Baseline clusters and the response to positive airway pressure treatment in obstructive sleep apnoea patients: longitudinal data from the European Sleep Apnea Database cohort

Ashraf Yassen[1,13], Katrin Coboeken[1,13], Sébastien Bailly[2], Rolf Burghaus[1], Jitka Buskova[3], Zoran Dogas[4], Marta Drummond[5], Haralampos Gouveris[6], Pavol Joppa[7], Joerg Lippert[1], Carolina Lombardi[8,9], Stefan Mihaicuta[10], Jean Louis Pépin[2], Ding Zou[11], Jan Hedner[11,12,14] and Ludger Grote[11,12,13] and the ESADA collaborators

[1]Pharmacometrics/Modeling and Simulation, Research and Development, Pharmaceuticals, Bayer AG, Leverkusen, Germany. [2]University Grenoble Alpes, Inserm, CHU Grenoble Alpes, Grenoble, France. [3]National Institute of Mental Health, Klecany, Czech Republic. [4]Department of Neuroscience, Sleep Medicine Center, University of Split School of Medicine, Split, Croatia. [5]Sleep and Non-Invasive Ventilation Unit of University Hospital São João, Medicine Faculty of Porto, Porto, Portugal. [6]ENT Department at Mainz University Hospital, Mainz, Germany. [7]Department of Respiratory Medicine and Tuberculosis, Faculty of Medicine, P.J. Safarik University and L. Pasteur University Hospital, Kosice, Slovakia. [8]Istituto Auxologico Italiano IRCCS, Sleep Disorders Center, San Luca Hospital, Milan, Italy. [9]Departmed of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy. [10]Centre for Research and Innovation in Precision Medicine of Respiratory Diseases, Department of Pulmonology, "Victor Babes" University of Medicine and Pharmacy, CardioPrevent Foundation, Timisoara, Romania. [11]Department of Internal Medicine and Clinical Nutrition, Center for Sleep and Wake Disorders, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. [12]Department of Pulmonary Medicine, Sleep Disorders Center, Sahlgrenska University Hospital, Gothenburg, Sweden. [13]Joint first authors. [14]Joint senior authors.

Corresponding author: Ludger Grote (ludger.grote@lungall.gu.se)

Shareable abstract (@ERSpublications)
20 164 patients from the European Sleep Apnea Database were assigned to seven phenotypic clusters at baseline. A limited reduction in daytime sleepiness following positive airway pressure treatment was shown in two out of seven clusters. https://bit.ly/3byAUHe

Cite this article as: Yassen A, Coboeken K, Bailly S, *et al*. Baseline clusters and the response to positive airway pressure treatment in obstructive sleep apnoea patients: longitudinal data from the European Sleep Apnea Database cohort. *ERJ Open Res* 2022; 8: 00132-2022 [DOI: 10.1183/23120541.00132-2022].

Received: 15 March 2022
Accepted: 30 July 2022

Abstract

Introduction The European Sleep Apnea Database was used to identify distinguishable obstructive sleep apnoea (OSA) phenotypes and to investigate the clinical outcome during positive airway pressure (PAP) treatment.

Method Prospective OSA patient data were recruited from 35 sleep clinics in 21 European countries. Unsupervised cluster analysis (anthropometrics, clinical variables) was performed in a random sample (n=5000). Subsequently, all patients were assigned to the clusters using a conditional inference tree classifier. Responses to PAP treatment change in apnoea severity and Epworth sleepiness scale (ESS) were assessed in relation to baseline patient clusters and at short- and long-term follow-up.

Results At baseline, 20 164 patients were assigned (mean age 54.1±12.2 years, 73% male, median apnoea–hypopnoea index (AHI) 27.3 (interquartile range (IQR) 14.1–49.3) events·h^{-1}, and ESS 9.8±5.3) to seven distinct clusters based on anthropometrics, comorbidities and symptoms. At PAP follow-up (median 210 [IQR 134–465] days), the observed AHI reduction (n=1075) was similar, whereas the ESS response (n=3938) varied: largest reduction in cluster 3 (young healthy symptomatic males) and 6 (symptomatic males with psychiatric disorders, −5.0 and −5.1 units, respectively (all p<0.01), limited reduction in clusters 2 (obese males with systemic hypertension) and 5 (elderly multimorbid obese males, −4.2 (p<0.05) and −3.7 (p<0.001), respectively). Residual sleepiness in cluster 5 was particularly evident at long-term follow-up (p<0.05).

Conclusion OSA patients can be classified into clusters based on clinically identifiable features. Importantly, these clusters may be useful for prediction of both short- and long-term responses to PAP intervention.

Introduction

Obstructive sleep apnoea (OSA) is a common disorder with considerable health burden [1]. Arterial hypertension and other cardiovascular diseases are present in a subgroup of ∼50% of OSA patients [2]. Excessive daytime sleepiness, cognitive dysfunction, upper airway structural and functional changes, obesity, hyperlipidaemia and diabetes have all been associated with the OSA disorder [3]. Mechanical remedies like positive airway pressure (PAP) are known to reduce OSA but both compliance with, and response to, the treatment may vary considerably between patients [4].

OSA severity is conventionally expressed in terms of the apnoea–hypopnoea index (AHI). However, the association between the AHI on one hand and symptoms, comorbidities and treatment outcome on the other is weak [5–8]. This suggests that current diagnostic methods are insufficient to correctly detect patients at particular risk or those specifically suitable for a particular form of therapy [9].

Several studies on phenotype explored physiological, structural, polysomnographic and clinical characteristics in order to overcome limitations of the conventional AHI-based OSA severity classification [10]. Many cluster studies, including our own previous studies of the European Sleep Apnea Database (ESADA) material, are cross-sectional, and there is therefore a need for expanded prospective, longitudinal analyses data in the field [11–14]. We applied a cluster analysis in the multinational ESADA cohort to address individual differences in the expression of OSA at baseline and if such differences might predict the outcome of PAP treatment. We hypothesised that the cluster approach unmasks patient groups with specific responses to PAP therapy.

Methods

The ESADA database

The ESADA is a Pan-European, multicentric registry that contains clinical data on OSA patients from 35 sleep clinics across 21 countries [15]. The ESADA was established to investigate the role of OSA on driving as well as on cardiovascular and metabolic morbidity. There is also a prospective component in the registry which captures tolerance, compliance and outcome of intervention in patients with sleep disordered breathing. Data collected in the ESADA are transferred from individual centres to the central database at the University of Gothenburg, Sweden.

Patients

Adult patients with suspected sleep apnoea had been enrolled in the ESADA during the period March 2007 to December 2020 (n=33 443, study flow chart figure 1). Patients referred for assessment at any of the participating centres and with suspected sleep apnoea were enrolled in the database; patients with

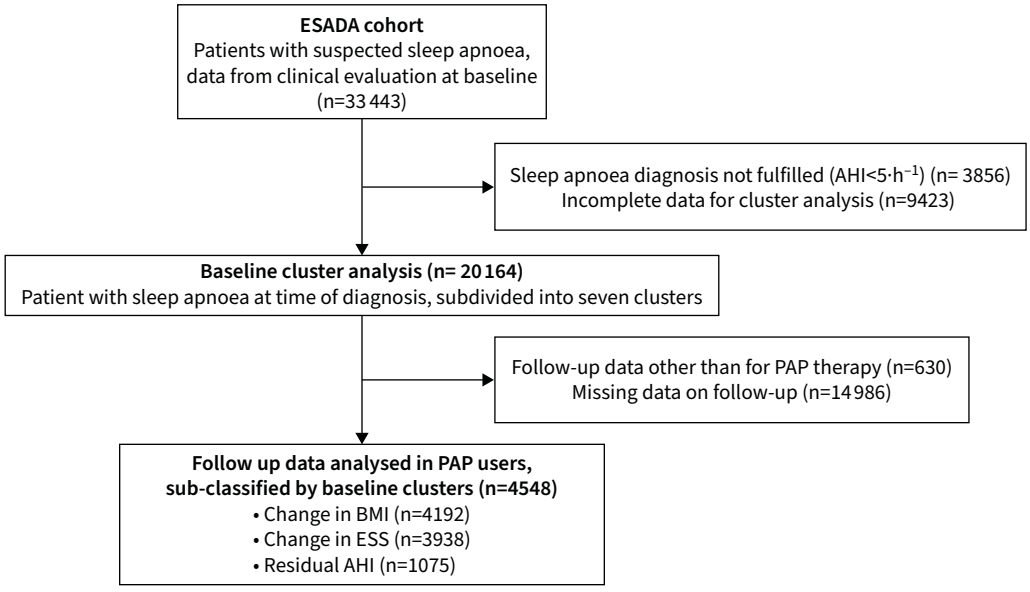

FIGURE 1 Study flow chart. ESADA: European Sleep Apnea Database; AHI: apnoea–hypopnoea index; PAP: positive airway pressure; BMI: body mass index; ESS: Epworth sleepiness scale.

diagnosed or treated OSA, ongoing substance abuse or short life expectancy were excluded. Only patients with an AHI ⩾5 events·h^{-1} and complete data for the cluster procedure were included in the final analysis set (n=20 164). At baseline, demographic, anthropometric and clinical variables, including measured body mass index (BMI), smoking history, comorbidities and medication use, were obtained from multiple sources (clinical interview, medical records, referral and/or medication list) and recorded for each patient. Intended therapy, including PAP treatment, was logged. Research ethics committee approval for the study was obtained at each of the participating centres. Oral and/or written informed consent was obtained from all participants.

A detailed analysis of the sleep study methodology used in the ESADA has been published elsewhere [16]. Either cardiorespiratory polygraphy (n=8603) or full polysomnography (n=11 561) was performed in accordance with local practices. All sleep data were manually edited according to standardised procedures and criteria published by the American Academy of Sleep Medicine (AASM) from 2007 including both recommended and alternative criteria for hypopnoeas [17]. Oxygen desaturation index (ODI) was defined as ⩾4% oxygen desaturations per hour of sleep/analysis time. The Epworth sleepiness scale (ESS) score was used to assess subjective daytime sleepiness [18].

Cluster analysis

The cluster analysis was performed in various consecutive steps.

1. Cluster analysis relied on nine clinical baseline variables (continuous variables: age, BMI, mean subjective sleep length, mean subjective sleep latency; categorical variables: sex, cardiovascular comorbidities, metabolic comorbidities, pulmonary comorbidities, other comorbidities; for details see tables 1 and 2).
2. A random sample of 5000 individuals was drawn from the ESADA database and clusters were identified using the Partitioning Around Medoids (PAM) algorithm (R cluster package version 2.0.6) [19, 20]. The dissimilarity matrix was calculated using a Gower distance to account for the mixture of numerical and categorical variables [21].
3. A conditional inference tree (R package party function ctree) [22] was trained to predict the cluster membership of the patients in the random sample and subsequently used to predict the cluster membership in the remaining patients. The obtained conditional inference tree predicted the correct cluster in 95.5% of patients.
4. Various cluster sizes ranging from 2 to 10 were evaluated. For each cluster number the steps 1 to 3 were repeated 10 times, each time with a different set of randomly chosen 5000 individuals for step 1. The number of clusters was chosen such that the Jaccard coefficient [23, 24] in a bootstrapping procedure as a measure of cluster robustness was maximised. The cluster number 7 that generated the largest Jaccard coefficient was finally selected.

TABLE 1 Patient baseline characteristics for the full population (All) and by cluster (mean±SD) or median (interquartile range) for AHI and ODI

	All	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7	p-value
Subjects n	20 164	3386	3488	5053	1600	2017	2553	2067	
Age years	54.1±12.2	57.1±10.7	58.4±10.5	47.3±11.8	59.2±10.2	61.1±10.0	48.8±12.0	54.3±11.5	<0.001
Female %	27	12	20	0.02	92	14	16	100	<0.001
BMI kg·m^{-2}	32.1±6.6	33.5±6.3	31.8±6.1	31.0±5.8	35.1±7.8	33.2±6.4	30.7±6.2	31.8±7.9	<0.001
AHI events·h^{-1}#	27.3 (14.1–49.3)	35.0 (19.0–57.6)	28.0 (14.9–48.9)	26.0 (13.8–50.0)	26.4 (13.7–48.7)	32.4 (17.6–54.0)	24.0 (12.1–43.7)	19.2 (10.7–34.0)	<0.001
ODI events·h^{-1}#	22.4 (10.1–45.8)	31.4 (15.0–57.0)	23.0 (11.0–44.0)	21.1 (9.7–46.0)	23.0 (11.0–47.0)	28.1 (13.6–51.1)	15.7 (7.1–35.4)	15.1 (7.1–31.7)	<0.001
ESS score	9.8±5.3	9.8±5.2	9.4±5.2	10.0±5.3	10.0±5.3	9.6±5.1	10.3±5.4	9.8±5.5	<0.001
Sleep length h	6.9±1.6	6.7±1.6	6.9±1.5	6.8±1.4	7.0±1.8	6.9±1.7	7.0±1.6	6.9±1.5	<0.001
Sleep latency min	25.5±29.2	26.4±31.9	23.4±26.0	21.9±25.0	33.4±34.5	25.5±29.9	25.5±29.7	29.9±31.9	<0.001
PAP-Tx %	46.9	52.4	42.5	45.9	53.6	51.2	42.8	43.5	-
ESS data at follow-up %	19.5	24.2	18.2	15.5	24.9	23.8	21.3	13.5	-

BMI: body mass index; AHI: apnoea–hypopnoea index; ODI: oxygen desaturation index; ESS: Epworth sleepiness score; sleep length: mean subjective sleep length (h); sleep latency: mean subjective sleep latency (min); PAP-Tx: patients assigned to positive airway pressure treatment at the end of the baseline diagnostic workup. #: for AHI and ODI the median and interquartile range (25th to 75th percentile of data) rather than mean±SD were reported given their skewed distributions.

TABLE 2 Patient comorbidity characteristics for the full population (All) and by cluster

	All	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	Cluster 6	Cluster 7	p-value
Subjects n	20 164	3386	3488	5053	1600	2017	2553	2067	
Cardiovascular comorbidities %									
Systemic hypertension	47.2	80.2	86.3	6.3	73.6	81.5	7.4	14.1	<0.001
Ischaemic heart disease	9.1	14.5	12.2	0.7	11.2	28.3	1.9	1.9	<0.001
Status post myocardial infarction	2.4	3.3	3.4	0.1	1.7	9.9	0.2	0.2	<0.001
Cardiac failure	2.7	4.5	3.9	0.1	4.1	8.5	0.2	0.2	<0.001
TIA or stroke	2.3	2.9	4.2	0.1	3.1	6.3	0.7	0.7	<0.001
Valvular heart disease	1.4	1.9	1.9	0.1	1.9	4.4	0.6	0.4	<0.001
Left ventricular hypertrophy	1.4	1.8	1.7	0.6	1.1	2.6	0.7	2.0	<0.001
Pulmonary hypertension	0.5	0.7	0.8	0	0.6	1.5	0	0.3	<0.001
Metabolic comorbidities %									
Hyperlipidaemia	23.2	62.5	0.1	6.7	45.0	46.2	13	7.4	<0.001
Diabetes, noninsulin dependent	13.4	27.1	0	3.5	39.1	39.2	3.1	3.6	<0.001
Diabetes, insulin dependent	2.4	4.8	0	0.4	5.8	9.0	0.4	0.6	<0.001
Hyperuricaemia	3.3	9.4	0	0.7	5.0	9.0	1.1	0.3	<0.001
Pulmonary comorbidities %									
Asthma	5.7	4.8	5.8	3.4	12.4	5.4	5.4	7.5	<0.001
COPD	5.7	8.6	6.5	2.9	6.4	10.5	3.2	3.8	<0.001
Respiratory failure	0.8	0.9	0.8	0.2	1.4	1.4	0.8	0.6	<0.001
Other comorbidities %									
Malignant disease	2.0	0.7	1.5	0	4.7	5.7	4.0	1.9	<0.001
Inflammatory disease	1.9	0.8	1.0	0	6.0	3.5	4.0	2.0	<0.001
Neurological disease	4.8	2.2	3.2	0	10.1	9.1	14.7	2.2	<0.001
Gastrointestinal disease	8.6	2.1	2.8	0	24	25.5	21.4	4.6	<0.001
Psychiatric disease	9.5	3.2	6.0	0	26.1	9.5	33.3	5.3	<0.001

TIA: transitory ischaemic attack.

Treatment outcome analysis

The follow-up was undertaken in the subgroup of patients with current PAP treatment (see table 1 for proportion of patients assigned for PAP and figure 1 for the actual number of patients with follow-up data). AHI, ESS score, BMI and adherence with treatment at follow-up were captured at the follow-up visits. Differences for these variables in relation to the baseline values were calculated and summarised for each of the clusters. Given the large variation in timing (30 days to >1 year) and frequency (*e.g.* multiple visits within 6 months *versus* one visit/year) of follow-up visits between the centres, a subsequent longitudinal treatment outcome analysis was conducted. To this end, the follow-up time was classified as short-term (30 to ⩽180 days), mid-term (181 to ⩽365 days) or long-term (>1 year), restricted up to and including follow-up visits 1 and 2. In cases with multiple visits within a given time window the median value was used for analysis. Acceptable adherence with PAP treatment was defined as mean user time ⩾4 h/night [25].

Statistical analysis

Statistical analysis was performed using R (version 3.5.3). The categorical variables were calculated as per cent within one cluster. Numerical variables, including the AHI, the 4% ODI and the ESS were presented as mean±SD or as median (IQR, 25th to 75th percentile) and categorical variables as count (%). Differences among clusters were analysed by ANOVA analysis for the numerical variables and by chi-square test for the categorical variables. Changes in AHI, ESS and BMI were computed for each cluster and for each follow-up period. A p-value <0.05 is considered statistically significant.

Results

Segmentation of OSA patients by clusters

Median age was 55 (IQR: 46–63) years and there was a strong male dominance (73%) (table 1). The median/mean AHI, ODI and ESS scores were 27.3 (IQR 14.1–49.3) events·h^{-1}, 22.4 (IQR 10.1–45.8) events·h^{-1} and 9.8±5.3, respectively.

The analysis identified seven clusters each with a specific profile with respect to age, symptoms, anthropometrics and comorbidities (tables 1 and 2, figure 2). A detailed description of the main

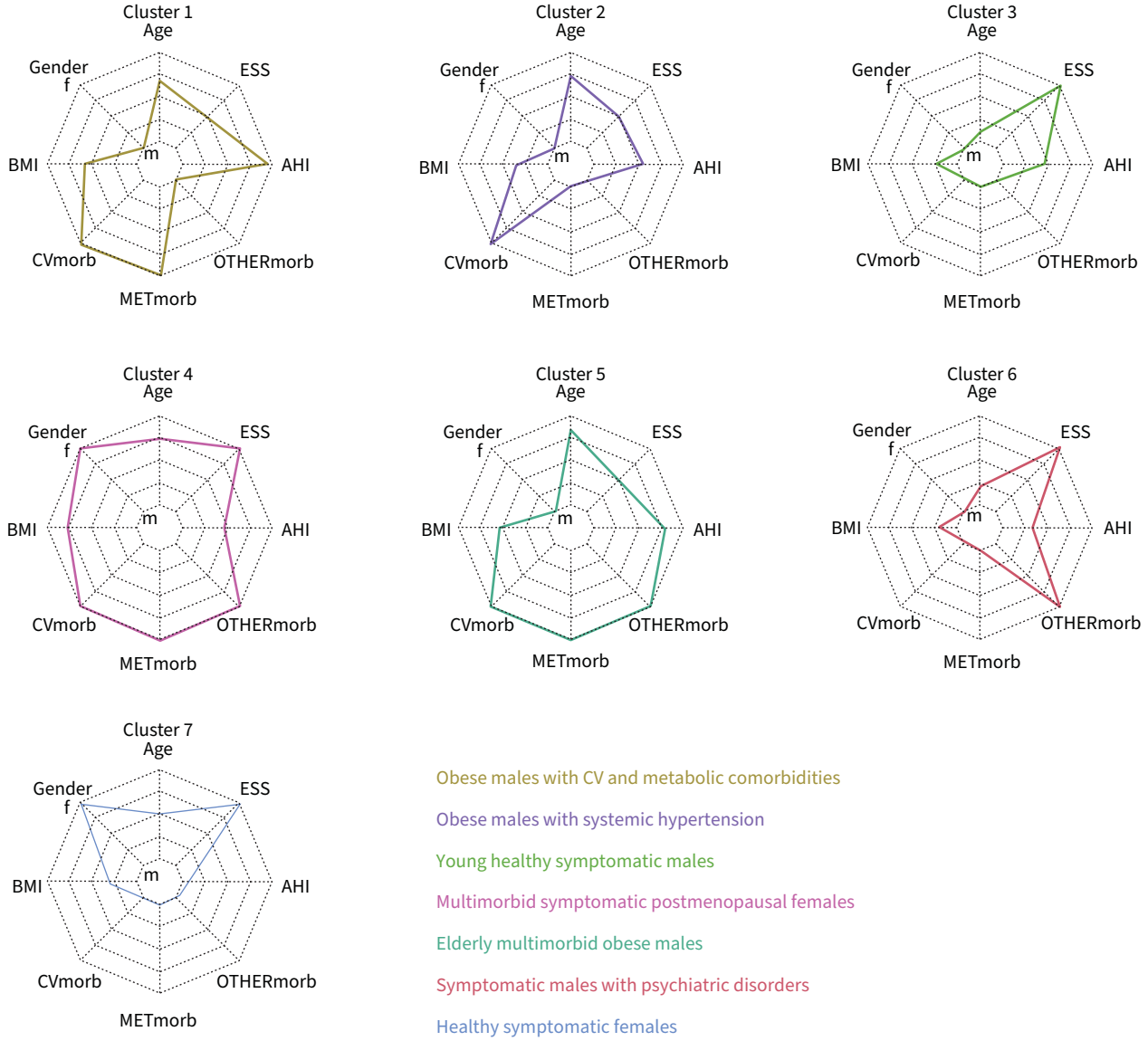

FIGURE 2 Spider charts of characteristics of obstructive sleep apnoea (OSA) patients to highlight the differences among the seven clusters. The variables displayed in the spider charts that reflect characteristics of OSA patients are body mass index (BMI), age, sex, apnoea–hypopnoea index (AHI), Epworth sleepiness scale (ESS), cardiovascular comorbidities (CVmorb), metabolic comorbidities (METmorb) and other comorbidities (OTHERmorb). For the respective clusters the median (categorical variables) or mean (continuous variables) value was calculated for each of the variables and represented by solid lines in the spider chart. For cardiovascular, metabolic and other comorbidities the related median values are either 0 (comorbidities not present) or 1 (comorbidities present). For sex, the related median values correspond to males (m) or females (f). In the spider plot the continuous variables are ranked from lowest mean (in the centre of the spider plot) to highest mean (edge of the spider plot). See table 1 for the range of mean values for continuous variables and table 2 for the comorbidities summary statistics.

characteristics for each cluster is provided below. In general, women dominated two clusters (4 and 7) while three clusters (1, 2 and 5) included predominantly males. There was also a high prevalence of hypertension (>80%) in these clusters. Cluster 6 was characterised by male dominance with a high prevalence of psychiatric disorder (33.3%). Metabolic disorders were most prevalent in clusters 1, 4 and 5.

Cluster 1: Obese males with cardiometabolic disease

Obese males with cardiovascular and metabolic comorbidities dominated cluster 1. Arterial hypertension (80.2%), ischaemic heart disease (14.5%) and metabolic comorbidities (62.5%) were common in this cluster. This cluster harboured the most severe OSA cases in the cohort.

Cluster 2: Obese males with dominant cardiovascular disease

Patients in cluster 2 shared several similarities with cluster 1 in terms of age, BMI and OSA severity. However, metabolic comorbidities were not prevalent (<1% of patients) despite a high prevalence of cardiovascular disease (68.3% systemic hypertension and 12.2% ischaemic heart disease).

Cluster 3: Young healthy symptomatic males

Cluster 3 represented almost a quarter of all patients and contained younger, overweight males with very few comorbidities. This group did not differ from the other clusters with respect to sleepiness (mean ESS of 10±5.3) or sleep apnoea frequency.

Cluster 4: Multimorbid obese postmenopausal females

This cluster was almost completely composed of postmenopausal women (92%) with multiple comorbidities including cardiovascular, metabolic, respiratory, gastrointestinal tract and psychiatric disorders. Obesity was most prevalent in this female cluster (BMI 35.1±7.8 $kg \cdot m^{-2}$).

Cluster 5: Elderly multimorbid obese males

Patients in cluster 5 were among the oldest (median age of 61.1±10 years). Comorbidities including cardiovascular, metabolic, respiratory, gastrointestinal tract and psychiatric disorders were prevalent and mirrored the comorbidity spectrum of cluster 4. Male OSA patients (86%) with moderate-to-severe OSA dominated this cluster.

Cluster 6: Symptomatic males with psychiatric disorders

This cluster was mainly composed of male OSA patients with lower mean age, BMI and AHI compared with the other clusters (except cluster 3 and 7). Psychiatric and neurological (33.3% and 14.3%, respectively) as well as gastrointestinal disorders (21.4%) were prevalent in this cluster.

Cluster 7: Healthy symptomatic females

This cluster was composed of middle-aged females with low degree of sleep apnoea but with proportionally prevalent symptomatology. Comorbidities were relatively infrequent in this group, and this cluster shared several characteristics with the purely male cluster 3.

PAP treatment – outcome by clusters

General description of the follow-up cohort

The proportion of patients studied during PAP follow-up differed between clusters (table 1). Median follow-up duration was 210 (IQR 134–465) days. Information on changes in AHI, ESS and BMI at the first follow-up visit was available in 1075, 3938 and 4192 patients, respectively. This corresponded to 5.3% (AHI) and 19.5% (ESS) of the patients investigated at baseline. The distribution of follow-up data varied between 13.5% for cluster 7 and 24.9% for cluster 4 (ESS analysis). A treatment adherence of at least 4 h per day was reached by ∼75.5% of patients without clinically relevant difference between clusters (supplementary figure 1e).

Change in sleep apnoea activity following PAP treatment

Overall, the mean AHI reduction following PAP for each cluster-based subgroup was associated with the AHI at baseline. As shown in figure 3, there was a statistically significant mean reduction in AHI of 33.5 ±25.3 $events \cdot h^{-1}$ compared to baseline observed in cluster 1 ($p<0.05$; obese males with cardiometabolic disease). The results in figure 3 also show that there were no statistically significant differences in mean AHI reduction between clusters 2 to 7. Interestingly, a subsequent analysis of short-term (30–180 days), mid-term (181–365 days) and long-term (>1 year) outcome showed that numerically (and not statistically significant) the AHI reduction tended to vary between clusters, and in general the largest reductions in AHI were observed at short term, but both differences in AHI reduction between clusters and magnitude of AHI reduction within each cluster had decreased at long-term follow-up (figure 4, supplementary table 1e). Accordingly, residual sleep disordered breathing (AHI ⩾15) was low and did not differ between clusters.

Change in ESS score following PAP treatment

The overall mean reduction of ESS was 4.6±5.1 units, and statistically relevant differences in ESS reduction were observed between clusters (figure 3, supplementary table 2e). The largest reduction in ESS was observed in clusters 3 (young healthy symptomatic males) and 6 (symptomatic males with psychiatric disorders) with mean change of 5.0 and 5.1 units, respectively ($p<0.01$). This may be contrasted to clusters 2 (obese males with systemic hypertension) and 5 (elderly multimorbid obese males) where the reduction in ESS was 4.2 ($p<0.05$) and 3.7 ($p<0.001$) units, respectively. During treatment, the short-term

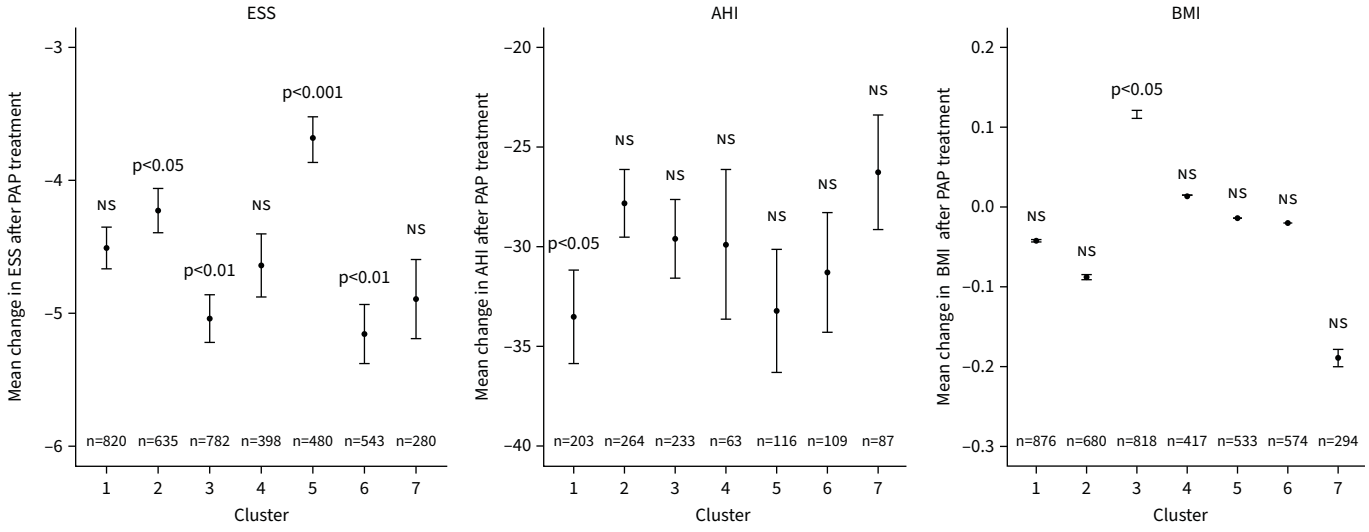

FIGURE 3 Mean±SE change in Epworth sleepiness scale (ESS), apnoea–hypopnoea index (AHI) and body mass index (BMI) at follow-up visit 1 for each cluster in patients treated with positive airway pressure (PAP). The number of obstructive sleep apnoea patients (n) and p-values (ANOVA) (NS: not significant) are depicted for each cluster.

improvements were stronger in cluster 6 ($p<0.001$) whereas the impaired ESS response in cluster 5 was even more evident at long-term treatment ($p<0.05$, figure 5).

Change in BMI during PAP treatment

Finally, when comparing clusters we identified a small BMI increase in cluster 3 (young healthy symptomatic males, $p<0.05$, figure 3) which was only seen at long-term follow-up.

Discussion

In this large, multinational OSA patient population study we identified seven distinct OSA subtypes that differed in terms of age, sex, comorbidities, symptoms and the degree of apnoea frequency. Two clusters

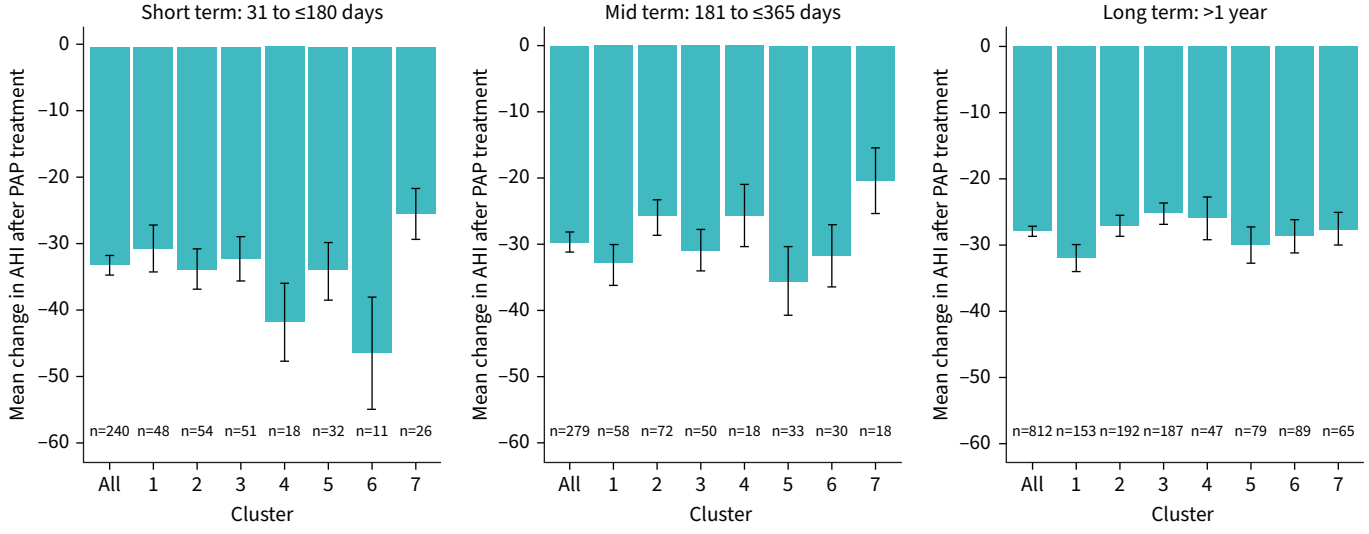

FIGURE 4 Mean±SE change in apnoea–hypopnoea index (AHI) at follow-up visit 1 or 2 for the full population (All) and for each cluster stratified by time of visit (short-term: 31 to ⩽180 days; mid-term: 181 to ⩽365 days and long-term: >1 year) relative to baseline visit. There was no statistically significant difference in the AHI change between clusters (ANOVA p=0.11 for short-term: 31 to ⩽180 days; ANOVA p=0.22 for mid-term: 181 to ⩽365 days, ANOVA p=0.34 for long-term: >1 year). PAP: positive airway pressure.

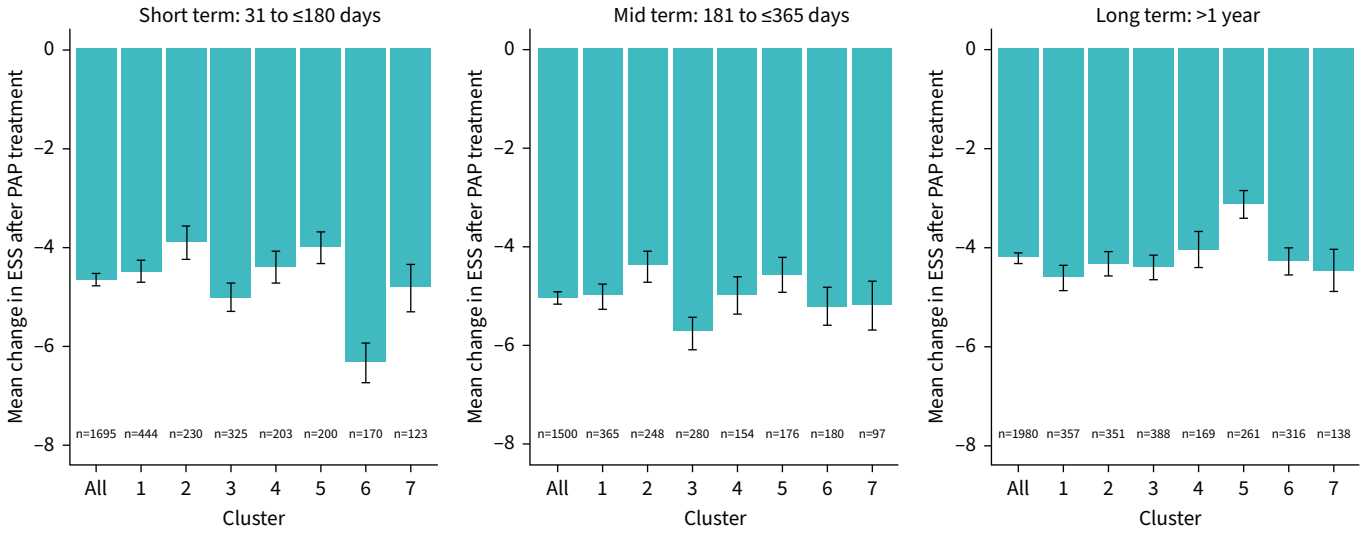

FIGURE 5 Mean±SE change in Epworth sleepiness scale (ESS) score from baseline to follow-up visit 1 or 2 is shown for the full population (All) and for each cluster stratified by time of visit (short-term: 31 to ⩽180 days; mid-term: 181 to ⩽365 days and long-term: >1 year) relative to baseline visit. Statistically significant difference in the ESS change from baseline between clusters within each class of visit time was observed (ANOVA p<0.001 for short-term: 31 to ⩽180 days, ANOVA p<0.05 for long-term: >1 year). No statistically significant (ANOVA p=0.08) differences in ESS change was observed in the visit window mid-term: 181 to ⩽365 days. PAP: positive airway pressure.

were dominated by females, three clusters had a high prevalence of hypertension whereas three additional clusters had a low prevalence of cardiometabolic comorbidities. At follow-up, PAP adherence was high across clusters (75% with PAP usage ⩾4 h·day^{-1}). Interestingly, the daytime sleepiness response to PAP therapy varied between clusters despite a homogeneous AHI reduction. Two clusters characterised by high cardiovascular comorbidity showed less improvement of daytime sleepiness. In conclusion, clustering of patients may identify specific OSA phenotypes, thereby predicting the response to therapy.

Several cluster analyses have attempted to phenotype OSA patients [11–14, 26–35]. An Icelandic cohort cluster study, which based the analysis on symptoms and comorbidities, identified three major clusters containing highly symptomatic, asymptomatic and sleep-disturbed patients [12]. In the current study insomnia was not systematically characterised in our patients, but we identified a cluster of multimorbid females with sleep complaints indicated as substantially increased sleep latencies (cluster 4). Clinical excessive daytime sleepiness according to the ESS score was almost equally distributed among clusters at baseline. With respect to response to PAP treatment the largest change in ESS was observed in symptomatic males with psychiatric disorders (cluster 6) and healthy males (cluster 3), while the smallest reduction in ESS was observed in clusters 2 and 5 (males with predominantly cardiovascular comorbidities). These findings are in line with results from the SAVE and RICCADSA studies showing that response to PAP treatment is of limited use in asymptomatic elderly OSA patients with established cardiovascular comorbidities [8, 36]. However, a direct comparison of the current findings with results from SAVE and RICCADSA should be done cautiously given that both studies are randomised clinical trials with strict inclusion/exclusion criteria, while in the current study a patient database (ESADA) was used reflecting “all-comers” to tertiary European sleep centres [37]. In addition and in contrast to the Icelandic study, cardiovascular morbidity was more prevalent in association with excessive daytime sleepiness in our cohort, and we identified the subgroup of multimorbid women with particularly prevalent cardiovascular disease. The reasons for these discrepancies remain unclear but may depend on the parameters included in the cluster analysis and referral patterns difference in the two studies.

Several approaches for OSA phenotyping have been presented recently [3]. One study used feature extraction from polysomnographic data to identify OSA phenotypes (clusters) and to assess the associations between phenotypes and cardiovascular outcomes [35]. Seven clusters of polysomnographic characteristics were identified and the cluster with frequent periodic limb movements showed the highest cardiovascular event rate during follow-up. Unfortunately, a detailed analysis of polysomnographic data was not performed in our study as the current format of the ESADA does not collect all detailed sleep recordings. Another study clustered patients according to pathophysiological characteristics of breathing

during sleep such as arousal threshold, loop gain, neuromuscular activation and anatomical factors in relation to upper airway collapse [38]. The analysis aimed to identify components useful for implementation of personalised medicine rather than prediction of outcome. In fact, a substantial overlap between physiologically defined apnoea-promoting factors, which has been described in a single patient, creates further challenges in treatment research [39]. Taken together, those studies addressing phenotyping or endotype will expand the classification of sleep apnoea beyond the traditional AHI-based severity matrix. Novel, clinically useful information may be gained from a combination of structural and functional characteristics, symptom burden and comorbidities of the individual OSA case [40].

Some of the considerable variability of OSA phenotypes described so far may be related to the heterogeneity of patient populations studied or the use of different diagnostic tools. In this context, the ESADA cohort represents one of the largest multicentric and multinational OSA patient cohorts. A recent latent class clustering analysis of the ESADA cohort also included information on concomitant medication and site of residence in the European region [14]. The objective of this previous study was to explore patient clusters at baseline in the ESADA. The study identified eight clusters and four of them were sex dominated. Important differences in prescription of treatment were identified between clusters suggesting that specific patient characteristics influence prescription patterns. The current study had the objective to evaluate outcome of OSA treatment using yet an additional cluster analysis methodology where sleep apnoea severity or the degree of daytime sleepiness at baseline were not included as cluster variables because these factors are already well known to drive adherence to PAP treatment [41]. Based on this approach and despite comparable degree of daytime sleepiness and AHI at baseline, and a similar compliance with PAP, we identified clusters with a particularly good (cluster 6) but also poor (cluster 5) response to therapy. Patient specific characteristics, *e.g.*, comorbidity spectrum or co-medication, may determine the perceived effect of OSA therapy.

Analysis of PAP outcomes according to baseline clusters has been performed in 709 patients of the Icelandic sleep cohort [42]. Using advanced statistical modelling, the authors demonstrated that the symptom improvement varied substantially between the three different clusters identified at baseline. This is in line with our findings. However, the study applied more comprehensive symptom evaluation before and during PAP treatment compared with the ESADA study design and data completeness was high. Analysis addressing if other factors than PAP treatment were responsible for the change in symptoms is also important [43]. Such factors may include changes in lifestyle, body weight, medication or socioeconomic factors. In our analysis of the ESADA, we aimed to show if subgroups of patients clustered based on baseline information may identify differences in response to PAP treatment. It was not the goal to analyse the adjusted effect size of PAP treatment on patient outcomes. A recent study in a multicentric French cohort of OSA patients studied the PAP outcome in 3090 patients [29]. At baseline, five clusters were identified by latent class analysis. PAP compliance was lower in the clusters labelled as “female OSA”, “mildly symptomatic OSA” and “comorbid OSA” compared with the cluster labelled as “severe OSA syndrome”. Interestingly, we could not identify a similar difference in adherence to PAP treatment between our seven clusters. Thereby, the current cluster analysis of the ESADA cohort advances the understanding of the heterogeneity of clinical OSA phenotypes in Europe regarding baseline characteristics as well as PAP treatment outcomes.

The strengths and limitations of our study need to be considered. First, this is to our knowledge among the largest prospective patient cohort studied by means of cluster analysis. The multicentric design increases the generalisability of our findings [44]. Second, our study provides a comprehensive description of comorbidities in the cluster analysis. Comorbidities were validated by sleep physicians and use of concomitant medication (ATC codes). Third, our study contains follow-up data controlling for PAP use and variable treatment duration in a considerable number of patients which allows for outcome analysis in patient subgroups. Fourth, the ESADA study protocol allows inclusion of almost all patients seen for evaluation of suspected sleep apnoea. It also allows the methodologies applied in clinical routine and follows the patients during the management process over time. Thereby, the ESADA can be viewed as a clinical quality registry providing a reference for the diversity of European OSA patient management. Indeed, we found a considerable overlap between cluster characteristics similar to what has been shown elsewhere.

A number of limitations need also to be stated. First, it is important to note that there was a considerable overlap between cluster characteristics similar to what has been shown elsewhere. It is possible that more specific clusters are needed to provide clinically useful tools for OSA severity classification and outcome prediction. Second, more detailed information including measures of hypoxic burden and upper airway collapsibility, upper airway imaging data, more detailed evaluation of daytime and night-time symptoms,

and socioeconomic factors was not available in the current analysis. Third, detailed information on insomnia diagnosis, concomitant sleep disorders like restless legs or circadian rhythm disorders were not available in our analysis. Fourth, the ESADA includes patients diagnosed with both polygraphy and polysomnography, and AHI at follow-up is captured by sleep recordings or from the PAP devices. These differences in methodology affect the accuracy of the AHI metric at both baseline and follow-up, but no data suggest that the difference in methodology would systematically be affected by cluster allocation. Further, AHI was an outcome, not a variable, in our cluster analysis at baseline. Finally, PAP treatment outcome analysis was performed in the subgroup of patients with actual data assessments at follow-up excluding 14 986 both treated and untreated OSA patients from analysis due to missing data. This substantial loss of patients at follow-up may create a bias towards patients with higher PAP adherence and thereby provides an incomplete picture of the patient cluster at baseline. Interestingly, this study limitation has been observed even in other large registry studies [29, 41].

Our study findings have important clinical applications. First, the current cluster analysis advances our understanding of the heterogeneity of clinical OSA phenotypes in Europe. Second, patient clusters characterised by high comorbidity load and older age may respond with less significant symptom improvement when compared with otherwise healthy OSA patients. Hence tailored OSA management plan and follow-up strategies are needed. On the other hand, although the ESS response to PAP treatment was statistically different between clusters, further studies are warranted to prove its clinical relevance. Third, our data suggest that PAP-treated patients may require long-term monitoring to document full control of OSA (AHI <5). Finally, the current clustering of patients by mathematical modelling is one opportunity to better understand the heterogeneity of OSA patients, and further development is needed to use OSA patient clustering in clinical routine.

In conclusion, OSA patients are heterogeneous and can be sub-classified into clusters based on clinically identifiable characteristics. Importantly, the identified cluster characteristics may be useful for prediction of symptom improvement after PAP intervention.

Provenance: Submitted article, peer reviewed.

ESADA collaborators: P. Steiropoulos (Sleep Unit, Department of Pneumonology, Democritus University of Thrace, Alexandroupolis, Greece), J. Verbraecken and E. Petiet E (Multidisciplinary Sleep Disorders Centre, Antwerp University Hospital and University of Antwerp, Antwerp, Belgium), G. Trakada (Pulmonary Medicine, National and Kapodistrian University of Athens, Athens, Greece), I. Fietze, T. Penzel and N. Laharnar (Schlafmedizinisches Zentrum, Charité – Universitätsmedizin Berlin, Germany), O. Ludka (Department of Cardiology, University Hospital Brno and International Clinical Research Center, St Ann's University Hospital, Brno, Czech Republic), I. Bouloukaki and S. Schiza (Sleep Disorders Unit, Department of Respiratory Medicine, Medical School, University of Crete, Greece), W.T. McNicholas (Department of Respiratory Medicine, St Vincent's University Hospital, Dublin, Ireland), S. Ryan (Pulmonary and Sleep Disorders Unit, St Vincent's University Hospital, Dublin, Ireland), R.L. Riha (Department of Sleep Medicine, Royal Infirmary, Edinburgh, UK), J.A. Kvamme (Sleep Laboratory, ENT Department, Førde Central Hospital, Førde, Norway), L. Grote, J. Hedner and D. Zou (Sleep Disorders Center, Pulmonary Department, Sahlgrenska University Hospital, and Center of Sleep and Wake Disorders, Sahlgrenska Academy, Gothenburg University, Gothenburg, Sweden), D. Pevernagie (Sleep Disorders Center, Ghent University, Ghent, Belgium), S. Bailly, J.L. Pépin JL and R. Tamisier (Université Grenoble Alpes, INSERM HP2 (U1042) and Grenoble University Hospital, Grenoble, France), H. Hein (Sleep Disorders Center, St Adolf Stift, Reinbeck, Germany), O.K. Basoglu and M.S. Tasbakan (Department of Chest Diseases, Ege University, Izmir, Turkey), J. Buskova (Department of Sleep Medicine, National Institute of Mental Health, Klecany, Czech Republic), P. Joppa (Department of Respiratory Medicine and Tuberculosis, Faculty of Medicine, P.J. Safarik University and L. Pasteur University Hospital, Kosice, Slovakia), R. Staats (Department of Respiratory Medicine, Hospital de Santa Maria, Lisbon, Portugal), D. Testelmans (Sleep Disorders Centre, University Hospital Gasthuisberg, Leuven, Belgium), H. Gouveris and K. Ludwig (ENT Department at Mainz University Hospital, Mainz, Germany), C. Lombardi and G. Parati (Istituto Auxologico Italiano, IRCCS, Department of Cardiovascular, Neural and Metabolic Sciences, St. Luke Hospital, Milan & Department of Medicine and Surgery; University of Milano-Bicocca, Milan, Italy), M.R. Bonsignore (PROMISE Department, University of Palermo, Palermo, Italy), F. Fanfulla (Unità Operativa di Medicina del Sonno, Istituto Scientifico di Pavia IRCCS, Pavia, Italy), M. Petitjean and G. Roisman (Unité de Médecine du Sommeil, Hopital Antoine-Beclere, Clamart, France), M. Drummond and M. van Zeller M (Pulmonology Department Hospital São João, Medicine Faculty of Porto University, Porto, Portugal), M. Treml and W. Randerath (Sleep Disorders Centre, Pulmonary Clinic, Solingen, Germany), Z. Dogas and R. Pecotic (Sleep Medicine Center, Department of Neuroscience, University of Split School of Medicine, Split, Croatia), A. Pataka A (Respiratory Failure Unit, G. Papanikolaou Hospital, Thessalonika, Greece), S. Mihaicuta (Pulmonary Department, Victor Babes University of

Medicine and Pharmacy, Victor Babes Hospital, Timisoara, Romania), U. Anttalainen and T. Saaresranta (Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital and Sleep Research Centre, Department of Pulmonary Diseases and Clinical Allergology, University of Turku, Finland), and S. Sliwinski (2nd Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland).

Author contributions: Data collection: all ESADA affiliated authors as well as all ESADA collaborators (see above); design of the study: A. Yassen, K. Coboeken, L. Grote, J. Hedner, D. Zou, R. Burghaus and J. Lipper; data analysis: K. Coboeken and A. Yassen; first draft of the manuscript: A. Yassen, L. Grote and J. Hedner; critical review of data analysis and statistical methods: S. Bailly and D. Zou; contribution to interpretation of data and review/editing of the final manuscript: all authors; acceptance of the final manuscript: all authors. The study was discussed on several occasions during the ESADA Annual Meetings amongst the authors and the ESADA collaborators.

Data availability: It is not intended to share the original data as this was not specified in the original protocol, the ethical application or the informed consent signed by the participants.

Conflict of interest: A. Yassen, K. Coboeken, R. Burghaus and J. Lipper are employees of Bayer AG. The ESADA network received a research grant from Bayer for the conduct of the study as well as enabling grants from RESMED and Philips Foundation outside the submitted work. J.L. Pépen has no conflict of interest about the submitted work. Outside the work he has received the following: grants/research support from Resmed, Philips, Fisher and Paykel, Agiradom, Astra Zeneca, Mutualia (research support), Vitalaire Air Liquide Foundation (research support) and SEFAM; honoraria or consultation fees from Resmed, Philips, Agiradom, AstraZeneca, JAZZ, ITAMAR, SEFAM and Bioprojet. J. Hedner has received grants from Itamar Medical, Resmed, Philips, AstraZeneca and Desitin outside the submitted work. J. Hedner is part owner of a licensed patent dealing with sleep apnoea therapy. L. Grote reports nonfinancial and other support from Itamar Medical, Resmed, Philips, AstraZeneca, Breas and Desitin outside the submitted work. In addition, L. Grote reports ownership in a patent on sleep apnoea therapy licensed. All remaining authors report no conflict of interest.

Support statement: The ESADA network was founded during the COST action B26 supported by the European Union. The ESADA network is one of the Clinical Research Collaborations funded by the European Respiratory Society (ERS). Unrestricted seeding grants from the ResMed Foundation and the Philips Respironics Foundation for establishment of the database in 2007 and 2011 are gratefully acknowledged. The current ESADA analysis has been enabled by collaborative work and grants provided by Bayer AG. L. Grote and J. Hedner are supported by the Swedish Heart and Lung Foundation (20180567 and 20180585) and the agreement concerning research and education of doctors (ALFGBG 725601 and ALFGBG 721521). J.L. Pepin and S. Bailly are partly supported by MIAI @ Grenoble Alpes (ANR-19-P3IA-0003). Support was also provided by the European Sleep Research Society and the ERS in terms of logistics for communication, meetings and data presentations for the ESADA collaborators. Funding information for this article has been deposited with the Crossref Funder Registry.

References

1 Benjafield AV, Ayas NT, Eastwood PR, *et al.* Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019; 7: 687–698.
2 Tkacova R, McNicholas WT, Javorsky M, *et al.* Nocturnal intermittent hypoxia predicts prevalent hypertension in the European Sleep Apnoea Database cohort study. *Eur Respir J* 2014; 44: 931–941.
3 Zinchuk A, Yaggi HK. Phenotypic subtypes of OSA: a challenge and opportunity for precision medicine. *Chest* 2020; 157: 403–420.
4 Sawyer AM, Gooneratne NS, Marcus CL, *et al.* A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev* 2011; 15: 343–356.
5 Duran J, Esnaola S, Rubio R, *et al.* Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med* 2001; 163: 685-689.
6 Punjabi NM, Caffo BS, Goodwin JL, *et al.* Sleep-disordered breathing and mortality: a prospective cohort study. *PLoS Med* 2009; 6: e1000132.
7 Kushida CA, Nichols DA, Holmes TH, *et al.* Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: The Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep* 2012; 35: 1593–1602.
8 McEvoy RD, Antic NA, Heeley E, *et al.* CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea. *N Engl J Med* 2016; 375: 919–931.
9 Pevernagie DA, Gnidovec-Strazisar B, Grote L, *et al.* On the rise and fall of the apnea-hypopnea index: a historical review and critical appraisal. *J Sleep Res* 2020; 29: e13066.
10 Zinchuk AV, Gentry MJ, Concato J, *et al.* Phenotypes in obstructive sleep apnea: a definition, examples and evolution of approaches. *Sleep Med Rev* 2017; 35: 113–123.

11 Joosten SA, Hamza K, Sands S, *et al.* Phenotypes of patients with mild to moderate obstructive sleep apnoea as confirmed by cluster analysis. *Respirology* 2012; 17: 99–107.
12 Ye L, Pien GW, Ratcliffe SJ, *et al.* The different clinical faces of obstructive sleep apnoea: a cluster analysis. *Eur Respir J* 2014; 44: 1600–1607.
13 Bailly S, Destors M, Grillet Y, *et al.* Obstructive sleep apnea: a cluster analysis at time of diagnosis. *PLoS ONE* 2016; 11: e0157318.
14 Bailly S, Grote L, Hedner J, *et al.* Clusters of sleep apnoea phenotypes: a large pan-European study from the European Sleep Apnoea Database (ESADA). *Respirology* 2021; 26: 378–387.
15 Hedner J, Grote L, Bonsignore M, *et al.* The European Sleep Apnoea Database (ESADA): report from 22 European sleep laboratories. *Eur Respir J* 2011; 38: 635–642.
16 Escourrou P, Grote L, Penzel T, *et al.* The diagnostic method has a strong influence on classification of obstructive sleep apnea. *J Sleep Res* 2015; 24: 730–738.
17 Iber C A-IS, Chesson A, Quan SF for the American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events – Rules, Terminology and Technical Specifications. 1st ed. Westchester, IL, American Academy of Sleep Medicine, 2007.
18 Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991; 14: 540–545.
19 Reynolds AP, Richards G, de la Iglesia B, *et al.* Clustering rules: a comparison of partitioning and hierarchical clustering algorithms. *J Math Model Algorithm* 2006; 5: 475–504.
20 Schubert E, Rousseeuw PJ. Faster k-Medoids clustering: improving the PAM, CLARA and CLARANS algorithms. *Lect Notes Comput Sci* 2019; 11807: 171–187.
21 Gower JC. General coefficient of similarity and some of its properties. *Biometrics* 1971; 27: 857.
22 Tagliamonte SA, Baayen RH. Models, forests, and trees of York English: was/were variation as a case study for statistical practice. *Lang Var Change* 2012; 24: 135–178.
23 Jaccard P. Distribution de la flore alpine dans le Bassin des Dranses et dans quelques regions voisines. *Bull Soc Vaudoise Sci Nat* 1901; 37: 241–272.
24 Tibshirani R, Walther G. Cluster validation by prediction strength. *J Comput Graph Stat* 2005; 14: 511–528.
25 Oh A, Grivell N, Chai-Coetzer CL. What is a clinically meaningful target for positive airway pressure adherence? *Sleep Med Clin* 2021; 16: 1–10.
26 Mazzotti DR, Keenan BT, Lim DC, *et al.* Symptom subtypes of obstructive sleep apnea predict incidence of cardiovascular outcomes. *Am J Respir Crit Care Med* 2019; 200: 493–506.
27 Kim J, Keenan BT, Lim DC, *et al.* Symptom-based subgroups of Koreans with obstructive sleep apnea. *J Clin Sleep Med* 2018; 14: 437–443.
28 Keenan BT, Kim J, Singh B, *et al.* Recognizable clinical subtypes of obstructive sleep apnea across international sleep centers: a cluster analysis. *Sleep* 2018; 41: zsx214.
29 Gagnadoux F, Le Vaillant M, Paris A, *et al.* Relationship between OSA clinical phenotypes and CPAP treatment outcomes. *Chest* 2016; 149: 288–290.
30 Lacedonia D, Carpagnano GE, Sabato R, *et al.* Characterization of obstructive sleep apnea-hypopnea syndrome (OSA) population by means of cluster analysis. *J Sleep Res* 2016; 25: 724–730.
31 Quan W, Zheng D, Douglas McEvoy R, *et al.* High risk characteristics for recurrent cardiovascular events among patients with obstructive sleep apnoea in the SAVE Study. *EClinicalMedicine* 2018; 2–3: 59–65.
32 Turino C, Bertran S, Gavalda R, *et al.* Characterization of the CPAP-treated patient population in Catalonia. *PLoS ONE* 2017; 12: e0185191.
33 Vavougios GD, George DG, Pastaka C, *et al.* Phenotypes of comorbidity in OSAS patients: combining categorical principal component analysis with cluster analysis. *J Sleep Res* 2016; 25: 31–38.
34 Nakayama H, Kobayashi M, Tsuiki S, *et al.* Obstructive sleep apnea phenotypes in men based on characteristics of respiratory events during polysomnography. *Sleep Breath* 2019; 23: 1087–1094.
35 Zinchuk AV, Jeon S, Koo BB, *et al.* Polysomnographic phenotypes and their cardiovascular implications in obstructive sleep apnoea. *Thorax* 2018; 73: 472–480.
36 Peker Y, Glantz H, Eulenburg C, *et al.* Effect of positive airway pressure on cardiovascular outcomes in coronary artery disease patients with nonsleepy obstructive sleep apnea. The RICCADSA randomized controlled trial. *Am J Respir Crit Care Med* 2016; 194: 613–620.
37 Reynor A, McArdle N, Shenoy B, *et al.* Continuous positive airway pressure and adverse cardiovascular events in obstructive sleep apnea: are participants of randomized trials representative of sleep clinic patients? *Sleep* 2022; 45: zsab264.
38 Taranto-Montemurro L, Messineo L, Wellman A. Targeting endotypic traits with medications for the pharmacological treatment of obstructive sleep apnea. a review of the current literature. *J Clin Med* 2019; 8: 1846.
39 Eckert DJ, White DP, Jordan AS, *et al.* Defining phenotypic causes of obstructive sleep apnea. Identification of novel therapeutic targets. *Am J Respir Crit Care Med* 2013; 188: 996–1004.

40 Randerath W, Bassetti CL, Bonsignore MR, *et al.* Challenges and perspectives in obstructive sleep apnoea: report by an ad hoc working group of the Sleep Disordered Breathing Group of the European Respiratory Society and the European Sleep Research Society. *Eur Respir J* 2018; 52: 1702616.

41 Palm A, Grote L, Theorell-Haglow J, *et al.* Socioeconomic factors and adherence to CPAP: the population-based course of disease in patients reported to the Swedish CPAP Oxygen and Ventilator Registry Study. *Chest* 2021; 160: 1481–1491.

42 Pien GW, Ye L, Keenan BT, *et al.* Changing faces of obstructive sleep apnea: treatment effects by cluster designation in the Icelandic sleep apnea cohort. *Sleep* 2018; 41: zsx201.

43 Carneiro-Barrera A, Amaro-Gahete FJ, Guillen-Riquelme A, *et al.* Effect of an interdisciplinary weight loss and lifestyle intervention on obstructive sleep apnea severity: the INTERAPNEA Randomized Clinical Trial. *JAMA Netw Open* 2022; 5: e228212.

44 Mansfield DR. Obstructive sleep apnoea phenotypes: the many faces of a public health monolith. *Respirology* 2021; 26: 294–295.