepiness Scale: minimum clinically important difference in obstructive sleep apnea. Am J Respir Crit Care Med 2018;197(7):961–3.
[45] Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol 2003;56(5):395–407.
[46] Ware Jr JE, Sherbourne CD. The MOS 36-Item Short-Form Health Survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30(6):473–83.
[47] Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. Contr Clin Trials 1989;10(4):407–15.
[48] King MT. A point of minimal important difference (MID): a critique of terminology and methods. Expert Rev Pharmacoecon Outcomes Res 2011;11(2):171–84.
[49] Parker SL, Adogwa O, Mendenhall SK, et al. Determination of minimum clinically important difference (MCID) in pain, disability, and quality of life after revision fusion for symptomatic pseudoarthrosis. Spine J 2012;12(12):1122–8.
[50] Parker SL, Godil SS, Shau DN, et al. Assessment of the minimum clinically important difference in pain, disability, and quality of life after anterior cervical discectomy and fusion: clinical article. J Neurosurg Spine 2013;18(2):154–60.
[51] Clement ND, Weir D, Holland J, et al. Meaningful changes in the Short Form 12 physical and mental summary scores after total knee arthroplasty. Knee 2019;26(4):861–8.
[52] Sandborn W, Reilly M, Brown M, et al. Determination of the minimally important difference in WPAI: CD score that indicates a relevant impact on work productivity [abstract P-046]. Inflamm Bowel Dis 2008;14(suppl 1):S24.