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Sleep apnoea phenotypes in women: A cluster analysis from the ESADA cohort☆

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ABSTRACT

Introduction: and Objectives: The clinical presentation of Obstructive Sleep Apnoea (OSA) differs between genders. This study aimed to identify the specific OSA phenotypes of women in the European Sleep Apnoea Database (ESADA) cohort.

Materials and methods: Latent class cluster analysis was applied to data from 9710 female OSA patients. Variables used included age, Body Mass Index (BMI), Epworth Sleepiness Scale (ESS), comorbidities (cardiovascular, pulmonary, psychiatric, metabolic, other) and the Apnoea Hypopnea Index (AHI).

Results: Four different clusters were found: Cluster 1"Women with ischemic heart disease" (38.3 %):middle aged (59 years [53–65]),overweight to obese (BMI 30.1 kg/m^2 [26.9–33.5]), AHI 22.9 events/h[17.4–30], ESS 9 [5,12] with the highest prevalence of ischemic heart disease (56 %). Cluster 2"Elderly women with comorbidities" (23 %): oldest (66 years[60–71]), obese (BMI 36 kg/m^2 [31.6–40.4]),AHI 46 events/h [30–60.1]),ESS 9 [6-13] with the highest prevalence of comorbidities. Cluster 3"Sleepy obese women" (16.2 %): the youngest (49 years [42–55]), sleepiest (ESS 12 [8-16]), most obese(BMI 43 kg/m^2[37.6–48.9]) females with severe OSA (AHI 53.3 events/h [32–80.5]). Cluster 4 "Women with mild OSA and low comorbidities" (22.5 %): middle aged (53.5 years [46–60]) with BMI 29 kg/m^2[25–34.1],ESS9 [5,13]),AHI 8.6events/h[6.9–10.4])and low prevalence of comorbidities. The distribution of the clusters differed across Europe. PAP administration was higher in Clusters 2 and 3 but low in Cluster 4.

Conclusion: Four distinct female phenotypes were identified with different clinical presentation and comorbidities. Sex-based phenotyping may provide improved risk stratification and personalized treatment.

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1. Introduction

Obstructive sleep apnoea (OSA) is one of the most frequent chronic diseases worldwide and is characterized by the repetitive occurrence of complete (apnoea) or partial (hypopnoea) obstruction of the upper airway during sleep [1]. OSA is heterogeneous concerning its underlying pathophysiological mechanisms, polysomnographic (PSG) findings, clinical presentations, and health consequences [2–5]. Different studies using cluster analyses have identified three to nine OSA phenotypes depending on the clustering methods and the cohorts studied. Most of the studies have used combinations of clinical symptoms and comorbidities, whereas others have included anatomical characteristics and indices from sleep studies [2–20]. However, studies specifically targeting OSA phenotypes in women are lacking. OSA has been considered a primarily male disease but more recent studies have found less male dominance in the general population [1] with a mean prevalence of 27 % in men and 22 % in women [21]. The clinical presentation [22,23] and the burden of cardiovascular consequences and comorbidities also differ between genders [21–24].

Cluster analysis was previously conducted in the European Sleep Apnoea Database (ESADA) [17–19]. In the first study from Saaresranta et al. [17] the clinical phenotypes characterized by insomnia were more frequent in women. The second analysis conducted by Bailly et al. [18] revealed eight distinct clinical phenotypes with two clusters including only women (i.e. Cluster 7: overweight women with insomnia and low PAP adherence and Cluster 8: older symptomatic obese women with severe OSA and comorbidities). The more recent analysis by Yassen et al. [19] identified two clusters including only females(i.e. Cluster 4: Multimorbid obese post-menopausal females with prevalent cardiovascular disease and Cluster 7: Healthy middle-aged symptomatic females with mild OSA) [19]. However, a detailed analysis for better understanding female OSA phenotypes in the ESADA large patient cohort has not been performed. The current study aimed to apply advanced cluster analysis solely in the female ESADA participants to identify specific phenotypes based on clinical presentation, sleep study findings and comorbidities.

2. Methods

The ESADA is a multicentre prospective database that assembled clinical data of patients clinically suspected of having OSA from a variety of centres to generate a representative real-world data source covering almost the entire Europe (Fig. 1). For this particular study, adult women with OSA diagnosis (Apnoea Hypopnoea Index, AHI≥5 events/hour) were included from 30 centres (18 countries). Data recorded from 2008 to 2023 were analysed and the data used were cross-sectional. The cohort protocol was approved by the local Ethics Committees of each participating centre. Patients were requested to provide oral and written informed consent for inclusion in the database.

At baseline, at the time of the sleep study, the following data were

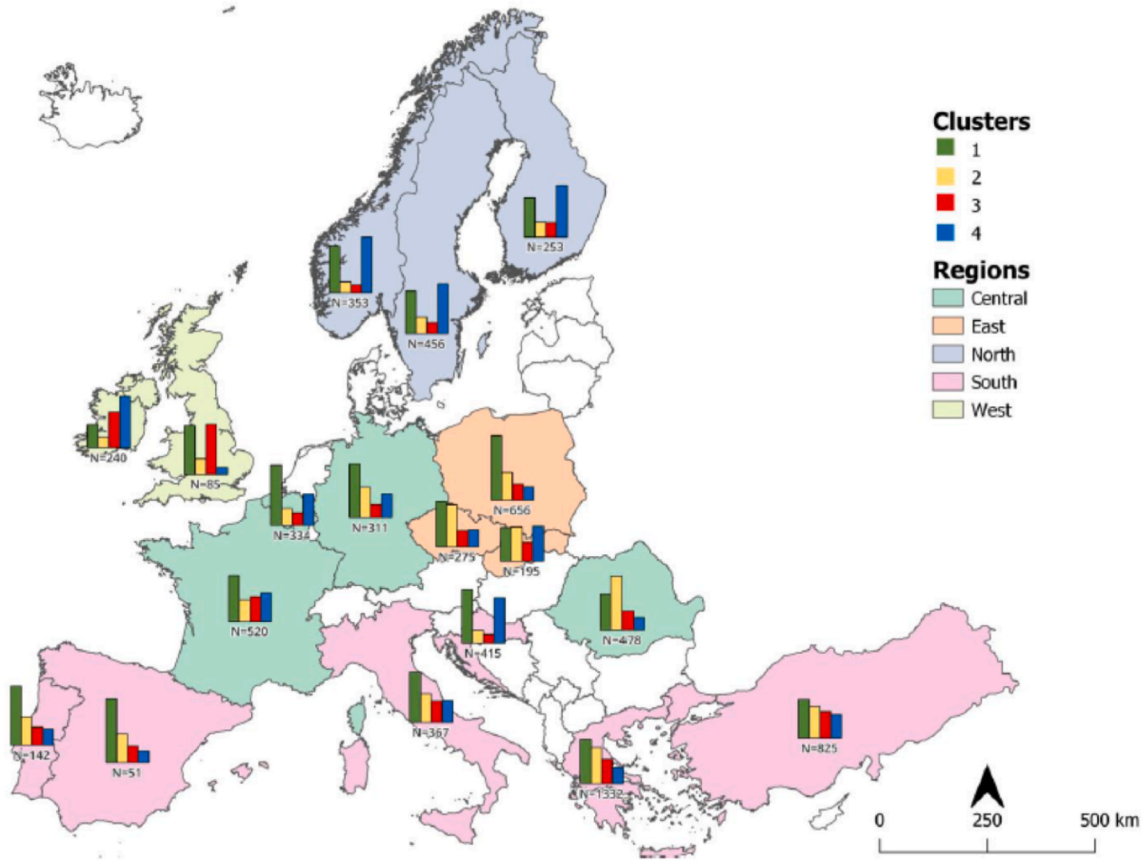
Table 2
Sleep characteristics according to cluster.

Variables Median [interquartile range or effective (%)]	Cluster 1 N = 2791 (38.3 %)	Cluster 2 N = 1678 (23.0 %)	Cluster 3 N = 1181 (16.2 %)	Cluster 4 N = 1638 (22.5 %)	P value	Missing values
ESS	9 [5; 12]	9 [6; 13]	12 [8; 16]	9 [5; 13]	<.01	0
Insomnia (%)[a]	2131 (76.4]	1271 (75.7)	903 (76.5)	1279 (78.1)	0.42	0
Physician reported Insomnia	140 (5.1)	79 (4.7)	26 (2.2)	92 (5.7)	<.01	119
Hypnotics (%)	637 (22.8)	407 (24.3)	312 (26.4)	474 (28.9)	<.01	0
Self-reported sleep duration ≤6h (%)	1575 (56.4)	902 (53.8)	696 (58.9)	908 (55.4)	0.05	0
AHI, events/h	22.9 [17.4; 30]	46 [30; 60.1]	53.3 [32; 80.5]	8.6 [6.9; 10.4]	<.01	0
ODI, events/h	18 [11.2; 26.9]	44 [27.9; 60] {1}	52.8 [27; 79] {1,2}	6 [3; 9.1] {1,2,3}	<.01	378
Mean nocturnal SaO2%	93.8 [92; 95]	91.9 [90; 93]	92 [89; 94]	94.8 [93.1; 96]	<.01	149
Minimal nocturnal SaO2%	82 [78; 86]	76 [68; 81]	75 [65; 81]	86 [82; 89]	<.01	192

ESS = Epworth Sleepiness Scale, AHI = Apnoea Hypopnea Index, ODI= Oxygen Desaturation Index.
[a] physician reported, use of hypnotic medications, self-reported sleep duration ≤ 6h, average sleep latency≥30min.

Table 1
Characteristics of the patients included in each cluster.

Variables Median [interquartile range or effective(%)]	Cluster 1 N = 2791 (38.3 %)	Cluster 2 N = 1678 (23.0 %)	Cluster 3 N = 1181 (16.2 %)	Cluster 4 N = 1638 (22.5 %)	P value	Missing values
Age, years	59 [53; 65]	66 [60; 71]	49 [42; 55]	53.5 [46; 60]	<.01	0
BMI, kg/m^2	30.1 [26.9; 33.5]	36 [31.6; 40.4]	43 [37.6; 48.9]	29 [25; 34.1]	<.01	0
Waist circumference, cm	102 [94; 110]	115 [105; 125]	125 [114; 135]	98.5 [88; 109]	<.01	742
Hip circumference, cm	110 [102; 117]	120 [110; 130]	130.5 [120; 142]	108 [100; 117]	<.01	832
Neck circumference, cm	37 [35; 39]	40 [38; 42]	41.8 [39; 44]	36.5 [34; 39]	<.01	579
Smoking	501 (18.1)	234 (14)	310 (26.3)	418 (25.6)	<.01	36
Menopausal status	1794 (64.3)	1536 (91.5)	282 (23.9)	702 (42.9)	<.01	0
Systolic Blood Pressure, mmHg	130 [120; 140]	135 [125; 145]	130 [120; 142]	128 [118; 140]	<.01	462
Diastolic Blood Pressure, mmHg	80 [71; 87]	80 [70; 88]	80 [73; 90]	80 [70; 86]	<.01	502
Heart Rate, beats/min	72 [66; 80.5]	75 [68; 83]	80 [72; 90]	72 [65; 81]	<.01	1247
Systemic Hypertension	1250(44.8)	1322(78.8)	578(48.9)	519(31.7)	<.01	0
Ischemic Heart Disease (%)	1562(56)	369(22.2)	22(1.9)	47(2.90	<.01	0
Stroke (%)	59 (2.2)	67 (4)	14 (1.2)	38 (2.4)	<.01	113
Diabetes mellitus type2 (%)	279 (9.9)	696(41.5)	307(26)	136(8.3)	<.01	0
Dyslipidaemia (%)	650(23.3)	738(44)	209(17.7)	244(14.9)	<.01	0
COPD (%)	89(3.2)	278(16.6)	68(5.8)	52(3.2)	<.01	0
Asthma (%)	243 (8.9)	216(12.9)	133 (13.9)	203 (12.4)	0.04	1417
Neurological Diseases (%)	137(4.9)	139(8.3)	34(2.9)	121(7.4)	<.01	0
Psychiatric Diseases (%)	379(13.6)	193 (11.5)	268(22.7)	270(16.5)	<.01	0
Other diseases (%)	508(18.2)	413 (24.6)	202(17.1)	327(20)	<.01	0



	Central N=1643 (22.5%)	East N=1126 (15.45%)	North N=1062 (14.6%)	South N=3132 (43%)	West N=325 (4.5%)	P value
Cluster 1	643 (39.1)	506 (44.9)	379 (35.7)	1183 (37.8)	80 (24.6)	<.01
Cluster 2	431 (26.2)	300 (26.6)	127 (12.0)	787 (25.1)	33 (10.2)	<.01.
Cluster 3	250 (15.2)	154 (13.7)	97 (9.1)	575 (18.4)	105 (32.3)	<.01.
Cluster 4	319 (19.4)	166 (14.7)	459 (43.2)	587 (18.7)	107 (32.9)	<.01.

Fig. 1. Geographical distribution of the ESADA and of each distinct cluster of female OSA patients.

included: anthropometric characteristics, comorbidities, medications using anatomical therapeutic chemical (ATC) codes, Epworth Sleepiness Scale (ESS) score, type of sleep study (respiratory polygraphy (PG) or PSG) allowing to characterize OSA severity (AHI and Oxygen Desaturation Index, ODI), sleep architecture and sleep fragmentation. All sleep data were manually scored according to the American Academy of Sleep Medicine (AASM) depending on the year of inclusion. Obstructive apnoeas were scored as >90 % reduction of the amplitude of "baseline" breathing for duration of >10 s with the presence of respiratory effort. The definitions for hypopnea were the 'recommended' rules: 'nasal pressure signal excursions drop by ≥ 30 % of baseline, lasting at least 10 s, with a ≥4 % desaturation from pre-event baseline' and the 'alternative' rule as 'nasal pressure signal excursions drop by ≥ 50 % of baseline, lasting at least 10 s, with a ≥3 % desaturation from pre-event baseline or the event is associated with arousal' before 2013 and 'recommended' rules: 'nasal pressure signal excursions drop by ≥ 30 % of baseline, lasting at least 10 s, with a ≥3 % desaturation from pre-event baseline and/or the event is associated with an arousal' and the 'alternative' rule as 'nasal pressure signal excursions drop by ≥ 30 % of baseline, lasting at least 10 s, with a ≥4 % desaturation from pre-event baseline' after 2013. In PG, respiratory events consistent with hypopnoea without desaturation were ignored, as no arousals were scored due to lack of EEG. Respiratory effort-related arousal (RERA) was defined as increased respiratory effort or flattening of the nasal pressure waveform, leading to an arousal when the sequence of breaths did not meet the criteria of hypopnea. The total AHI (PSG) or apneas/hypopneas per time in bed (PG) were recorded in the database. ODI was defined as ≥4 % oxygen desaturations per hour of sleep/analysis time.

The criteria used for insomnia-like symptoms were: physician-diagnosed insomnia and/or subjective sleep latency ≥30 min, and/or self-reported sleep duration≤6 h and/or use of hypnotics (ATC code N05) [17]. Hence, patients characterized as suffering from insomnia in our study may not fulfil the ICD or DSM criteria. However our criteria are important markers for clinically relevant insomnia. Menopausal status was defined with the threshold of age over 55 years to be allocated to post-menopausal status.

The population was stratified into five distinct European geographical areas [18]: 1) North including Norway, Sweden and Finland, 2) East including Czech Republic, Lithuania, Slovakia, Poland, Romania, 3) South including Greece, Spain, Turkey, Portugal, Italy, Croatia, 4) Central including Belgium, Germany, France and 5) West including Ireland and United Kingdom (Fig. 1).

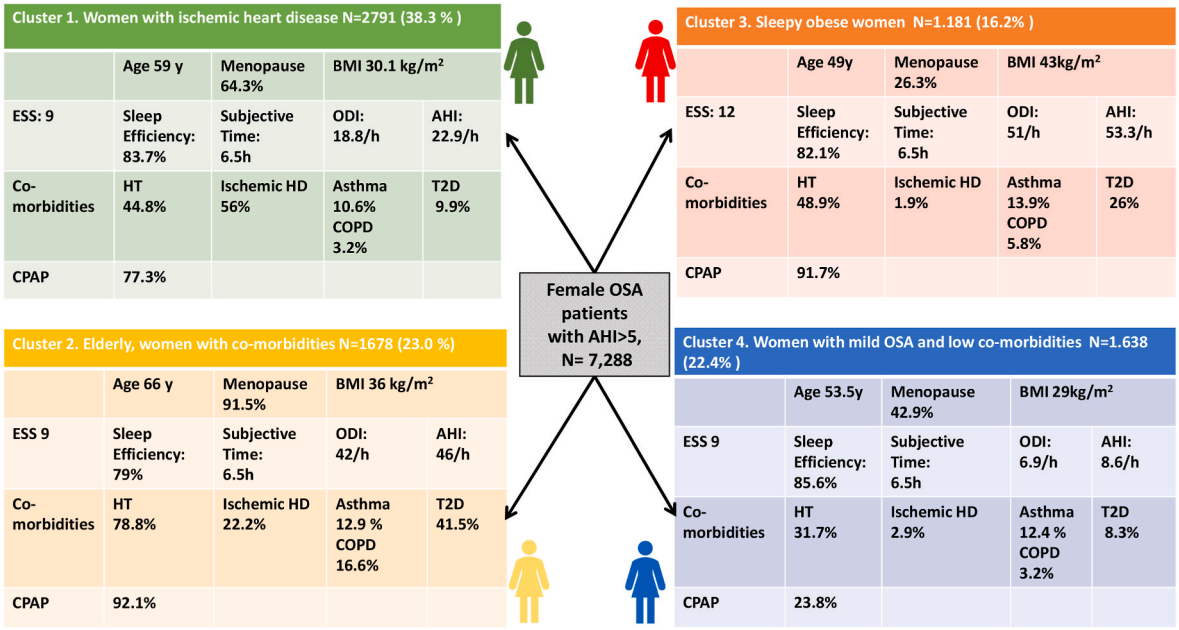


Fig. 2. Characteristics of the four distinct clusters of the female OSA patients of the ESADA.(ESS = Epworth Sleepiness Scale, BMI=Body Mass Index, AHI = Apnoea Hypopnea Index, ODI= Oxygen Desaturation Index, HT=Hypertension, HD=Heart Disease, T2D = Type 2 Diabetes).

2.1. Cluster analysis

A latent class analysis (LCA) [25] was used in order to identify different OSA phenotypes. LCA is a model-based approach for clustering that allows the identification of homogeneous subgroups of phenotypes (i.e. latent classes) from a large heterogeneous group [18]. Variables were selected after checking for their independence (V-Cramer test for co-linearity) and 17 variables were finally included in the final clustering model: age, Body Mass Index (BMI), AHI, ESS, cardiovascular comorbidities (hypertension, ischemic heart disease, cardiac failure, other cardiovascular diseases), chronic obstructive pulmonary disease (COPD), asthma, metabolic comorbidities (dyslipidaemia, hyperuricemia, other metabolic comorbidities, diabetes mellitus) and other comorbidities (neurologic diseases, psychiatric diseases, gastrointestinal diseases, other diseases). The optimal cluster number was identified by using the integrated completed likelihood criterion and a 5-fold cross-validation was performed to confirm the optimal number of clusters. The mean probability for each patient belonging to their cluster was computed.

2.2. Statistical analyses

Variables were presented as median and interquartile range (IR) for quantitative variables and number and frequency for qualitative variables. To identify the main differences between clusters, comparisons were performed using non-parametric Kruskal-Wallis tests for quantitative variables and Chi-square test for qualitative variables. Missing values are reported in Tables and as comparisons were explorative, no corrections for multiple tests were performed. Statistical analyses were performed with both SAS v9.4 and R v3.6.1 software.

3. Results

3.1. Study population

LCA was applied to the data of 9710 females among the 32,700 ESADA participants. From 9710 women, 2167 (22 %) had AHI≤5 events/h, 7288 (75 %) had AHI>5 events/h and in 255 (3 %) no AHI was recorded in the database. Therefore, clustering analysis was applied to 7288 women. The median age was 58 years (IR: 51–65), the median BMI was 32.4 kg/m^2 (IR: 27.9–38.1) and the median ESS score was 9 (IR: 5–13). The median AHI of the population was 23.9 events/h (IR: 12.9–41.7), with a median ODI of 20.4 events/h (IR: 9.5–39.8) and a median time with nocturnal oxygen saturation below 90 % (T90 %) 11.4 min (IR: 1.6–54.1). The diagnosis of OSA was made by PSG in 4031 (55.3 %) and by PG in 3228 (44.5 %).

Supplement Tables 1 and 2 include the comparison of the clustering variables between genders.

3.2. Phenotypes identification and description

The LCA revealed four distinct clusters, with the mean probability for a woman belonging to the assigned cluster ranging from 75 to 81 %. The size of clusters varied from 1181 (16.2 %) to 2791 (38.3 %) individuals. Anthropometric characteristics, comorbidities, sleep characteristics, medications and OSA primary therapies in the different clusters are presented in Tables 1 and 2, and Figs. 1 and 2.

The main characteristics of the clusters are summarized as follows.

- Cluster 1. "Women with ischemic heart disease": The largest cluster (N = 2,791, 38.3 %) including middle-aged, overweight-obese women, non-sleepy suffering from moderate OSA. An intermediate prevalence rate of comorbidities was found but the highest rate of ischemic heart disease (56 %) was identified compared to the other clusters.
- Cluster 2. "Elderly women with comorbidities" (N = 1,678, 23 %). This cluster included elderly, obese females with high AHI and ODI, but not sleepy. The patients of this cluster suffered from the highest rate of comorbidities (i.e. hypertension, diabetes, dyslipidaemia, COPD, neurologic and other disease) compared with the other clusters.
- Cluster 3. "Sleepy obese women" (N = 1181 (16.2 %): This cluster included the youngest population with the highest BMI. OSA was essentially severe with significant sleepiness. Psychiatric diseases and asthma were more frequent in this cluster, with other comorbidities such as hypertension and diabetes also being present.
- Cluster 4. "Women with mild OSA and low comorbidities (N = 1638 (22.5 %). Patients in this cluster were middle-aged, overweight-

Table 3
Sleep characteristics according to clusters for women who were diagnosed by PSG (N = 4031).

Variables Median [interquartile range or effective (%)]	Cluster 1 N = 1612 (40 %)	Cluster 2 N = 971 (24 %)	Cluster 3 N = 697 (17.3 %)	Cluster 4 N = 751 (18.7 %)	P value	Missing values
AHI, events/h	23.4 [17.9; 30.5]	48.5 [34.4; 62]	55.3 [33; 82]	8.9 [7.1; 10.7]	<.01	0
ODI, events/h	18 [11.2; 26.9]	44 [27.9; 60]	52.8 [27; 79]	6 [3; 9.1]	<.01	267
Mean nocturnal SaO2%	94 [92; 95]	92 [90; 93]	92 [89; 94]	95 [94; 96]	<.01	32
Minimal nocturnal SaO2%	83 [78; 86]	77 [70; 82]	76 [66; 82]	87 [84; 90]	<.01	53
Time below 90 %, min	6.5 [1; 26]	44 [10.3; 115.4]	40.4 [6; 125.9]	0.5 [0; 3.6]	<.01	593
Total subjective sleep time, h	6.5 [5.5; 8]	6.5 [5; 8]	6.9 [5; 8]	7 [6; 8]	<.01	987
Sleep Efficiency (%)	83.7 [72; 91.6]	79 [67; 89]	82.1 [70.6; 90.1]	85.6 [75.6; 92.1]	<.01	54
Stage1(%)	6.9 [3.5; 12.9]	7.4 [4.3; 15.6]	6.8 [3.6; 13.9]	5.5 [2.7; 10.1]	<.01	54
Stage2(%)	55.2 [44.3; 66.5]	58.9 [45.8; 72.4]	61.3 [48.2; 73.6]	55.5 [45.6; 65.2]	<.01	53
Stage3(%)	16.6 [8.4; 25.7]	13.5 [6.1; 25.4]	12.4 [6.3; 23.2]	16.4 [9; 25.8]	<.01	71
Stage REM(%)	14.1 [8.3; 19.9]	10.2 [5; 16.3]	10 [5.1; 16.2]	16.9 [10.6; 21.5]	<.01	76
PLM Index, events/h	2.4 [0; 12.1]	1.1 [0; 13.2]	0 [0; 7.7] {1,.}	2.5 [0; 14.4]	<.01	1609

PSG= Polysomnography, AHI = Apnoea Hypopnea Index, ODI= Oxygen Desaturation Index, REM = Rapid Eye Movements, PLM =Periodic leg movements.

obese, with mild OSA, low ESS score and low rate of comorbidities. Physician-diagnosed insomnia was more frequent in this group of patients. However, when a broader definition of insomnia was used no significant differences were found between clusters.

3.3. Sleep parameters in the PSG sub-group

In 4031 (55.3 %) women OSA was diagnosed with PSG. The sleep characteristics according to clusters for women who were diagnosed by PSG in the cohort are presented in Table 3. Cluster 2 presented the lowest sleep efficiency, whereas Cluster 4 presented the highest. The proportion of Sleep Stage 2 was higher in Cluster 3, whereas Stage 3 and REM sleep were higher in Clusters 1 and 4.

3.4. Patient medications

As Cluster 2 included the patients with the highest degree of comorbidities, it was associated with the highest rate of use of cardiovascular disease medications (76.8 %) (Table 4) compared with the other clusters.

Medications for type 2 diabetes were prescribed more frequently in Cluster 2 (27.2 %), followed by Cluster 3 (19.1 %). The use of hypnotic medications was reported in 28.9 % of women of Cluster 4 (Table 2). Anti-depressive medications were more frequently prescribed in Clusters 3 (14.9 %) and 4 (14.2 %).

Table 4
Pharmacological treatment according to clusters.

	Cluster 1 N = 2791 (38.3 %)	Cluster2 N = 1678 (23.0 %)	Cluster3 N = 1181 (16.2 %)	Cluster 4 N = 1638 (22.5 %)	P value
Digestive treatments (ATC A) (%)	653 (23.4)	777 (46.3)	389 (32.9)	408 (24.9)	<.01
Anti-diabetic medications (ATC A10) (%)	204 (7.3)	457 (27.2)	225 (19.1)	86 (5.3)	<.01
Cardiovascular treatments (ATC C) (%)	1300 (46.6)	1288 (76.8)	557 (47.2)	629 (38.4)	<.01
HTA (ATC C02) (%)	89 (3.2)	78 (4.6)	38 (3.2)	28 (1.7)	<.01
Diuretics (ATC C03) (%)	289 (10.4)	514 (30.6)	164 (13.9)	129 (7.9)	<.01
B blockers (ATC C07) (%)	470 (16.8)	578 (34.4)	209 (17.7)	262 (16)	<.01
Calcium channel blockers (ATC C08) (%)	269 (9.6)	350 (20.9)	116 (9.8)	136 (8.3)	<.01
Angiotensin II receptor antagonists (ATC C09 (%))	730 (26.2)	825 (49.2)	332 (28.1)	287 (17.5)	<.01
Statins (ATC C10) (%)	505 (18.1)	573 (34.1)	166 (14.1)	216 (13.2)	<.01
Anti-depressive medications (ATCN06A) (%)	313 (11.2)	134 (8)	176 (14.9)	232 (14.2)	<.01
Respiratory system (ATC R) (%)	347 (12.4)	355 (21.2)	192 (16.3)	251 (15.3)	<.01
Drugs for obstructive airway diseases (ATC R03) (%)	230 (8.2)	270 (16.1)	147 (12.4)	153 (9.3)	<.01

ATC: anatomical therapeutic chemical classification. HTA = Antihypertensives, No missing values were observed for treatment.

3.5. Geographical variability of clusters

The distribution of the clusters differed across Europe. Cluster 1 was the most frequent in Central, Eastern and Southern Europe, whereas Cluster 4 in Northern and Western Europe. The prevalence of clusters differed 2-3-fold between European regions (Cluster 4, 43.2 % Northern vs. 14.7 % Eastern Europe; Cluster 3, 9.1 % Northern vs. 32.3 % Western Europe) (Fig. 1).

3.6. OSA primary treatments

OSA treatments differed according to clusters (Table 5).
Positive airway pressure (PAP) device was prescribed in the majority

Table 5
OSA primary therapies according to different clusters.

Variables Median [interquartile range or effective (%)]	Cluster 1 N = 1612 (40 %)	Cluster 2 N = 971 (24 %)	Cluster 3 N = 697 (17.3 %)	Cluster 4 N = 751 (18.7 %)	P value	Missing values
PAP	1762 (77.3)	1319 (92.1)	875 (91.7)	272 (23.8)	<.01	1481
Oral devices	161 (7.0)	33 (2.3)	11 (1.1)	175 (15.0)	<.01	1395
Surgery	22 (1.0)	8 (0.6)	18 (1.9)	36 (3.1)	<.01	1481
Active weight reduction	532 (23.4)	451 (31.5)	372 (39.0)	298 (26.1)	<.01	1481

PAP= Positive Airway Pressure.

of patients in Clusters 2 (92.1 %) and 3 (91.7 %), followed by Cluster 1 (77.3 %), whereas it was indicated for only 23.8%of patients in Cluster 4. Mandibular advancement devices (MADs) were more frequently used in Cluster 4 (15 %), compared with the other clusters. Active weight reduction was applied more often in Clusters 3 (39 %) and 2 (31.5 %).

4. Discussion

Four distinct clinical OSA phenotypes were identified in female OSA patients of the ESADA database. These clusters differed by age, BMI, OSA severity and comorbidities and presented a substantial variation in regional distribution. Primary therapies for OSA differed among clusters reflecting the different management strategies according to phenotypes. Several cluster analysis studies have evaluated different OSA phenotypes making a report on female population and some even describing separate female clusters [3,6,10,13–20]. However, our study is the first to assess a large multinational database specifically for female phenotypes.

The clinical presentation, symptoms and comorbidities of OSA differ between sexes [21–27]. The anatomy of the upper airway, fat distribution, alterations in hormonal status (pre- and post-menopause), and the different endotypes account for these differences [21–24]. Studies report that females with OSA exhibit lower AHI, less hypoxic burden, shorter apnoeic episodes and more apnoeas during REM sleep [22,23]. Males and females perceive sleepiness differently with ESS being a more sensitive measure of sleepiness in males [26]. In the current analysis, only Cluster 3 presented the more 'classic' OSA phenotype, whereas the other three clusters did not show significant sleepiness. Females with OSA report nonspecific symptoms such as fatigue, morning headache, insomnia and depression [22,23]. Additionally, they present more frequently nocturia, frequent awakenings and restless legs syndrome (RLS) [22,26]. Co-morbid insomnia and sleep apnoea (COMISA) has been recognized as a distinct disorder, resulting in additional impairment to patients' sleep and quality of life leading to worse outcomes and increased mortality [27,28]. A higher prevalence of COMISA has been reported in females compared to males (35.5 % vs. 23.1 %) [27] and in our analysis, Cluster 4 included females with more frequently physician-diagnosed insomnia.

Clinical-based studies have demonstrated a female predisposition to REM-OSA irrespective of menopausal status [29]. REM-OSA is of clinical significance as it has been associated with adverse outcomes, such as increased risk of cardiovascular disease, hypertension and early signs of atherosclerosis [30,31]. In addition, differences in sleep architecture were found between the clusters of our analysis with those suffering from more severe OSA presenting lower Stage 3 and REM sleep. The highest sleep efficiency despite the highest prevalence of physician-diagnosed insomnia in Cluster 4 could be explained by the different criteria used for insomnia in the analysis; when all the different definitions of insomnia were used no significant differences were found between clusters. In addition, Cluster 4 included patients with mild OSA and that may also explain the higher sleep efficiency in this group.

Cluster analyses have been previously performed on OSA patients from the multinational ESADA with a strong female predominance in some of the clusters [17–19]. Apart from the ESADA, other studies have also reported distinct female phenotypes. Subtype C of the study of Zinchuk et al. [3] consisted of females with insomnia or poor sleep, medium severity of OSA, moderate frequency of comorbidities and low PAP adherence. In a study using photoplethysmography (PPG) [32], a distinct clinical phenotype of older women with mild OSA phenotype was identified with higher cardiovascular risk during the post-menopausal period. In a recent study conducted in Portugal [33], a separate cluster of middle-aged women with morning headaches, increased neck circumference and non-repairing sleep was found. The study of Topîrceanu [14]reported that all the unique female phenotypes presented hypertension, followed by obesity and sleepiness. A very recent cross-sectional study of 1886 women diagnosed with OSA in a single centre revealed also four female phenotypes [34]. A cluster with middle-aged paucisymptomatic women without cardiovascular disease (CVD) risk factors (27 %), a cluster of older paucisymptomatic women with established CVD and severe OSA (12 %), a cluster of middle-aged women with "classic" symptoms and CVD risk factors (47 %), and a cluster of middle-aged women with mood disorders, nonrestorative sleep and CVD risk (14 %) were found. In that study, the cluster that included the majority of patients was that with the 'classic' OSA symptoms. On the other hand in our study cluster 1 'Women with ischemic heart disease' included the majority of patients. This difference may be explained by the multicentre origin of the data in the ESADA cohort.

The differences between genders in the severity of OSA tend to attenuate during the post-menopausal years [35]. The exposure of women to OSA consequences, as intermittent hypoxia, is delayed until menopause, and this may explain the later appearance of comorbidities in females. Cluster 2 presented the highest rate of comorbidities, whereas Cluster 4 had the lowest. Cluster 3 included sleepy obese women with more prevalent asthma and psychiatric disease. Comorbidities as asthma, thyroid disease and depression are more commonly reported in women with OSA [21–23]. In a previous analysis of the ESADA [36], physician-diagnosed asthma prevalence was almost two times higher in women than in men (7.9 % vs. 3.7 %, $p < 0.0001$). In addition, women of Cluster 1 suffered more frequently from ischemic heart disease. It has been found that female OSA patients suffering from severe disease are at increased cardiovascular risk [24,35]. There is also evidence that female patients suffering from moderate OSA present with more severe endothelial dysfunction and higher levels of pro-inflammatory cytokines such as IL-6 than males [37], suggesting that women are more vulnerable to the cardiovascular consequences of OSA [38].

The effect of gender on OSA treatment indications has not been well-studied. As OSA is under-diagnosed in women, its treatment is delayed compared to men. A randomized controlled trial has found a positive PAP effect on blood pressure, but not metabolic outcomes in women [39]. In the current analysis, PAP was prescribed in the majority of patients in Clusters 2 and 3, followed by Cluster 1, but only in the minority of patients in Cluster 4. PAP prescription was provided after a sleep study (not simply clinical suspicion) according to each centre's guidelines. Patients in Cluster 1 had a lower PAP prescription rate compared with Clusters 2 and 3, because they were not very sleepy and they suffered from moderate OSA. On the other hand in Cluster 2, even though the patients were not very sleepy, they were elderly, obese with high AHI and ODI, and with the highest rate of comorbidities and in Cluster 3, they were sleepy.

As women appear to suffer more frequently from REM-related OSA and given the association of REM-related OSA with cardiovascular and metabolic outcomes, there is a need for women to apply PAP during REM, i.e., the latter part of the night [24,35,39]. Cluster 4 presented the highest percentage of REM sleep. Unfortunately, REM AHI was not evaluated in our study but it would be of importance as PAP treatment was less applied in this cluster. MADs were more frequently used in Cluster 4 and active weight reduction in Clusters 2 and 3. Mandibular appliances seem to be more effective in women, regardless OSA severity; however, data are limited [40]. The weight loss effect on OSA improvement demonstrated gender-specific effects, with a greater reduction of AHI in men [41].

Cultural differences have a significant impact on OSA; from lifestyle behaviors as eating and drinking habits, to the knowledge of sleep disordered breathing in the general population and to the healthcare system for proper diagnosis and treatment. The differences in cluster distribution according to geographical boundaries may represent the underlying cultural, economic, political status and demographics of a region on individuals' health. However, even neighboring countries that may be grouped together for scientific reasons may have large ethnic, cultural, economic, and political differences that have an impact in

healthcare and specifically OSA [42]. Attitudes towards illness prevention, alcohol and smoking consumption, diet and sleep can have cultural roots and may impact OSA presentation. In addition, the reluctance of women to seek medical help for OSA symptoms and cultural values specific to male sex (i.e. smoking, alcohol) may affect the referrals of patients for possible sleep disordered breathing and their treatment, in concordance to the guidelines of the national health system of each country. Apart from our study, the influence of geographical location on OSA phenotypes has been evaluated in the ESADA population before. An insomnia-related phenotypic variation was revealed when patient data were evaluated according to geographical classification (North, South, East, West and Central Europe [43], while data-driven clustering also identified variation in phenotypes according to geographical region [18]. Differences between countries in overall health, diagnosis, and adherence to treatment have been also found [44–46]. Additionally, beyond the ESADA, other studies have shown OSA phenotypic differences in USA and Japan [47] and between different ethnic groups [48]. On the other hand the complexity of this issue is also reflected in the genetic heterogeneity of OSA even according to gender [49].

Our study has strengths and limitations. This is one of the largest prospective cohort studies and the first examining an OSA population consisting only of women by cluster analysis in a large cohort of women from multiple geographic locations in Europe. The multicentric large sample size including several geographical areas across Europe provides further generalizability of our findings. The variation of the procedures to diagnose OSA using PSG or PG, differences in scoring rules and referral bias in different centres, cultural and linguistic differences may present limitations of this multicentric analysis. However, the large population size may limit this problem [23]. In addition, the majority of the participants in the different sleep centres were over-weight or obese. The criteria used in the ESADA did not exclude participants with normal BMI who may have OSA but in fact obesity is a significant risk factor of OSA. For that, patient with normal BMI may be under -referred and this could limit the generalizability of our results in this group of patients.

The main message of our paper is that the clinical presentation, symptoms and comorbidities of OSA are different in females. The identification of different clinical phenotypes in females may provide more efficacious, alternative treatments towards OSA management. A future prospective study aiming to evaluate survival and possible treatment benefits according to phenotype would be of importance as it may lead to an individual risk assessment approach to identify and treat OSA beyond the CPAP-focused, “one size fits all" approach [50]. In addition, future research could also focus on women who did not meet the established criteria for OSA but were referred for suspected sleep disordered breathing and prospectively investigate their symptomatology, sleep architecture, comorbidities and the evolution of possible different clinical phenotypes of OSA over time.

CRediT authorship contribution statement

A. Pataka: Writing – original draft, Validation, Data curation, Conceptualization. **J.L. Pepin:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **M.R. Bonsignore:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **S. Schiza:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **T. Saaresranta:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **I. Bouloukaki:** Validation, Methodology, Investigation, Data curation. **P. Steiropoulos:** Supervision, Methodology, Investigation, Data curation. **G. Trakada:** Validation, Project administration, Methodology, Investigation, Data curation. **R. Riha:** Validation, Resources, Investigation, Conceptualization. **Z. Dogas:** Validation, Supervision, Investigation, Data curation. **D. Testelmans:** Validation, Methodology, Investigation, Data curation. **O.K. Basoglu:** Validation, Resources, Investigation, Conceptualization. **S. Mihaicuta:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis. **F. Fanfulla:** Validation, Methodology, Investigation, Conceptualization. **L. Grote:** Writing – review & editing, Validation, Supervision, Methodology, Investigation, Data curation, Conceptualization. **S. Bailly:** Writing – original draft, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of interest

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2024.10.015.

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