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The different clinical faces of obstructive sleep apnoea: a cluster analysis

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ABSTRACT Although commonly observed in clinical practice, the heterogeneity of obstructive sleep apnoea (OSA) clinical presentation has not been formally characterised.

This study was the first to apply cluster analysis to identify subtypes of patients with OSA who experience distinct combinations of symptoms and comorbidities. An analysis of baseline data from the Icelandic Sleep Apnoea Cohort (822 patients with newly diagnosed moderate-to-severe OSA) was performed.

Three distinct clusters were identified. They were classified as the ''disturbed sleep group'' (cluster 1), ''minimally symptomatic group'' (cluster 2) and ''excessive daytime sleepiness group'' (cluster 3), consisting of 32.7%, 24.7% and 42.6% of the entire cohort, respectively. The probabilities of having comorbid hypertension and cardiovascular disease were highest in cluster 2 but lowest in cluster 3. The clusters did not differ significantly in terms of sex, body mass index or apnoea–hypopnoea index.

Patients with OSA have different patterns of clinical presentation, which need to be communicated to both the lay public and the professional community with the goal of facilitating care-seeking and early identification of OSA. Identifying distinct clinical profiles of OSA creates a foundation for offering more personalised therapies in the future.

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This study identified 3 different subtypes of patients with obstructive sleep apnoea based on clinical presentations http://ow.ly/AjuEZ

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Introduction

Although commonly observed in clinical practice, the various clinical presentations of obstructive sleep apnoea (OSA) have not been formally characterised. Lack of knowledge of the heterogeneity of OSA clinical presentation may pose critical challenges to its clinical recognition, resulting in missed or delayed diagnosis. Unsupervised cluster analysis has recently been used to identify subtypes of patients who are diagnosed with a particular disorder, such as asthma, chronic obstructive pulmonary disease (COPD), fibromyalgia and Parkinson's disease [1–4]. With the goal of better understanding the heterogeneity of OSA clinical presentations, this study innovatively applied cluster analysis to identify subgroups of OSA patients who experience distinct combinations of symptoms and comorbidities. In addition, we examined whether patient subgroups differed with regard to patient demographics and other characteristics such as sex, age, body mass index (BMI), apnoea–hypopnoea index (AHI), and health status.

Methods

Study subjects

Subjects in our analysis are from the Icelandic Sleep Apnoea Cohort (ISAC), a clinic-based patient cohort from the entire population of Iceland. Detailed descriptions of the ISAC have been published previously [5–7]. The study inclusion criteria was patients with moderate-to-severe OSA (AHI $\geqslant$15 events·hour^{-1}), referred for positive airway pressure (PAP) treatment to the Dept of Pulmonary Medicine and Sleep, the National University Hospital of Iceland, Reykjavik, the sole provider of PAP therapy in Iceland (total population 320 000). In Iceland all patients with AHI $\geqslant$15 events·hour^{-1} are referred for PAP therapy. Over 90% of eligible and approached subjects agreed to participate. Among the detailed assessments performed at baseline prior to starting PAP, each participant completed a type three sleep study, physical examination and a survey about sleep-related health issues. Our sample included 822 patients from the ISAC who had baseline data available. The study was approved by the Iceland National Bioethics Committee, the Data Protection Authority of Iceland, and the Institutional Review Board at the University of Pennsylvania (Philadelphia, PA, USA).

Questionnaires

Several standardised and previously validated instruments were embedded in the survey to evaluate sleep-related symptoms and health status, including the Basic Nordic Sleep Questionnaire (BNSQ) [8], Epworth Sleepiness Scale (ESS) [9], and 12-item Short Form Health Survey (SF-12) [10]. Patients also answered questions about restless leg syndrome (RLS) symptoms [11] and their medical history such as physician-diagnosed hypertension and diabetes.

The BNSQ is a scale assessing the frequency of subjective sleep complaints in the past 3 months, ranging from 1 (never or less than once per month), 2 (less than once a week), 3 (once or twice a week), 4 (three to five times a week), to 5 (every night or almost daily) [8]. The BNSQ is frequently used in epidemiological and genetic research for OSA with demonstrated validity [12] and has been used widely in routine clinical practice in the Nordic countries [8].

Choosing symptom and comorbidity variables for cluster analysis

We included a total of 23 variables in the cluster analysis to represent clinically significant and prevalent symptoms and comorbidities in the OSA population (a full list of variables is outlined in the results section).

The majority of symptom variables were dichotomised variables derived from responses to the questions on the BNSQ. In general, we defined a specific symptom as ''present'' if it occurred at least once or twice per week (response score: 3–5). To capture the existence of clinically significant snoring and whether the snoring disturbed the spouse's sleep, we coded the snoring variable as 0 (doesn't snore loudly), 1 (snores loudly but doesn't disturb their spouse's sleep), and 2 (snores loudly and disturbs their spouse's sleep). Given our clinical observation that RLS is common among patients with untreated OSA, we included the presence of RLS in the cluster analysis using the same definition we adopted in a previous epidemiological study [13]. In addition, we included the ESS score as a continuous variable to indicate the overall degree of daytime sleepiness.

The presence of four comorbid conditions was included in the analysis: hypertension, diabetes, cardiovascular disease and obstructive lung disease. These conditions were most commonly reported on the survey and were, thus, included in the cluster analysis. The diagnosis of each comorbidity was validated against medical records. Hypertension and diabetes were defined as a physician diagnosis combined with treatment with appropriate medication. Cardiovascular disease was defined as a physician diagnosis of coronary artery occlusion (myocardial infarction or heart attack), heart failure and/or stroke. Obstructive lung disease was defined as a physician diagnosis of COPD, emphysema and/or asthma.

Statistical analysis

Latent class analysis (LCA) [14, 15] was used to cluster subjects into groups based on symptoms and presence of comorbidities. The basic principle of cluster analysis is that individuals are grouped together based on specified variables so that members of each cluster are as similar as possible to others within the cluster, but as different as possible compared with those in other clusters. Two tests of model fit, the likelihood ratio test and Bayesian information criterion, were used to determine the optimal number of clusters. Conditional probabilities or the cluster-specific probabilities were calculated, indicating the probability of a specific symptom or comorbid condition being present in the cluster. Probabilities between clusters were compared *via* odds ratios, with unadjusted $p \leqslant 0.002$ being considered statistically significant after a Holm's adjustment for multiple comparisons. LCA was performed using M*plus* 5.1 (www.statmodel.com) [16].

After the clusters or patient subgroups were identified, differences among clusters with regard to patient demographic and other characteristics, including sex, age, BMI, AHI, oxygen desaturation index (ODI), minimum oxygen saturation during the sleep study and health status (SF-12 scores), were examined *via* Chi-squared, ANOVA, or Kruskal–Wallis equality-of-populations rank tests, as appropriate. Analyses were conducted using StataMP (Stata Statistical Software, Release 12; StataCorp, College Station, TX, USA) and p-values <0.05 were considered statistically significant.

Results

Sample characteristics

The total cohort sample characteristics are summarised in table 1. The sample consisted predominantly of middle-aged obese males with severe OSA. The frequencies of each symptom and comorbid condition for the entire cohort are detailed in table 2.

Three distinct clusters

Three distinct clusters were identified based on symptom experiences and the existence of major comorbidities. Table 2 lists the conditional probabilities of each symptom and comorbid condition present in each cluster, which are compared between clusters in table 3. To highlight the major differences between clusters, figure 1 presents the probability of having certain symptoms within each cluster in a comparable manner.

Cluster 1 was the "disturbed sleep group". Members of cluster 1 (32.7% of the entire cohort) had the highest probability of experiencing insomnia-related symptoms, including difficulty falling asleep at night (44.3%), waking up too early and difficulty falling back to sleep (60.8%), and most prominently, waking up often during the night (90.3%). Other nocturnal symptoms were also prominent, such as heavy perspiration (61.7%), being restless (74.8%), RLS symptoms (42.6%), and sudden awakening due to gasping for breath (21.1%).

Cluster 2 was the "minimally symptomatic group," consisting of 24.7% of the entire cohort. For the majority of symptoms, the probability was markedly lower in cluster 2 than in the other two clusters. Members of cluster 2 were much more likely to feel rested upon waking up (78.3%) compared with those in cluster 1 (38.7%) or in cluster 3 (24.3%).

Cluster 3 (42.6% of the cohort) was the "excessive daytime sleepiness group," with a significantly higher ESS score (15.7±0.6) than cluster 1 (9.5±0.7) and cluster 2 (7.9±0.6), and a markedly higher probability

TABLE 1 Demographic and clinical characteristics of the total cohort and by clusters

	Total cohort	Cluster 1	Cluster 2	Cluster 3	p-value
Subjects n	822	269	203	350	
% of total	100	32.7	24.7	42.6	
Males n (%)	666 (81.0)	211 (78.4)	170 (83.7)	285 (81.4)	0.336
Age years	54.5±10.6	54.1±11.0	56.6±10.3	53.6±10.3	0.005
BMI kg·m^{-2}	33.5±5.7	33.3±5.6	33.0±5.6	34.0±5.8	0.130
AHI events·hour^{-1}	44.9±20.7	43.8±20.4	43.1±18.9	46.7±21.7	0.181
ODI events·hour^{-1}	35.5±20.2	34.0±18.4	33.5±18.9	37.8±21.9	0.117
Minimum oxygen saturation %	76.2±8.0	76.5±7.8	76.7±7.7	75.7±8.4	0.385
SF-12 physical component score	40.3±10.9	39.7±10.5	45.4±9.9	37.7±10.7	<0.001
SF-12 mental component score	48.3±10.9	46.9±11.2	52.9±9.6	46.6±10.7	<0.001

Data are presented as mean±SD, unless otherwise stated. BMI: body mass index; AHI: apnoea–hypopnoea index; ODI: oxygen desaturation index; SF-12: 12-item Short Form Health Survey.

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of complaining of sleepiness-related symptoms, such as falling asleep involuntarily during the day (64.6% *versus* 11.1% in cluster 1 and 8.6% in cluster 2), and dozing off when driving (38.2% *versus* 3.4% in cluster 1 and 4.4% in cluster 2). They also had a somewhat higher likelihood of presenting with classic OSA symptoms, such as night-time breathing pauses and loud snoring disturbing their spouse's sleep.

Among the three clusters, the probabilities of having comorbid hypertension, diabetes and cardiovascular disease were highest in cluster 2 but lowest in cluster 3. For example, cluster 2 was more likely to have comorbid hypertension (49.6% *versus* 41.6%, OR=1.38; $p<0.001$) and cardiovascular disease (18.3% *versus* 11.9%, OR=1.67; $p=0.001$) when compared with cluster 3.

We ran two additional analyses to ensure the stability of the three clusters in this sample. First, we repeated the cluster analysis by defining symptoms as ''present'' if they occurred at least three to five times a week. Although the selection of this higher threshold led to an overall lower prevalence of symptoms, a similar set of three distinct clusters were identified based on the combination of symptoms and comorbidities. Secondly, we included age, sex and AHI in the cluster analysis in addition to the original 23 variables. Similar results were identified with the additional three variables in the model.

Differences among the three clusters

As indicated in table 1, no statistical difference was observed in sex, BMI, AHI, ODI or the minimum oxygen saturation among the three clusters. Although mean age was statistically different among clusters, this difference (54.1 *versus* 56.6 *versus* 53.6 years) was unlikely to be clinically meaningful. Both the SF-12 physical and mental component scores significantly differed among clusters ($p<0.001$), even after adjusting for sex, age and BMI, with the highest scores indicating the best physical and mental health status being reported by members of cluster 2. In addition, we examined the use of hypnotics and found that the frequency of hypnotic use was significantly higher in members of cluster 1 (16.4%; $p=0.017$) than those of cluster 2 (8.9%) and cluster 3 (10.1%).

TABLE 2 Symptom experiences and comorbidities of subjects in the total cohort and by clusters

	Total cohort	Cluster 1	Cluster 2	Cluster 3
Symptoms present				
I feel rested when I wake up	42.6	38.7	78.3	24.3
I feel sleepy/drowsy during the day	87.8	90.9	68.3	97.1
I have difficulties falling asleep at night	28.9	44.3	13.6	25.8
I wake up too early/it is difficult to fall back to sleep	44.9	60.8	26.8	43.3
I wake up often during the night	73.0	90.3	43.5	77.0
I feel physically tired during the day	87.8	96.3	59.6	98.1
I wake up with a headache	23.7	24.6	6.4	33.2
I'm restless in my sleep	60.4	74.8	24.9	70.5
I perspire heavily during the night	49.5	61.7	24.7	54.8
I wake up suddenly and feel as if I can't breathe	18.0	21.1	1.8	25.3
I fall asleep involuntarily during the day	32.8	11.1	8.6	64.6
I fall asleep if I relax (TV)	77.5	60.1	65.0	98.8
I take a nap during the day	45.4	49.4	25.7	54.0
I doze off at the steering wheel when driving	18.1	3.4	4.4	38.2
My nose is congested at night	48.4	54.4	27.5	56.3
I have been told that I stop breathing at night	77.1	75.0	67.5	84.6
Presence of clinically significant snoring				
I snore loudly but it does not disturb my spouse's sleep	9.9	13.6	10.3	6.9
I snore loudly and it disturbs my spouse's sleep	81.9	79.2	71.7	89.8
Presence of restless leg syndrome symptoms	36.8	42.6	14.5	45.6
ESS total score mean±SE	11.7±0.2	9.5±0.7	7.9±0.6	15.7±0.6
Major comorbidities present				
Hypertension	45.7	47.8	49.6	41.6
Diabetes	8.7	8.8	10.5	7.5
Cardiovascular disease	14.4	14.6	18.3	11.9
Obstructive lung disease	18.7	21.3	16.2	18.2

Data are presented as %, unless otherwise stated. ESS: Epworth Sleepiness Scale.

TABLE 3 Odds ratios for comparisons of probabilities between clusters

	Cluster 1 *versus* cluster 2		Cluster 1 *versus* cluster 3		Cluster 2 *versus* cluster 3	
	OR	p-value	OR	p-value	OR	p-value
Symptoms present						
I feel rested when I wake up	0.18	**0.001**	1.97	**0.001**	11.24	0.003
I feel sleepy/drowsy during the day	4.65	0.092	0.30	0.130	0.07	0.029
I have difficulties falling asleep at night	5.06	0.017	2.28	**0.001**	0.45	0.009
I wake up too early/it is difficult to fall back to sleep	4.25	**<0.001**	2.03	**<0.001**	0.48	**<0.001**
I wake up often during the night	12.06	0.016	2.76	0.038	0.23	**0.001**
I feel physically tired during the day	17.68	0.202	0.51	0.357	0.03	0.094
I wake up with a headache	4.75	0.024	0.66	**0.002**	0.14	0.006
I'm restless in my sleep	8.97	0.004	1.24	0.006	0.14	0.003
I perspire heavily during the night	4.90	**0.001**	1.33	**<0.001**	0.27	**0.001**
I wake up suddenly and feel as if I can't breathe	14.63	0.649	0.79	**0.002**	0.05	0.651
I fall asleep involuntarily during the day	1.33	0.206	0.07	0.035	0.05	0.059
I fall asleep if I relax (TV)	0.81	0.050	0.02	0.169	0.02	0.192
I take a nap during the day	2.82	0.003	0.83	**<0.001**	0.30	**0.001**
I doze off at the steering wheel when driving	0.77	0.207	0.06	0.060	0.07	0.059
My nose is congested at night	3.15	**<0.001**	0.93	**<0.001**	0.29	**<0.001**
I have been told that I stop breathing at night	1.44	**0.001**	0.55	**0.001**	0.38	**<0.001**
Clinically significant snoring						
I snore loudly but it does not disturb my spouse's sleep	2.83	0.034	0.44	0.091	0.15	0.028
I snore loudly and it disturbs my spouse's sleep	1.51	0.008	0.43	0.007	0.29	**0.001**
Restless leg syndrome symptoms	4.37	0.003	0.89	**0.001**	0.20	**0.001**
Major comorbidities present						
Hypertension	0.93	**0.002**	1.29	**0.001**	1.38	**<0.001**
Diabetes	0.83	0.083	1.20	0.079	1.44	0.023
Cardiovascular disease	0.76	0.012	1.27	0.007	1.67	**0.001**
Obstructive lung disease	1.40	0.007	1.21	**0.001**	0.87	**0.002**

Bold font indicates variables with statistically significant differences between clusters/groups ($p \leqslant 0.002$).

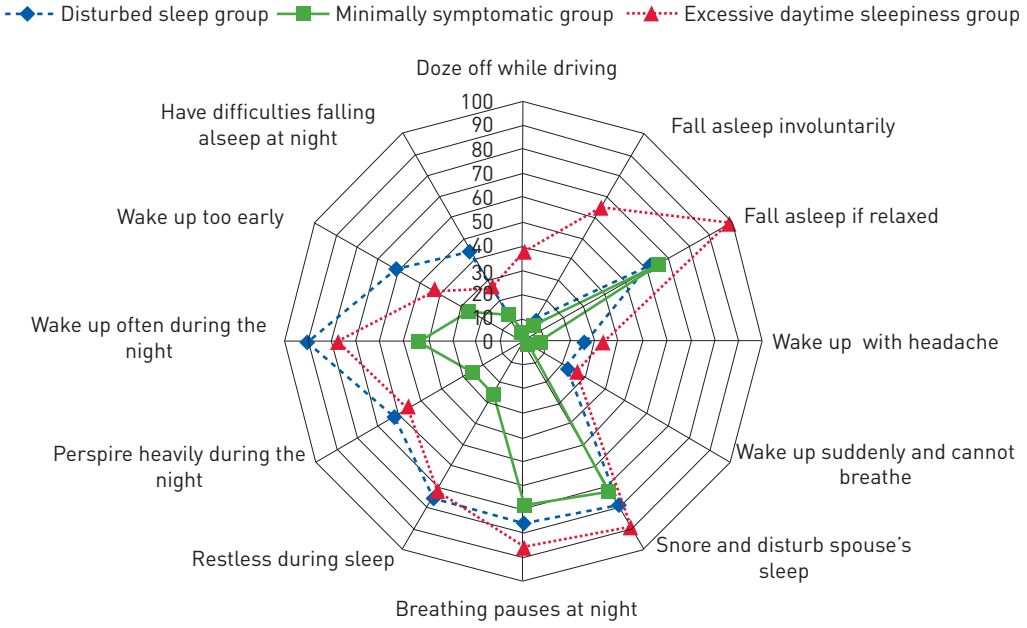

FIGURE 1 Probability of having a symptom within each cluster. The conditional probabilities of 12 symptoms (selected from the complete list in Table 2) are shown to highlight the major differences among clusters.

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Discussion

To the best of our knowledge, this is the first attempt to explore the heterogeneity of OSA clinical presentations using a data-driven approach. Our results suggest that there are different clinical subtypes of OSA. The major strengths of this study are innovative data analysis and the large clinical cohort representing patients with OSA who need PAP treatment across the entire population of Iceland. Furthermore, the inclusion of a comprehensive number of symptoms enhances our understanding of the OSA symptom experience.

As a novel approach with the potential to refine phenotypic diagnostic criteria [17], cluster analysis has been used in other medical conditions to identify symptom patterns and clinical phenotypes [1–4]. A recent study using cluster analysis identified five distinct clinical phenotypes of asthma, illustrating heterogeneity in the clinical presentation of asthma and clinically relevant differences in treatment outcomes among various phenotypes [3]. Another example of this approach is illustrated by an analysis of the presenting symptoms for myocardial infarction: five clusters or patient subgroups with distinct symptom patterns were identified, with none of these clusters including all of the symptoms that are considered typical of myocardial infarction [18].

Understanding differences in patterns of OSA clinical presentation is especially important. Patients in cluster 1 and cluster 2, which together made up over half of the sample, were less likely to present with clinically significant daytime sleepiness (*i.e.* mean ESS score <10). Although the majority of the individuals in cluster 1 and cluster 2 reported other classic OSA symptoms such as breathing pauses at night and loud snoring that disturbed their spouses' sleep, they were less likely to do so than patients in cluster 3. As supported by the seminal Wisconsin Sleep Cohort Study [19], more individuals with OSA in the community who may be less symptomatic have not yet been referred and diagnosed. Therefore, current clinical practice and research, which emphasise only a few ''typical'' symptoms such as snoring and daytime sleepiness, may have created a potentially problematic image of a stereotypical OSA patient.

Although OSA severity is widely classified using the AHI [20], this objective index does not consider the marked heterogeneity of differing clinical presentations of OSA. Remarkably, as demonstrated by our observation, in three patients with essentially identical AHIs, one can be a loud snorer with excessive daytime sleepiness, another may mainly complain of disturbed sleep, while the third may not be bothered by any major OSA-related symptoms but is more likely to have coexisting hypertension or cardiovascular disease. Our findings suggest that identifying clinical presentations based on combinations of symptoms and comorbidities can more fully capture the spectrum of the OSA experience than relying solely on indices such as AHI or ODI.

Members of cluster 1 are distinguished by having the most disturbed sleep, particularly showing insomnia symptoms. A relatively high prevalence of other symptoms, such as RLS, nocturnal sweating [5] and frequent awakening due to gasping for breath, may also have contributed to their insomnia complaints. Although numerous studies, including studies using an insomnia severity scale to quantify insomnia, have documented the high prevalence of insomnia symptoms in patients with OSA [21–27], the evaluation of insomnia has not been recommended as part of routine screening for OSA [28]. A recent study in family medicine patients found insomnia to be a significant predictor of a clinical diagnosis of OSA, independent of BMI and excessive daytime sleepiness [29]. The relatively high likelihood of hypnotic use in these patients further emphasises the need to develop strategies for adequately managing comorbid insomnia.

Unlike typical patients with insomnia disorder [30], members of cluster 1 had a higher probability of daytime napping. The disturbed sleep may have exacerbated daytime sleepiness in these untreated OSA patients [22]. Meanwhile, untreated OSA could worsen insomnia in these patients. It is likely that repeated breathing disturbances in untreated OSA results in sleep fragmentation and hence difficulties maintaining sleep. Repeated arousals that result from abnormal respiratory events may also further aggravate the hyperarousal associated with typical insomnia. Insomnia symptoms in a group of OSA patients have been reported to significantly improve after 24 months of PAP treatment [26]. By contrast, a recent study conducted by our team found that PAP treatment only significantly reduced symptoms of difficulties maintaining sleep [31]. We found that other subtypes of insomnia, including difficulties initiating sleep and early morning awakenings, tended to persist regardless of PAP treatment and that difficulty falling asleep even negatively impacted PAP adherence [31]. These results highlight the importance of assessing insomnia subtypes in the management of OSA. Specific treatment for insomnia prior to or combined with PAP treatment, such as cognitive behavioural therapy, could be beneficial, at least for some OSA patients affected by difficulty falling asleep.

We found that members of cluster 2, the minimally symptomatic group, reported the most favourable physical and mental health status. This finding supports symptom status as a key predictor of quality of life,

and the importance of comprehensive evaluation of symptoms for improving quality of life in patients with OSA [32]. In contrast to the finding that excessive daytime sleepiness was associated with an increased risk of future cardiovascular disease in community-dwelling elderly individuals [33], members of cluster 3, the excessive daytime sleepiness group, had a lower probability of having comorbid hypertension, diabetes and cardiovascular disease than members of other clusters. The lag time between initial OSA symptoms and OSA diagnosis can vary widely, with the average duration reported to be approximately 10 years [34]. Members of cluster 3, who were sleepier and more likely to report classic features of OSA, may have had a shorter lag time. By contrast, members of cluster 2 who were minimally symptomatic may have had a longer lag time, leading to a longer duration of exposure to untreated OSA and, thus, a higher probability of developing comorbidities. Nevertheless, they were neither more obese nor significantly older, and they did not have higher AHIs, than other members of the cohort. In addition to lag time prior to OSA diagnosis, other factors that were not examined in this study, such as the existence of a bed partner, may have a significant impact on the clinical presentations of OSA and deserve further investigation.

Our study focuses on one of the goals of personalised medicine: to identify distinct subtypes among individuals with a particular disease with the goal of more precisely targeted therapies. As such, our study population is not intended to be a community-based cohort. Thus, we recruited 822 consecutively diagnosed patients with OSA in Iceland. There have been extensive efforts in Iceland to educate primary care and other physicians about OSA, resulting in a high level of awareness of this disorder. All patients with identified OSA are referred to a single location for treatment. The high participation rate for research in Iceland is another substantial advantage. Thus, the ISAC cohort is representative of all patients recently diagnosed with OSA in one country, minimising referral bias.

Nevertheless, one limitation of this study is that data were collected exclusively from persons with moderate-to-severe OSA. Our subjects were predominately middle-aged obese males, who are typical of patients with more severe OSA. Although we have conducted additional analyses to ensure the stability of the clusters, further validation in independent cohorts including a wider variety of demographics and levels of OSA severity is needed. Although the overall patterns of clinical presentations of OSA were not significantly influenced by patient age, sex and AHI in our sample, these important sociodemographic variables may account for different clinical presentations of OSA [35] and should be carefully considered in future investigations with more diverse samples. Some symptoms and/or comorbidities that may be common in the OSA population, such as depression and cognitive decline, were not included in this study. Future investigations need to consider more fully the existence of comorbid conditions. Finally, although we did not observe differences among clusters in AHI, AHI may have been underestimated among individuals with insomnia symptoms, given the inability to precisely measure total sleep time using type 3 portable monitors.

In conclusion, our findings are clinically significant in two major aspects. First, identification of subtypes of OSA improves our knowledge and awareness of the heterogeneity of OSA clinical presentation. Communication of this knowledge to both the lay public and the professional community can facilitate care-seeking and early identification of OSA. This is particularly important for individuals with ''atypical'' OSA symptom experiences and those who are less symptomatic. Although debate persists regarding the need for treatment of ''asymptomatic'' OSA, a number of studies have demonstrated that minimally symptomatic individuals with OSA are still at increased cardiovascular risk [36–38]. Secondly, identifying distinct clinical profiles of OSA creates a foundation for offering more personalised therapies in the future. Follow-up studies are needed to examine whether the response to treatment differs among OSA patients with distinct patterns of clinical presentations, particularly in terms of changes in symptom presentation, blood pressure and cardiovascular comorbidities. Further investigation is also needed to explore the underlying mechanisms of distinct clinical phenotypes, including the genotypic differences associated with different clinical presentations.

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