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THE EUROPEAN SLEEP APNOEA DATABASE (ESADA)

-- REPORT FROM 22 EUROPEAN SLEEP LABORATORIES

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Abstract

Introduction: The European Sleep Apnoea Database (ESADA) reflects a network of 22 sleep disorder centres in Europe enabled by a COST action B26 program. This ongoing project aims to describe differences in standard clinical care of patients with obstructive sleep apnoea (OSA) and to establish a resource for genetic research in this disorder.

Methods: Patients with suspected OSA are consecutively included and followed up according to local clinical standards. Anthropometrics, medical history, medication, daytime symptoms and sleep data (polysomnography or cardiorespiratory polygraphy) are recorded in a structured web-based report form.

Results: 5103 patients (1426 females, age 51.8±12.6 years, 79.4% with AHI≥5 events/hr) were included from March 15, 2007 to August 1, 2009. Morbid obesity (BMI≥35 kg/m^2) was present in 21.1% of men and 28.6% of women. Cardiovascular, metabolic, and pulmonary comorbidities were frequent (49.1, 32.9 and 14.2%, respectively). Patients investigated with a polygraphic method had a lower AHI than those undergoing polysomnography (23.2±23.5 vs. 29.1±26.3 events/hour, $p<0.0001$).

Conclusion: The ESADA is a rapidly growing multicentric patient cohort that enables unique outcome research opportunities and genotyping. The first cross sectional analysis reveals a high prevalence of cardiovascular and metabolic morbidity in patients investigated for OSAS.

Keywords: comorbidity, European sleep apnoea database, genetic, multi-centre cohort, obstructive sleep apnoea syndrome

Introduction

The obstructive sleep apnoea (OSA) syndrome is a highly prevalent disorder, affecting at least 4% of adult males and 2% of adult females [1,2]. The disorder is associated with recurring episodes of partial or complete upper airway occlusion during sleep which results in marked sleep disturbance, excessive daytime sleepiness (EDS), irritability and morning headache, among others. Sleep apnoea is strongly associated with impaired neuropsychological function, reduced quality of life and social functioning [3]. Daytime sleepiness leads to an increased risk for traffic and industrial accidents [4]. OSAS is also independently associated with several cardiovascular complications, not only systemic hypertension but also ischaemic heart disease and stroke [5-7].

A collaborative European network was established in 2005, as part of the European Union Cooperation in Science and Technology (COST) Action B26 programme, for the purpose of investigating the impact of OSA as a public health burden in Europe. The primary objectives of COST Action B26 were to assess the role of OSA as a possible cause of increased cardiovascular risk and to coordinate studies on pathogenetic mechanisms of increased cardiovascular risk associated with exposure to intermittent hypoxia. Secondary objectives were to promote exchanges between European research groups on the following topics: (i) diagnosis of OSA and patient management; (ii) EDS and medico-legal implications of OSA; (iii) a common protocol to be adopted by all participating centres for data collection during clinical follow-up of treated and untreated OSA patients representative of the European population; (iv) genetic mechanisms of OSA with particular reference to cardiovascular disease, obesity and metabolic

syndrome.

In the frame of COST B26 activities, a collaborative project was initiated, named European Sleep Apnoea Database (ESADA), with the objective to recruit a large prospective cohort of patients with suspected OSA. This paper deals with a number of questions addressed by the ESADA project. Since the project includes patient data from 22 centres throughout Europe and Israel, the database allows an assessment of clinical practices in different countries relating to OSA and to assess how differences in local practices may influence diagnosis and treatment decisions. The data also allows an assessment of different patient profiles among European sleep centres and to explore whether previously described relationships between sleep apnoea and anthropometrics/co-morbidities still pertain despite different clinical/diagnostic procedures used in different European countries.

The present paper addresses the methodological details of the ESADA project, including the study design and the techniques employed for data collection across participating centres. The cross sectional data collected also provides the basis for longitudinal follow-up of the patient cohort.

Methods

General design of the ESADA

The project aims to generate a multinational European database containing data from patients referred to sleep centres due to suspected OSA. In order to obtain a full cross sectional sample patients are included irrespective of comorbidity, concomitant medication and degree of sleepiness. Participating centers individually determine the proportion of locally referred patients to be included in the database but each center is encouraged to enroll as many patients as possible and no specific selection criteria have been applied to those to be enrolled. Thus, centers are requested not to limit recruitment to factors such as clinician on duty, clinics addressing specific patient groups or certain weekdays. These measures aim to limit unintended bias in the recruitment process. Moreover, each centre employs its own established clinical and diagnostic procedures with no attempt to enforce conformity on this process. Data on anthropometrics, clinical and laboratory findings as well as questionnaire based data are transferred and stored in a central database based at the University of Gothenburg, Sweden. A joint scientific committee was formed comprising representatives from the different participating centres to supervise the data collection and analysis, to resolve any practical issues related to the study as well as to coordinate and direct all scientific issues related to the ongoing projects.

Study centres

Study centres were recruited from those represented by the participating members of the COST Action B26. In total, 22 centres (20 of which are university affiliated sleep clinics)

representing 16 countries participate. The affiliation of the centers represent pulmonary medicine, neurology and stand alone units. All centres receive referrals from hospital specialists as well as from general practitioners. The clinical evaluation procedure includes an interview by a sleep physician followed by either an attended/unattended overnight polysomnography (PSG) (n=1602) or polygraphic study (n=3258) according to local practice but performed according to internationally accepted guidelines. Sleep records are scored at each of the centres based on standardized criteria.

Inclusion and exclusion data

Patients suspected for OSA (male or female gender, aged 18-80 years) are eligible for inclusion in the study. Patients must be able to speak, read and understand the local language and possess the ability to respond to questions and follow instructions. Exclusion criteria include patients with already treated sleep apnoea, a limited life expectancy due to illness unrelated to sleep apnoea (e.g. HIV, advanced renal disease, uncontrolled malignancies) as well as a documented alcohol- or drug abuse within one year prior to inclusion in the study.

Ethical considerations

The agreed upon basic protocol was locally approved by the appropriate ethics committee at each of the centres. Future added protocols will be subject to ethical consideration according to local regulations. Wherever appropriate, patients are requested to provide written informed consent for participation in the database.

Web-based data collection format and data quality assurance

ESADA employs a specifically designed web-based data collection format constructed for transfer of data to the central database at the University of Gothenburg, Sweden. Each centre is equipped with a unique log-in to a uniform clinical report format (CRF) module containing 6 predefined submodules (all in the English language) for recording of data. The patient registry is coded and the identity of the patient is kept at the reporting centre and secured with a written patient identity log. Each centre has full access to data stored on its own patients. In order to ensure uniform data entry procedures and data quality, each centre has appointed a specific data manager who was individually instructed by a central study monitor from Gothenburg regarding the type of data in the database, entry procedures and other quality control measures. This has been followed by a practical training session for the study monitor in each of the centres. A detailed protocol describing methods for data acquisition, calculation and reporting has been distributed to all participating centers. The quality assurance program also includes detailed instructions on sleep study scoring rules, classification of comorbidities and coding of concomitant medication. Data quality and completeness is continuously checked by a study monitor with full access to the complete database. The ESADA web report format also enables new and specific CRF modules for specific sub-studies (e.g. specific patient groups, interventional trials, health economy evaluations) that may be initiated by participating centres within the network.

Study flow

Each new patient is evaluated at base line and, if applicable, at clinically relevant follow-up visits (figure 1). Separate CRF modules are provided for each new visit. A CRF page addresses a specific part of the clinical work-up. The protocol does not state a fixed time to follow-up but follows the clinical routine currently applied at each participating centre.

Database structure

Anthropometric data, medical history and concomitant medication

A set of mandatory variables for each entry includes age at diagnosis, gender, race, height, weight, circumference of the neck, waist and hip, heart rate, systolic and diastolic blood pressure (sitting position). A medical history including cardiovascular (e.g. hypertension, ischaemic heart disease, cerebrovascular disease), metabolic (e.g. diabetes, hyperlipidaemia, thyroid disease), pulmonary and psychiatric diseases as well as sleep disorders and other chronic diseases is collected for each patient. Information on all ongoing medications is obtained and reported individually according to the Anatomical Therapeutic Chemical (ATC) Classification System [8] for drug used.

Sleep data

The database has been constructed to accept either cardiorespiratory polygraphic or PSG data pending local practice. The protocol states that limited channel polygraphic recordings including minimum 4 channels (level 3 devices according to the American Association of Sleep Medicine, AASM) [9]. All sleep data is visually examined and manually edited according to protocol definitions before entry into the database. Scoring rules applied according to the protocol are those proposed by the AASM in 2007 [10].

Thus, in a polygraphic recording an apnea/hypopnea event may be scored if there is a clear decrease (≥50%) in the amplitude of a valid measure of airflow (either by thermistors or nasal cannula pressure transducer) during sleep (in case of a hypopnoea a ≥3% oxygen desaturation is required) or the combination of a ≥30% reduction in airflow (compared to pre-event baseline) with at least a 4% reduction of oxygen saturation. A minimum event duration of 10 seconds is required. In a polysomnographic study, in addition to the criteria above, an event (with ≥50% flow reduction) that is associated with arousal is also classified as a hypopnea.

No specific distinction between apnoea and hypopnoea events is made in the report page. Data referring to calculation of indices is based on actual sleep time (polysomnography) or on time lapsed between lights off and lights on (limited channel polygraphic recordings). Polygraphic recordings are requested to include at minimum the following information and indices: analyzed time, subjective sleep time, apnoea hypopnea index (AHI), oxygen desaturation index (ODI-4%), mean SaO_2 and lowest SaO_2. The following indices are reported in PSG recordings in addition to polygraphic recordings: total sleep time, sleep efficiency, percentage of different sleep stages, periodic limb movement (PLM) index, PLM arousal index, respiratory related arousal index, spontaneous arousal index. In the PSG based recordings, respiratory disturbance index (RDI) is additionally calculated as AHI plus respiratory related arousal index. Each recording is graded in terms of technical quality on a three level rating scale. A separate section in the database includes information on follow-up studies.

Blood tests

The protocol states an option to include sampling of blood for analysis of total cholesterol, triglycerides, C-reactive protein, creatinine/urine albumin (optional) and HbA1c. Added protocols include specific blood samples to test various research hypotheses including genetic analysis. Currently obtained blood samples for genetic analysis are kept under coded conditions at the discretion of each participating centre.

Questionnaire data

A variety of questionnaire based instruments are administered at the different centres according to local practice. The following information is used for the purpose of the ESADA database: sleep habit data are based on one question on usual sleep length and one question on usual sleep latency, results from the Epworth Sleepiness Scale (ESS) [11]. Data on health related life style and habits include alcohol consumption (units/week) and smoking (yes/no). Severity of disease is assessed by a Clinical Global Impression rating scale (CGI-S and CGI-I). This is a 7-point scale that requires the clinician to rate the severity of the patient's illness (sleep disordered breathing) at the time of assessment relative to the clinician's experience. Information about driving licence (yes/no, according to European standard classification A/B versus C/D/E) and estimated distance of driving (km/year) is obtained.

Statistics

Continuous data were presented as mean ± SD and compared by independent student t-test. Ordinal data were presented as median and interquartile range and compared by

Mann-Whitney test (SPSS 17.0, Chicago, USA). A P-value less than 0.01 was considered statistically significant.

RESULTS

A total of 22 sleep laboratories currently participate in the ESADA project. Together, the centres have examined 5103 patients, 3677 males and 1426 females (27,8%), suspected for OSA from March 15, 2007 to August 1, 2009 and the recruitment rate in the study has increased to approximately 200 new cases per month. The number of recruited patients per centre ranged from 18 to 856. A blood sample for genetic analysis has been obtained from 744 (14.6%) patients. The incompleteness of various items in the database corresponds to 0.5-10%. Sleep recording quality assessment ranged from excellent (88.3%), 1-2 missing channels (10.4%) to 3-4 channels missing/poor quality (1.3%).

The mean age of the analyses cohort was 51.8 (median 53.0, 95% C.I. 51.5-52.2) years and the BMI was 31.1 (median 30.1, 95% C.I. 31.0-31.3) kg/m^2. Male patients were slightly younger and slightly less overweight compared with females (table 1). The distribution of obesity differed slightly between genders with more females in the normal as well as the morbidly obese range groups when compared with males (20.1 vs.12.4% and 28.6 vs. 21.1%, respectively). Alcohol consumption was higher and smoking history was more frequent in male patients.

Daytime sleepiness was moderate with a median ESS score of 10.0 [8]. Subjectively reported sleepiness was identical in men (10.0 [8], n=3359, ESS>10 in 43.8%) and in women (10.0 [8], n=1315, ESS>10 in 46.5%).

Sleep apnoea (AHI≥5) was diagnosed in 79.4% of included patients (men 83.6%, n=3300 and women 68.5%, n=1275) and the average severity was substantially higher in men compared with women (AHI 27.4±24.7 and 18.3±22.4/h, respectively, p<0.001). The proportion of patients with severe sleep apnea (≥30) is shown in figure 2. The method for diagnosis varied considerably between centres from exclusively PSG to exclusively cardiorespiratory polygraphy. Overall, PSG was used for diagnosis in 33.0% of all included patients. The proportion of patients investigated with PSG at each participating centre is shown in figure 3. Interestingly, patients investigated by PSG had approximately 20% higher AHI when compared with patients investigated by cardiorespiratory polygraphy (29.1±26.3, n=1343 vs. 23.2±23.5, n=3245, p<0.0001, respectively, tables 2 and 3). The mean analysed sleep time in polygraphic recordings was 434±59.2 minutes while the mean objectively assessed total sleep time in patients undergoing PSG studies was 385±81.6 minutes. The difference in AHI between the two groups could not be explained by differences in gender, age, BMI or self reported sleepiness (ESS) (data not shown).

Cardiovascular co-morbidity was frequent (49.1%, table 1) among referred patients and included systemic hypertension, ischaemic heart disease and to a lesser extent cerebrovascular disease. Other common co-morbidities included metabolic disease (32.9%), mainly hyperlipidaemia and diabetes (table 1). Pulmonary disease was also prevalent (14.2%) in the patient cohort. All together, the patients' populations in sleep disorder centres across the ESADA network expressed a high overall co-morbidity both in males and females. Interestingly, cardiovascular co-morbidity was present in 48.6%

and 50.4% of patients investigated by polygraphy and PSG, respectively, suggesting that the sleep diagnostic test procedure was not affected by co-morbidity.

The distribution of comorbidities after stratification of patients according to BMI classes <25, ≥25-<30 and ≥30 kg/m^2 is illustrated in table 4. As expected the severity of OSA expressed as AHI increased linearly from 19±16 to 25±19 and 36±5 per hour across the three groups. Similarly, the prevalence of systemic hypertension, all cardiovascular disease, metabolic disease, pulmonary disease as well as ESS score increased with BMI class and was, with the exception of pulmonary disease, consistently higher in patients with OSA within each BMI class.

Discussion

The ESADA study has been initiated to systematically investigate patient characteristics, diagnostic procedures and treatment outcome at European sleep disorders centres. This project that specifically addresses patients referred to a sleep centre with suspected OSA diagnosis currently involves 22 sleep centres from 16 countries across Europe. The web-based report format has enabled rapid recruitment and the database represents a growing resource for assessment of morbidity, co-morbid conditions, medication and health economical evaluation in OSA. Moreover, the database will enable future outcome research, strategic search for biological markers of disease and risk, and genetic studies in sleep apnoea.

The ESADA cohort was started as a result of a collaborative network of researchers in the European COST action B26 program recognizing that health care allocations for diagnosis and treatment of OSA are unevenly distributed across Europe. Hence, the program aims to identify improved standard of care and better conformity in sleep medicine practice. The ESADA has also recognized the lack of a large scale sleep laboratory patient cohort that includes systematically collected information on sleep study data, anthropometrics, prevalence of co-morbid conditions, and records of ongoing medication. It is believed that such cohorts are needed to enable future genetic and outcome research in OSA.

The first data analysis of the ESADA has demonstrated an approximately four fold difference between centres in terms of reported severe sleep apnoea. This difference appears to reflect considerable variation in referral patterns and possibly variable public and professional awareness of OSA across Europe. The sleep study method, which varied between centres, appeared to influence the reported AHI as the average severity was approximately 20% higher in patients investigated with PSG and not explained by gender, age, BMI or subjective sleepiness. It is likely the wider definition of hypopnea, that includes a classification based on arousal, in part accounted the difference. Another explanation would be that the analysis time (lights off to lights on) includes wake periods during the night leading to a dilution of the reported AHI value as demonstrated by data from the Sleep Heart Health Study [12]. In fact, this interpretation was supported by the 13% difference between patients with objectively assessed total sleep time by PSG and analyzed time in patients undergoing polygraphic recording.

In this study, sleep apnoea severity was higher among males than females as expected [13] whereas there was no difference between men and women in terms of self reported measures of sleepiness. This finding appears to support those of another population study the used an AHI cut-off of 15 and reported a similar proportion of men and women in the sleepy and non-sleepy groups [14]. Other observations include the high prevalence of cardiovascular and metabolic disease which confirms previously published studies [15-17]. Moreover, consistent with several of these studies both sleep apnea and obesity appears to contribute to cardiovascular and metabolic morbidity. Taken together it appears that the ESADA, by representing a sleep laboratory cohort, will recruit

proportionally far more severe cases with sleep disordered breathing than those reported in other large scale population studies such as the Sleep Heart Health Study [18] and the Wisconsin Sleep Cohort [1].

The ESADA cohort represents a unique cohort in several aspects. However, the applied recruitment system offers both strengths and weaknesses. The inclusion criteria in the study were adapted to the locally applied clinical routines at each centre in order to visualize differences in medical practice and referral patterns. Data obtained will therefore reflect current practice and will be influenced by geographical differences and differences in health care systems. This degree of local conformity has enabled an acceleration of patient recruitment with more than 5000 patients included into the study during the first 28 months. One additional facilitating factor is the web-based report format that guarantees conformity of reported data sets. Instructions were given to avoid preselection bias during recruitment and centres were asked to apply randomness in the inclusion of new patients into the cohort. Recruited patients will therefore reflect those produced by the local referral patterns. Data on comorbid conditions and medications will reflect the characteristics of patients referred for suspected OSA across European centres. Similarly, routines for treatment will vary between centres as well as the applied standards for follow-up of treated patients. The protocol is not designed to change any currently applied routines and the data base will therefore contain patients with various forms of treatment investigated at different time points after initiation of treatment.

Some methodological weaknesses of the ESADA cohort represent compromises to the recruitment environment. For instance, the non-standardization of sleep test equipment

may be seen as a weakness that may lead to a reduced sharpness of OSA severity classification. However, by accounting for type of diagnostic equipment used, a future prospective analysis will provide a unique possibility to evaluate if the recording technique used has an influence on patient outcome. Blood samples for risk factor classification are obtained in all participating patients but the timing of sampling has not been standardized. Hence, samples may be affected by diurnal variation and in some cases non-fasting conditions. Information on comorbidity is obtained by different methods such as hospital registry data, subjective report from the patient, or by information obtained from the referral notes. Admittedly this may lead to incomplete information and classification. Only 14.3% of this sleep laboratory cohort is normal weight (up to 25kg/m^2). Thus analyses of comorbidities in normal-weight OSA may be less powerful than in over-weight OSA. Clinical investigations for classification of end-organ damage by e.g. echocardiography, radiological investigation or electrocardiography are not systematically performed for evident reasons. Hence, conditions such as left ventricular hypertrophy or cardiac arrhythmia may be consistently underreported as no objective data is obtained. It is also possible that additional resources should be focused at improved phenotypic characterization of sleep apnoea cases. This may be particularly interesting considering that blood samples for genetic analysis are obtained in the study. Phenotypic information, such as facial structure, upper airway structural measures using various imaging techniques, were considered too complex for general application in the protocol but the continued recruitment into the database may enable future sampling of this type of data in one or several participating centres.

In summary, the ESADA study represents a large scale multi-centric collaborative approach to rapidly recruit one of the worlds largest ongoing observational cohorts of patients with sleep disordered breathing. This first cross sectional analysis has confirmed a high prevalence of cardiovascular and metabolic morbidity in referred patients. The cohort is expected to enable a unique opportunity to perform in-depth analyses of local referral patterns and to define occurrence of co-morbid conditions in patients seen at different European sleep centres. Other opportunities include large scale outcome research based on genotyping and potentially identification of biomarkers for sleep disordered breathing.

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Table 1. Selected anthropometric data, modifiable risk factors and co-morbid conditions

	Gender								
	Female			Male			Total		
	Mean	N	Std. Deviation	Mean	N	Std. Deviation	Mean	N	Std. Deviation
Age (years)	53.6	1426	12.6	51.2	3677	12.6	51.8	5103	12.6
BMI (kg/m^2)	31.5	1420	7.6	31.0	3658	6.1	31.1	5078	6.5
Normal Weight BMI<25	20.1%			12.4%			14.5%		
Overweight BMI ≥25-30	28.1%			37.5%			34.8 %		
Obese BMI ≥30-35	23.2%			28.9%			27.5 %		
Morbidly obese BMI≥35	28.6%			21.2%			23.2 %		
Waist (cm)	102.3	1399	17.0	108.5	3505	15.0	106.8	4904	15.9
Hip (cm)	109.7	1399	19.6	107.6	3498	14.2	108.2	4897	16.0
Neck (cm)	37.5	1404	5.0	42.5	3520	4.1	41.0	4924	4.9
Waist/Hip ratio	0.96	1399	0.23	1.02	3497	0.16	1.00	4896	0.19
% Current smoker	21.3%	296/ 1388		26.0%	936/ 3596		24.7%	1232/ 4984	
Alcohol consumption (units/week)	1.9	971	3.7	4.7	2726	7.8	4.0	3697	7.1
Overall cardiovascular co-morbidity (CVD)	48.7%	670/ 1376		49.3 %	1747/ 3542		49.1 %	2417/ 4918	
Number of CVD diagnosis									
1	35.7 %	491		34.4 %	1217		34.7 %	1708	
2	9.4 %	129		10.8 %	384		10.4 %	513	
3	2.2 %	30		3.1 %	110		2.8 %	140	
≥4	1.4 %	20		1.1 %	36		1.1 %	56	
Overall metabolic disease (MD)	35.0%	487/ 1389		32.1%	1145/ 3575		32.9 %	1632/ 4964	
Number of MD diagnosis									
1	26.6%	370		23.4%	835		24.3%	1205	
2	6.7%	93		7.3%	260		7.1%	353	
≥3	1.7%	24		1.4%	50		1.5%	72	

Table 2. Selected sleep data on sleep and breathing in subjects examined with polygraphy in the ESADA cohort.

	Gender								
	Female			Male			Total		
	Mean	N	Std. Dev.	Mean	N	Std. Dev.	Mean	N	Std. Dev.
AHI (n/hr)	16.9	929	21.1	25.7	2316	23.9	23.2	3245	23.5
No sleep apnoea AHI <5	33.2%			18.2%			22.5%		
Mild sleep apnoea AHI 5-<15	30.8%			26.4%			28.6%		
Moderate sleep apnoea AHI ≥15-<30	19.2%			22.2%			20.4%		
Severe sleep apnoea AHI ≥ 30	16.8%			33.2%			28.5%		
ODI (n/hr)	14.5	788	20.8	22.3	1860	23.4	19.9	2648	22.9
Mean SaO_2 (%)	93.8	918	4.3	93.2	2267	3.4	93.4	3185	3.7
Lowest SaO_2 (%)	82.5	914	9.4	80.8	2259	9.5	81.3	3173	9.5
Subjective sleep time (min)	359.2	580	97.7	365.2	1427	98.0	363.4	2007	97.9
Analysed sleep time (min)	439.2	843	53.1	432.2	2002	61.5	434.2	2845	59.2

Table 3: Sleep study results on patients investigated by polysomnography

	Gender								
	Female			Male			Total		
	Mean	N	Std. Deviation	Mean	N	Std. Deviation	Mean	N	Std. Deviation
AHI (n/hr)	22.3	365	25.0	31.7	978	26.3	29.1	1343	26.3
No sleep apnoea AHI <5	26.0%			12.2%			15.9%		
Mild sleep apnoea AHI 5-15	28.2%			21.1%			23.9%		
Moderate sleep apnoea AHI >15-30	20.9%			23.1%			22.4%		
Severe sleep apnoea AHI > 30	24.9%			42.6%			37.8%		
ODI (n/hr)	17.6	426	23.5	23.5	1141	24.8	21.9	1567	24.6
Mean SaO_2 (%)	93.6	428	3.7	93.1	1154	4.6	93.2	1582	4.4
Lowest SaO_2 (%)	83.7	428	10.2	81.2	1149	11.1	81.9	1577	11.3
Total Sleep time(min) by PSG	385.1	428	82.7	384.9	1151	81.3	385.0	1579	81.6
Subjective sleeptime (min) by questionnaire	402.6	230	91.5	396.6	690	91.4	398.1	920	91.4

Table 4: Prevalence of various comorbidities in patients with or without OSA stratified for body mass index (BMI) according to WHO criteria

Weight status	Normal weight (<25 kg/m^2) N=644 Mean (SD) BMI 23±2 kg/m^2		Overweight (≥25-<30 kg/m^2) N=1583 Mean (SD) BMI 28±1 kg/m^2		Obesity (≥30 kg/m^2) N=2273 Mean (SD) BMI 36±5 kg/m^2	
OSA status	No OSA AHI 2±1 /h	OSA AHI 19±16 /h	No OSA AHI 2±1 /h	OSA AHI 25±19 /h	No OSA AHI 2±1 /h	OSA AHI 37±27 /h
Prevalence systemic hypertension (%)	11.8	27.9	21.8	38.1	30.6	58.5
Prevalence all CV disease (%)	18.7	38.9	29.2	47.7	40.3	64.9
Prevalence all metabolic disease (%)	11.3	20.9	22.6	28.9	32.5	43.6
Prevalence all pulmonary disease (%)	8.9	14.3	14.6	13.5	20.0	18.5
Prevalence hypersomnia defined by ESS ≥10 (%)	34.9	39.0	41.1	43.1	43.3	49.3

Figure 1: Overview of the ESADA study patient flow

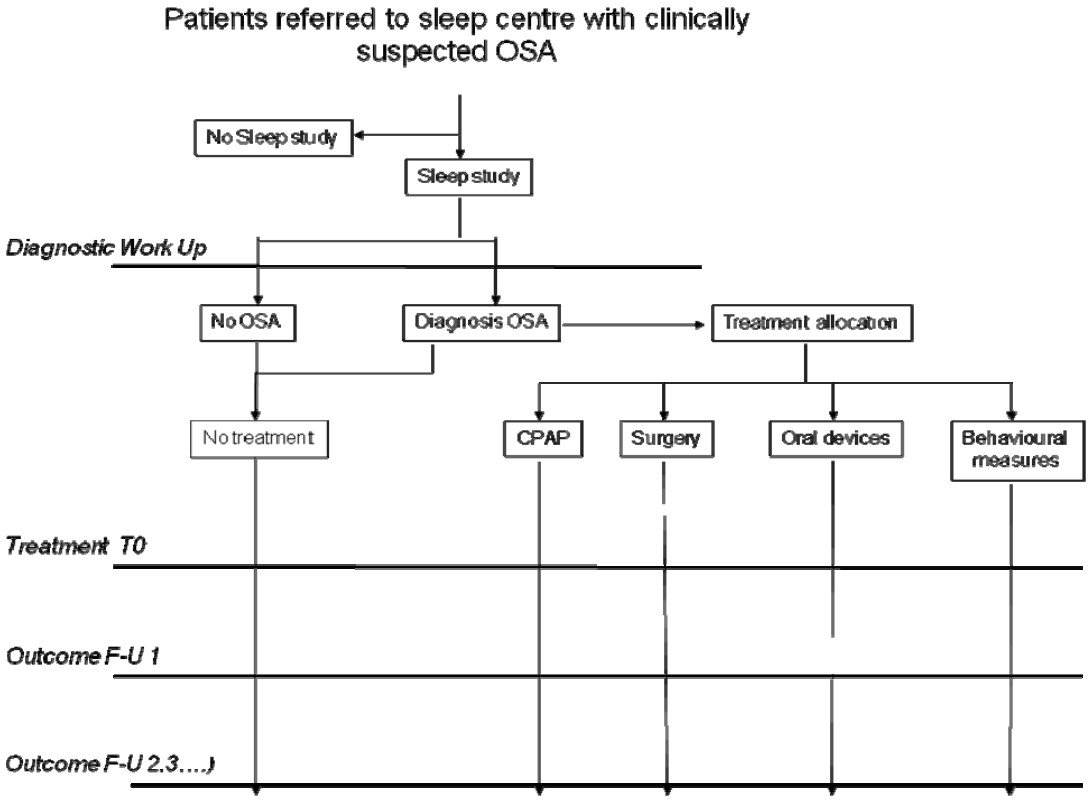

Figure 2. The proportion of patients with severe OSA (AHI≥30) at each centre participating in the ESADA study.

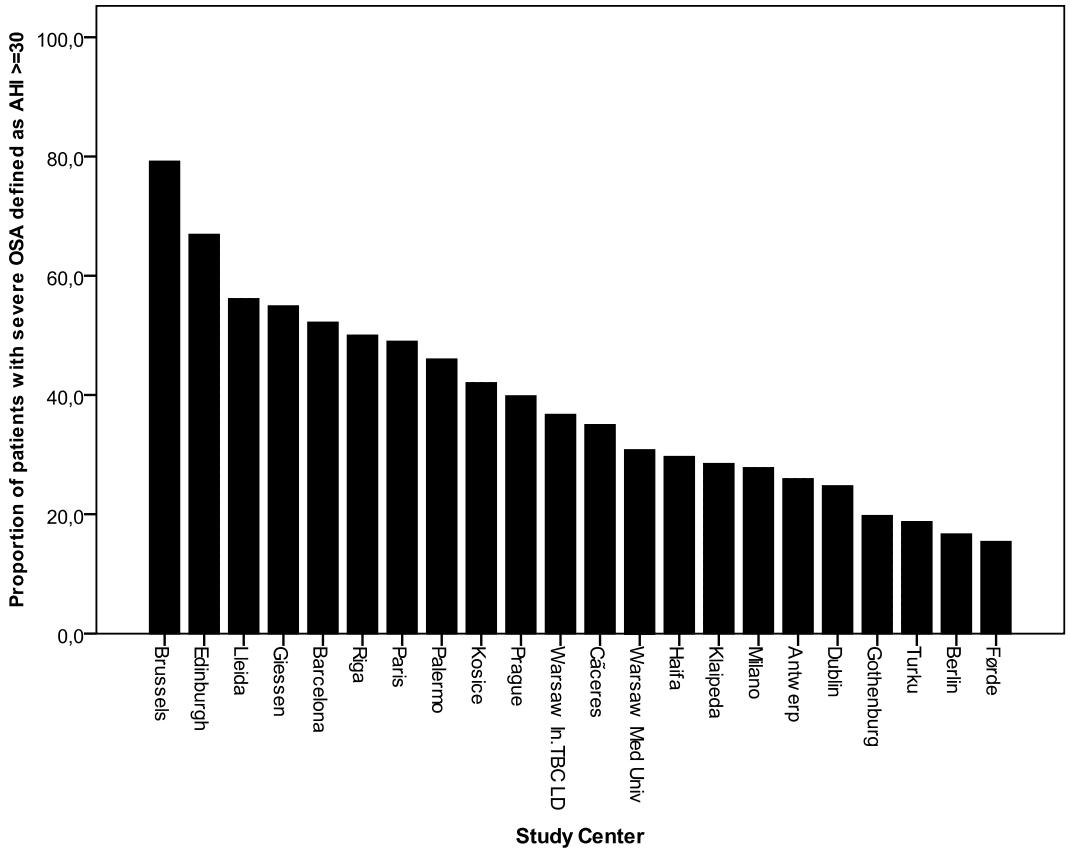

Figure 3. The proportion of patients studied with a polysomnographic sleep study at each centre participating in the ESADA study.