Characterisation of patients who present with insomnia: is there room for a symptom cluster-based approach?

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ABSTRACT

Study objectives: This study examined empirically-derived symptom cluster proliles among patients who present with insomnia using clinical data and polysomnography (PSG).

Methods: Latent profile analysis was used to identify symptom cluster profiles of 175 individuals with insomnia disorder (ID; 63% female) based on total scores on validated self-report instruments of day- and night-time symptoms (Insomnia Severity Index, Glasgow Sleep Effort Scale, Fatigue Severity Scale, Beliefs and Attitudes about Sleep, Epworth Sleepiness Scale, Pre-Sleep Arousal Scale), mean values from a 7-day sleep diary (sleep onset latency [SOL], wake after sleep onset [WASO] and sleep efficiency [SE]), and total sleep time [TST] derived from a laboratory PSG.

Results: The best fitting model had three symptom cluster profiles: "High Subjective Wakefulness" (HSW), "Mild Insomnia" (MI) and "Insomnia-Related Distress" (IRD). The HSW symptom cluster profile (26.3% of the sample) reported high WASO, high SOL, and low SE, and despite relatively comparable PSG-derived TST, reported greater levels of daytime sleepiness. The MI symptom cluster profile (45.1%) reported the least disturbance in the sleep diary and questionnaires and had the highest sleep efficiency. The IRD symptom cluster profile (28.6%) reported the highest mean scores on the insomnia-related distress measures (e.g., sleep effort and arousal) and waking correlates (fatigue). Covariates associated with symptom cluster membership were older age for the HSW profile, greater obstructive sleep apnoea (OSA) severity for the MI profile, and, when adjusting for OSA severity, being overweight/obese for the IRD profile.

Conclusion: The heterogeneous nature of insomnia disorder is captured by this data-driven approach to identify symptom cluster profiles. The adaptation of a symptom cluster-

based approach could guide tailored patient-centered management of patients presenting with insomnia, and enhance patient-care.

Keywords: Insomnia Disorder, latent profile analysis, symptom profile, symptom clusters

INTRODUCTION

Insomnia is the experience of the difficulty falling asleep, difficulty staying asleep, or early morning awakenings. About one-third to one-half of adults complains of these symptoms.[1] Frequently, other complaints, such as sleepiness, fatigue, and hyperarousal, will occur with nocturnal sleep disturbance. An insomnia disorder is defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5[2] as the combination of the nocturnal sleep disturbance with one of these waking complaints at least 3 nights a week for at least 3 months. About 8-10% of the adult population meets these criteria.[3,4]

Insomnia disorder is a heterogeneous condition.[5] This can pose a challenge for optimal patient care, because a 'one size fits all' approach does not provide treatment that is tailored to the patient's unique combination of symptoms. The field of oncology has made great strides towards personalised/precision medicine[6] by acknowledging the heterogeneity within the disease and matching treatment based on the individual's symptom/genetic profiles. Many other areas have followed suit, and we believe that there is room for the same type of personalised medicine in insomnia and that this could greatly improve patient care. A management approach to insomnia disorder that is not confined to diagnostic boundaries and instead considers symptom cluster profiles, might offer a more targeted management by treating the most relevant symptoms. This would translate to assessment and treatment decisions informed by a profile based on the level of severity of each symptom.

This hypothesis is based partly on results from our previous mixed-methods study,[7] which revealed that patients with multiple sleep symptoms tend to understand the symptoms and consequences better than diagnostic categories of sleep disorders. Yet, we as clinicians make decisions largely based on diagnostic categories. Empirically deriving

symptom clusters for those who present with insomnia complaints might yield a model for a patient-centred approach. There have been previous attempts to identify nighttime-and daytime symptom cluster profiles in patients with insomnia disorder using data-driven approaches.[8-13] Similar attempts have been published characterising the heterogeneity of obstructive sleep apnoea.[14,15] However, most of these studies used cluster analysis to characterise this heterogeneity . In contrast, mixture models, such as latent class or profile analysis (LPA), have certain advantages over cluster analysis as described further in the statistical analysis section.

In general, the primary aim of LPA is to classify individuals into symptom profiles reflecting symptom clusters that consist of homogeneous individuals with regards to continuous observed variables being studied.[18] While ensuring homogeneity *within* a symptom profile, the different profiles are distinct from each other and are viewed as representing the unobserved heterogeneity *across* individuals. Therefore, this person-centered analytic technique uses *actual empirical data*, and not arbitrary dichotomization (such as diagnostic categories), to create quantitatively and qualitatively distinct profiles of individuals based on their dimensional presentation of day- and night-time symptoms of insomnia. Another strength of the analyses is the ability to examine covariates of symptom cluster membership. These may be tested in association with distinct outcome variables, such as treatment response, relapse risk or obstructive sleep apnea (OSA) risk, in future reports.

To our knowledge, only two studies have used mixture models, such as latent profile or class analysis, to identify symptom cluster profiles within insomnia.[16,17] Those studies, however, did not explore symptom profiles among patients who met criteria for an insomnia disorder. [16,17] The purpose of this study was to examine whether distinct

symptom profiles could be identified across a heterogeneous sample of insomnia patients who are representative of those presenting to a sleep clinic, including those with comorbidities such as Periodic Limb Movement Disorder (PLMD) or OSA. We hypothesised that distinct symptom cluster profiles would emerge. We believe that empirically derived symptom profiles can provide an impetus for a dimensional profile of sleep health,[19] which might be useful for reducing the gap between patient understanding and clinical decision making based on categories.

METHODS

Study Sample

Baseline assessments from two independent projects were used for this analysis. Individuals underwent a structured interview for sleep disorders[20] and had to meet quantitative criteria for insomnia[21] as determined by a 7-day sleep diary. Eligible participants had to be psychologically and medically stable, as evaluated by a structured interview for clinical disorders (SCID[22]) and medical exam by a physician (study 2 only) respectively. Lastly, individuals who were not fluent in English were excluded. Individuals who were taking sedative-hypnotic medications were only eligible if they stopped the medication under supervision of their prescribing physician.

There were minor differences in the inclusion criteria for both studies: study 1 targeted individuals over 21 years of age with psychophysiological insomnia[23], and study 2 targeted individuals over 18 years of age with insomnia disorder and comorbid OSA[24]. For study 1, insomnia had to be present for at least 6 months to meet criteria for chronicity,[25] whereas for study 2 insomnia had to be present for at least 3 months (ICSD-3[26] and DSM-5 criteria[2]). For study 2, unless agreeing not to drive, individuals who were excessively

sleepy were also excluded. Excessive sleepiness was defined by scores on the Epworth Sleepiness Scale[27] score >16 or a score of 3 (high chance) on the ESS question about risk of dozing "In a car, while stopped for a few minutes in traffic" or a report of falling asleep at the wheel, an MVA, or near-miss accident due to sleepiness in the past 24 months, which in the judgment of the study physician was not attributable to acute sleep loss. All participants also had to be naïve to CPAP and CBT-I.

By merging data from these two studies collected at the last step of the screening process (in –lab polysomnography, see below) we were able to capitalise on the homogeneity with regards to inclusion criteria (i.e., both studies included individuals with insomnia disorder) while retaining some heterogeneity with regards to exclusion criteria (i.e., in this analysis we included those who were excluded in both studies i.e., individuals with comorbid OSA [in study 1] and comorbid periodic limb movement [study 1 and 2]).

Procedures

The standard baseline assessment for both studies was designed to mimic common clinic procedures for new patients' evaluations at a sleep clinic. The baseline assessment consisted of a brief phone screen, an in-person interview, and an in-lab polysomnograph (PSG). All individuals provided written informed consent. The institutional review board at Rush University Medical Center approved both studies. Data from participants who had successfully completed the baseline assessment were merged into one dataset.

Measures

At baseline, individuals completed a range of self-report questionnaires, a 7-day sleep diary, and a screening PSG.

Insomnia Severity Index (ISI).[28] The ISI is a brief 7-item scale assessing nocturnal and daytime symptoms of insomnia, which has been used as both a screening and outcome measure in treatment research. Total scores range from 0-28, with higher scores indicative of increase insomnia severity. The ISI has adequate internal consistency with evidence supporting concurrent, predictive, and content validity.[29,30]

Glasgow Sleep Effort Scale (GSES).[31] The GSES measures sleep-related effort as experienced in the past week. The seven items are reverse coded so that a higher score (range 0-14) indicates increased sleep effort (e.g., "I feel I should be able to control my sleep at night"). Adequate reliability and validity of this measure has been established.[30]

Beliefs and Attitudes about Sleep Scale (BAS).[32] The BAS is a 30-item measure of sleep-related dysfunctional thinking. Individuals are asked to indicate the level of agreement on statements related to sleep; a strong endorsement of these statements is suggestive of dysfunctional beliefs and attitudes about sleep. The total scores were computed by summing all items, thus scores ranged from 0-300. The short-form version has acceptable internal consistency (Cronbach's alpha between 0.8 and 0.8) and adequate test-retest reliability across a 2-week interval (r= .8).[33]

Pre-Sleep Arousal Scale (PSAS).[34] The PSAS is a 16-item questionnaire that assesses both cognitive and somatic arousal typically experienced during the sleep onset period. The total score ranges from 16-80 with a higher score reflective of increased arousal at bedtime.

Fatigue Severity Scale (FSS).[35] The FSS is a 9-item measure providing a global score of the intensity of an individual's fatigue and has good internal consistency (α = 0.8-0.9[34]). Scores range from 9-63 with increased scores reflective of increased fatigue.

Epworth Sleepiness Scale (ESS).[27] The ESS is a brief 8-item questionnaire measuring the propensity for drowsiness or falling asleep in eight common situations and correlates

moderately with sleep latency at night and during daytime naps.[27] Total scores range from 0-24 with higher scores indicating increased subjective sleepiness.

Sleep diary. Prospective sleep diaries were completed daily across a 7-day period. The following variables were derived for analyses and were included in the analytic model (see statistical analysis): sleep onset latency (SOL), wake after sleep onset (WASO) and sleep efficiency (SE, computed as the percent of time asleep relative to the time in bed). Study 1 used an in-house sleep diary that is similar to the consensus sleep diary, but did not separate WASO from early morning awakenings (EMA); study 2 used the consensus core sleep diary.[36] For study 2, EMA was added to WASO, so that this measure was comparable to study 1.

Polysomnography (PSG). Each participant completed a technician-monitored, in-laboratory PSG to collect objective measures of sleep and respiratory events. Each study was scored by a registered polysomnography technologist and reviewed by a board-certified sleep medicine physician in accordance with the AASM Manual for the Scoring of Sleep and Associated Events.[37] For our analyses the following variables were extracted: total sleep time [PSG-measured total sleep time (TST)], and Apnoea-Hypopnea Index (AHI).

Statistical Analysis

Preliminary statistical analyses included descriptive statistics and assessment of normality of distributions. Data for continuous variables are presented as means and standard deviations and were compared between profiles using independent *t*-tests. Categorical variables are presented as percentages and were compared with the chi-squared test. The Statistical Package for the Social Sciences (SPSS) version 19.0 was used for all preliminary analyses.

Latent Profile analysis (LPA) was used to characterise insomnia symptom profiles. LPA is an empirically driven approach, which uses continuous variables (or indicators) to derive latent clusters of individuals with a particular symptom profile. Symptom cluster membership is inferred by examining the patterns of interrelationships among individuals with the goal of maximizing homogeneity *within* class (or symptom cluster profile) and heterogeneity *between* classes. Therefore, underlying this method is an emphasis on differentiating *individuals* (individual-based approach) based on scores on *various indicators*, rather than on one particular variable (variable-based approach). The following continuous indicators were used to characterise insomnia symptom profiles: total scores on the 1) ISI, 2) GSES, 3) FSS, 4) BAS, 5) ESS, and 6) PSAS, as well as mean self-reported 7) SOL, 8) WASO, and 9) sleep efficiency from a 7-day sleep diary and 10) PSG-measured TST. We used PSG- (rather than diary-) derived TST because of mounting evidence that insomnia with objective short sleep may form a distinct subtype of insomnia.[10,38-42] The optimal number of symptom cluster profiles was determined after examination of the following fit indices: the Akaike information criteria (AIC), the Bayesian information criteria (BIC), the sample-size adjusted BIC (ABIC), log-likelihood (LL), entropy, the adjusted likelihood ratio test (ALRT), and the parametric bootstrapped likelihood ratio test (BLRT).[43]

Important advantages of LPA over standard cluster techniques have been identified in the literature.[43] These include, for example, the ability to simultaneously include varying scales data in the same model, formal statistical criteria for selecting best fitting models, and most relevant to this study: the ability to examine associations between covariates and emerging profiles. Given this advantage, analyses were conducted in a two-step manner. First, the continuous indicators listed above were included in the model to identify

insomnia symptom cluster profiles. Second, covariates of symptom profiles were added to the model to examine cross-sectional associations between relevant covariates and symptom cluster profiles, using multinomial logistic regression. The following variables were entered as covariates: age, gender, education, race, ethnicity, BMI and AHI. Odds ratios (OR) of belonging to a symptom cluster with a specific symptom profile were estimated for each covariate. All tests were two-sided and $\alpha<0.05$ was considered to be statistically significant. Mplus version 6.0 was used for all LPA analyses.

RESULTS

Descriptive Characteristics

Our sample was comprised of 175 individuals (n=110 female). Approximately 52.60% of individuals in our study identified as Caucasian, whereas 34.9%, 5.8%, 1.2% and 1.2% of the sample were African American, Asian, American Indian and Native Hawaiian, respectively. In regards to ethnicity, 8.8% of the sample identified as Hispanic/Latino. Mean age and education were 48.8 (SD=13.5) and 15.9 (SD=3.1) years, respectively. Mean AHI was significantly higher among men (M=21.0, SD=24.3) when compared to women (M=11.8, SD=19.2). No other significant differences in study variables were found across gender. In regards to AHI categories, 25.1% of the sample had mild OSA (AHI ≥5 and <15), 20.6% had moderate OSA (AHI ≥15 and <30) and 14.3% had severe OSA (AHI ≥30).

Detailed descriptive characteristics of the study sample are presented in Table 1.

Characterisation of Insomnia Symptom Profiles

Multiple LPA models were examined with the number of symptom profiles (or latent clusters) ranging from 1 to 6. Fit indexes for all models are presented in Table 2. The AIC, BIC, aBIC and LL values decreased as the number of classes increased, which suggests that a greater number of clusters fit the data progressively better. Similarly, the BLRT was significant across comparisons of progressively greater number of clusters. Entropy values for the 3- to 6-cluster solution ranged from 0.838 to 0.945, indicating good fit to the data across all clusters. The ALRT test, however, suggested that the three-cluster solution was the best fitting model as it was shown to perform significantly better than the 2-cluster solution (p=0.028). Further, the ALRT indicated that the 4-cluster solution was not significantly better than the three-cluster solution (p=0.161). In fact, proportion of individuals belonging to each cluster pronouncedly decreased as the number of clusters increased, and the 4-cluster solution included one symptom cluster profile comprised of only 8 individuals (5% of total sample). After collectively accounting for model fit indexes, as well as the size of each cluster, the 3-cluster solution was selected as best representing the data.

Based on visual examination of the severity and presentation of symptoms within the different profiles and discussion amongst the authors (MRC, DAC, JCO), the three latent symptom profiles were labeled the “High Subjective Wakefulness”, “Mild Insomnia”, and “Insomnia-related Distress”. The “Mild Insomnia” symptom cluster profile was the largest comprising 79 (45.1%) individuals, followed by the “Insomnia-related Distress” and the “High Subjective Wakefulness” symptom cluster profile with 50 (28.6%) and 46 (26.3%) individuals, respectively.

Means and standard deviation of all indicators (self-report scales, 7-day sleep diary variables, and PSG TST) across each symptom cluster profile are presented in Table 3. As

shown in Figure 1 and 2 —the graphical representations of the 3 symptom profiles— the "High Subjective Wakefulness" symptom cluster profile had the highest levels of daytime sleepiness (M=10.2; Z-score=0.5), and WASO, lasting on average 144 minutes, (Z-score=1.3), high SOL (M=36.0, Z-score=0.5), and the lowest sleep efficiency (56.3%; Z-score=-1.3) in spite of a relatively comparable objective total sleep time to the other two profiles (M=364.8, Z-score=-0.2). In contrast, the "Mild Insomnia" symptom cluster profile presented with relative low means across most self-report and sleep diary variables and the highest diary-based sleep efficiency of all three symptom cluster profiles (M=83.3%; Z-score:0.6). Finally, the "Insomnia-related Distress" symptom cluster profile was characterised by the highest overall means on self-report instruments measuring sleep arousal (PSAS M=40.4; Z-score=0.7), effort (GSES M=9.5; Z-score= 0.8) and symptomatic severity (ISI M=20.9; Z-score=0.7), as well as cognitions about sleep (BAS M=156.86, Z-score=0.86) and daytime fatigue (FSS M=44.4; Z-score=0.7).

Symptom Cluster Membership Covariates

The inclusion of covariates to the model (age, gender, education, race, ethnicity, AHI category and BMI category) did not significantly alter the indicator mean scores for each symptom cluster profile, which further confirms the stability of the 3-cluster solution. Unadjusted mean values and percentages for each predictor by the three insomnia symptom cluster profiles are presented in Table 3.

Participants across all insomnia symptom cluster profiles were comparable in terms of gender, education, race and ethnicity. However, significant predictors of symptom cluster membership included age, OSA severity, and BMI category (see Table 4 for

unstandardized odds ratios for all variables). In terms of age, older participants were significantly more likely to belong to the "High Subjective Wakefulness" profile than the "Insomnia-related Distress" profile (OR=1.052, *p*=0.025) or the "Mild Insomnia" profile (OR=1.046, *p*=0.019). This indicates that for every one year increase in age participants were 5% more likely to belong to the "High Subjective Wakefulness" profile when compared to the "Insomnia-related Distress" or "Mild Insomnia" profile. No significant differences in age were found between the "Mild Insomnia" and "Insomnia-related Distress" profiles. In regards to AHI, participants with higher degree of OSA severity were significantly more likely to belong to the "Mild Insomnia" profile when compared to the "Insomnia-related Distress" (OR=1.870, *p*=0.018) or the "High Subjective Wakefulness" (OR=1.639, *p*=0.047) profiles. In fact, for every progressive increase in OSA severity category (no OSA vs. mild vs. moderate vs. severe), there was an 87% increase in the odds of belonging to the "Mild Insomnia" as compared to the "Insomnia-related Distress"profile. Similarly, for every progressive increase in OSA severity category, there was a 64% increase in participant's odds of belonging to the "Mild Insomnia" profile as compared to the "High Subjective Wakefulness" profile. Finally, when adjusting for OSA severity, participants with greater degree of obesity were more likely to belong to the "Insomnia-related Distress" than the "Mild Insomnia" (OR=1.804, *p*=0.008) profile. This indicates that overweight/obese participants had an 80% increase in their odds to belong to the "Insomnia-related Distress" profile when compared to the "Mild Insomnia" profile. No significant differences in BMI category were found between the "High Subjective Wakefulness" profiles and the other two symptom cluster profiles.

DISCUSSION

Considering the heterogeneity of insomnia disorder, a symptom-based approach is a timely consideration. The aim of our study was to generate symptom cluster profiles, which could guide development of models of patient-centered care. A symptom cluster-based approach might provide a more personalised, precise management of the patient's primary complaints. Unique patterns nested within the symptom cluster would otherwise be lost.[59] To do this, we used a different data-driven approach (latent profile analysis, LPA) in a sample of individuals who represent patients presenting to a sleep clinic for insomnia symptoms.

Compared to most previous studies, we used data-driven methods here to characterise the heterogeneity, rather pre-determined categories as used in other studies. For example, pre-determined categories have included insomnia disorder subtypes, such as psychophysiological, paradoxical, idiopathic insomnia, insomnia related to a mental disorder, wich have been associated with different disease characteristics,[44-46] treatment perceptions[46,47] and treatment responses.[46,48] Nightly insomnia symptoms (sleep onset or sleep maintenance problems or early morning awakenings) have also been associated with different disease characteristics[49-55] and treatment responses.[56,57] More recently, the heterogeneity driven by objective total sleep time has garnered attention. A number of studies have highlighted differential outcomes associated with short vs. long objective sleep.[38-42,58] In contrast to these top-down approaches, data-driven methods, such as cluster analysis, have been applied to this area and have revealed that daytime symptoms such as sleepiness, fatigue, mood and sleep hygiene practices,[9] nighttime symptoms such as objective sleep parameters,[10] night-to-night variability and longitudinal development of subjective sleep variables[11,16] and dysfunctional beliefs about sleep[12] uniquely fall together

in identifiable and meaningful clusters. Others have used both sleep and psychiatric history, and daytime and nighttime symptoms to identify symptom clusters.[8]

To our knowledge, only two studies to date have used sophisticated mixture models to derive symptom cluster profiles in individuals with sleep disturbances [17] or from a population-based sample.[16] Foley and colleagues identified four symptom clusters ("weekly sleep disturbance and distressed", "transient sleep disturbances", "early morning awakenings" and "comorbid & non-restorative sleep"). Also using latent class analysis, Green and colleagues derived four symptom profiles, "healthy with low reports of sleep problems", "episodic reports of sleep problems", "developing over the 20 years" and "chronic problems of both sleep onset and maintenance problems". [16] Our latent profile analysis reported here, builds on these previous studies. The symptom cluster profiles that emerged in our study were characterised by the following symptoms: increased self-reported wakefulness ("High Subjective Wakefulness"), low reporting of insomnia symptoms ("Mild Insomnia") and high distress about sleeplessness and its consequences, ("Insomnia-related Distress").

"High Subjective Wakefulness" symptom cluster profile

The "High Subjective Wakefulness" symptom cluster profile was best characterised by the significant subjective sleep disruption as reported on sleep diary (high SOL & WASO and low SE). This symptom cluster profile has similarities with one of Foley et al.'s symptom profiles[17]: the "difficulty maintaining sleep" group also reported high rates of sleep maintenance problems. Interestingly, PSG-derived total sleep time of the HSW symptom cluster profile did not vary greatly from the other two profiles (10-20 minute difference),

yet the HSW reported taking 30 minutes longer to fall asleep than those with the mild insomnia profile and 90 minutes more wakefulness in the middle of the night than the other two symptom cluster profiles, which suggest potential overestimation of subjective wakefulness in the HSW symptom cluster profile. It is noteworthy, however, that this study used one night of PSG to determine objective total sleep time, compared to an average 7-day sleep diary, hence measurement bias reduces the ability to estimate true extent of the sleep misperception. In addition, the use of only one PSG night raises the potential influence of "first-night effects". Future replications, ideally with multiple consecutive nights, are needed at this stage; however it is worth mentioning that recent evidence emerged indicating the validity of one PSG night in the classification of short vs. long objective total sleep time for individuals with insomnia.[60]

The statistical method of latent profile analysis enabled us to examine predictors of symptom cluster membership. Because participants of older age were more likely to belong to the HSW symptom cluster profile than to the other two symptom cluster profiles, it is possible that the observed elevation in subjective wakefulness might be explained in part by age-related increase in WASO.[61] The average objective total sleep time for this symptom cluster profile —just above 6 hrs.— was below the sample's overall average, thus individuals with this symptom profile might benefit from therapeutic approaches that lead to rapid sleep consolidation, for example sleep restriction, stimulus control or sedative-hypnotics. Whether some of these individuals present with similar characteristics and sequelae as the symptom cluster profile "insomnia with objective short sleep"[10,38-40,42,58] remains to be elucidated in future studies.

"Mild Insomnia" symptom cluster profile

The Mild Insomnia symptom cluster profile had less severe insomnia, less fatigue, more consolidated sleep and the least sleep-interfering mental activity (dysfunctional beliefs, sleep-related effort and pre-sleep arousal) of all profiles. There are similarities between this symptom cluster profile and Sánchez-Ortuño and colleagues' "low endorsement" symptom profile.[12] Sánchez-Ortuño's profile scored low on all subscales of the beliefs and attitudes about sleep scale, reported least number of nights with insomnia complaints and had the lowest insomnia severity score.

The results in the current study indicated that this symptom profile had the highest percent of cases with OSA overall and per severity level among the three symptom profiles. This symptom cluster profile might represent individuals with comorbid OSA and insomnia, who may not identify insomnia as their chief complaint. In a previous study on OSA and comorbid insomnia, we found that a quarter of the sample (24.1%) identified OSA (rather than insomnia) as their primary complaint.[7] This finding has important clinical implication and could improve the precision and cost-effectiveness of evaluations conducted at sleep disorders clinics. Specifically, whereas PSG is not currently recommended for the routine assessment of insomnia,[62] a patient presenting for the treatment of insomnia whose symptom profile fits the "Mild Insomnia" symptom cluster profile might benefit from a PSG to evaluate the possible presence of OSA. The danger of OSA going undetected among insomnia patients has been previously documented. Krakow and colleagues found that in patients endorsing insomnia but no sleep disordered breathing (SDB) symptoms, most nighttime awakenings actually followed respiratory events, unbeknownst to the patient,[63] and 50% of the sample met criteria for OSA. Fung et al. found that nearly half of study participants with insomnia suffered from occult SDB (AHI

≥ 15), and the presence of excessive daytime sleepiness was the distinguishing factor between occult and non-existent SDB.[64] In the primary care setting, insomnia was found to predict OSA irrespective of age.[65] Cronlein and colleagues found that occult OSA was most likely to be found on PSG in older and overweight individuals with insomnia, alluding to the possible necessity for PSGs in these patients.[66] men with insomnia who frequently reported dry mouths were likely to have occult sleep apnoea even after been screened for possible OSA.[67] Our findings complement these studies by highlighting the risks of occult OSA in insomnia patients, and this might be particularly prominent in those with the "Mild Insomnia" symptom profile. For this profile, treatment of insomnia using brief behavioural therapy[68-70] might suffice, and these patients might require concomitant treatment for both insomnia disorder and OSA.

We did not include participants who were excluded *prior* to the PSG screening evaluation (e.g., those who had a high [study 1] or low risk [study 2] for OSA based on subjective symptoms such as snoring or witness apnoeas or based on medical examination). This selection method might have biased our results, as we are left with two distinct samples at two extremes of the continuum: insomnia + no OSA for study 1, and insomnia + OSA for study 2. This selection bias might lead to an overrepresentation of the mild insomnia profile. In contrast, our analysis did include participants who underwent a screening PSG, even if they were excluded *post*-PSG from each individual parent study, which increases the selection of insomnia patients with comorbidities to a greater extent that most previous studies have done.

"Insomnia-related Distress" symptom cluster profile

Finally, the "Insomnia-related Distress" symptom cluster profile was characterised by the highest reports of sleep-interfering mental activity and of fatigue. This profile is very similar to previously reported clusters> Sánchez-Ortuño and colleagues' "worried and symptom focused" and "worried and medication biased" clusters; Edinger and colleagues' "bedtime arousal" cluster; and Foley et al's "distressed" cluster.[8] These clusters are all characterised by pre-sleep arousal, distress, worry or dysfunctional beliefs about sleep. Interestingly, in the current study, those belonging to the "Insomnia-related Distress" symptom cluster profile were more likely to have no or mild OSA. Thus PSG evaluation would not likely be indicated, unless other risk factors such as snoring or witness apnoeas have been reported. Particularly noteworthy are the high rates of fatigue in this cluster, despite relatively comparable levels of daytime sleepiness to the other profiles (see table 3 and figure 1, 2); this dichotomy is not present in other symptom cluster profile. The dissociation between fatigue and sleepiness ratings has been highlighted previously, with the former more frequently reported in insomnia.[73,74]

Controlling for OSA severity, overweight/obese participants were more likely to belong to the "Insomnia-related Distress" than the "Mild Insomnia" symptom cluster profile. Our findings report on cross-sectional data, thus preclude inference about causal relationships between insomnia-related distress and obesity; however these results might suggest avenues for further investigation. Others have reported an association between obesity, insomnia and emotional stress,[71] and psychological stress has been associated with changes in the production of appetite regulating hormones, such as ghrelin.[72]

Patients who present with a symptom profile consistent with the "Insomnia-related Distress" symptom cluster profile might benefit from a treatment plan that includes

cognitive therapy, mindfulness or relaxation strategies to reduce the arousal, and distress and a mix of cognitive and behavioural components to address fatigue.

One notable limitation that is relevant to this symptom profile is that parent study 1 specifically recruited individuals with psychophysiological insomnia, thus individuals with heightened somatic and cognitive arousal at bedtime were overrepresented in this sample. This sample selection might have contributed to an overrepresentation of this symptom profile.

Implications for clinical practice

With our analysis we supplement previous data-driven attempts to characterise the symptoms cluster profiles within insomnia disorder. Symptom cluster profiles add important clinical data that may be lost when individuals are grouped within one single diagnostic boundary. These symptom cluster profiles might also transcend diagnostic boundaries: in clinical practice, insomnia patients often share symptoms with other medical, psychiatric or sleep disorders, and so treatment decisions that are guided by symptom clusters, will not be biased by symptom overlap across comorbidities. We hope that these results, along with other attempts, will inform clinical practice by guiding patient-centered care. We can see the success of these approaches in other areas such as oncology, [75] asthma,[76] and various psychiatric disorders.[77] The heterogeneity within insomnia disorder, lends itself to such an approach.

We currently define insomnia disorder as a distinct entity, and our management of insomnia disorder is a one-size-fits-all approach, simply because we do not have sufficient evidence for a) valid and meaningful symptom cluster profiles, and b) whether treatments can be tailored to these symptom cluster profiles. The attempts to date, including ours and

future studies will help to move the needle towards a more patient-centred approach, which is gaining popularity in the US. With established and validated symptom clusters, we envision the practitioner can make assessment and treatment decisions based on the symptom cluster each individual patient reports. These findings are hopefully a catalyst for a dimensional profile of sleep health[19] which might be useful for reducing the gap between patient experiences, and clinical decision making based on categories. A symptom profile based approach represents the middle ground on the dimension from very individualised medicine on the one side, and a one-size-fits-all approach on the other side. This approach would be more effective than the one-size-fits-all approach, because symptoms specific to the individual's symptom profile are targeted, but more feasible in our current health system (particularly in the US) than an entirely individualised one, where time and cost limitations play a considerable role. We envision that established and validated symptom profiles will offer the practitioner with a model for patient-centered management of insomnia disorder.

Summary

Our results revealed three different symptom clusters in a group of individuals presenting with insomnia complaints, highlighting the symptom heterogeneity within insomnia disorder. Hopefully, these results provide an impetus for a symptom-based approach to the management of insomnia disorder. We intentionally selected self-reported variables for the profile analysis that have been recommended for the clinical evaluation of insomnia[86] so that these results can easily translate to clinical practice. The vision is that the patient's profile from these clinical measures could guide clinical decision-making when treating

insomnia. Undoubtedly though, before this approach can be translated into a model for interdisciplinary sleep clinics, further research is needed.

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Table 1. Descriptive characteristics of the study sample

	Total Sample (n=175)	Men (n=65)	Women (n=110)	*p*-value
	Mean (SD)/%	Mean (SD)/%	Mean (SD)/%	
Demographic				
Age, years	48.8 (13.5)	46.6 (12.9)	50.1 (13.8)	0.106
Race, Caucasian	53.5	56.3	51.9	0.147
Education, years	15.9 (3.2)	15.4 (3.4)	16.2 (3.0)	0.101
Biological				
Body Mass Index, kg/m^2	29.2 (8.8)	29.3 (8.3)	29.2 (9.1)	0.964
Apnoea Hypopnea Index,	15.2 (21.6)	21.0 (24.3)	11.8 (19.2)	**0.007***
Sleep Diary and PSG				
Sleep Onset Latency, minutes	43.3 (37.2)	40.6 (40.4)	44.9 (35.4)	0.461
Wake After Sleep Onset, minutes	58.9 (51.0)	50.8 (44.2)	64.1 (54.0)	0.077
Awakenings, number	2.3 (1.6)	2.4 (1.9)	2.3 (1.5)	0.958
Total Time in Bed, minutes	463.3 (99.4)	468.8 (71.6)	460.1 (112.4)	0.582

Total Sleep Time, minutes	343.4 (116.2)	355.5 (88.1)	336.5 (129.4)	0.302
Sleep Efficiency, %	74.4 (14.0)	75.7 (13.9)	73.7 (14.1)	0.377
PSG Total Sleep Time, minutes	379.2 (62.0)	381.4 (66.1)	378. (59.8)	0.727
Self-Report Instruments				
Insomnia Severity Scale	17.4 (4.8)	16.9 (4.8)	17.7 (4.8)	0.304
Glasgow Sleep Effort Scale	7.0 (3.4)	6.8 (3.4)	7.1 (3.3)	0.563
Fatigue Severity Scale	35.1 (12.8)	34.1(13.)	35.7 (12.7)	0.440
Beliefs and Attitudes about Sleep	123.5 (38.9)	120.8 (37.7)	125.2 (39.7)	0.491
Epworth Sleepiness Scale	9.4 (4.9)	9.5 (4.9)	9.4 (5.0)	0.919
Pre-Sleep Arousal Scale (PSAS)	33.5 (10.2)	31.6 (9.6)	34.7 (10.4)	0.061

*$p<0.05$; PSG= Polysomnography.

Table 2. Fit indexes for latent profile analysis

No. of clusters	No. of parameters	AIC	BIC	aBIC	LL	Entropy	ALRT (*p*)	BLRT (*p*)
1	20	14052.602	14115.897	14052.563	-7006.301	-	-	-
2	31	13893.546	13991.655	13893.487	-6915.773	0.891	**0.003***	**<0.001**
3	42	13765.682	13898.603	13765.602	-6840.841	0.838	**0.028***	**<0.001**
4	53	13660.647	13828.380	13660.546	-6777.323	0.945	0.161	**<0.001**
5	64	13599.327	13801.873	13599.205	-6735.662	0.878	0.251	**<0.001**
6	75	13557.234	13794.593	13557.091	-6703.617	0.889	0.550	**<0.001**

AIC=Akaike information criterion; BIC=Bayesian information criterion; aBIC=Adjusted BIC; LL=log-likeliho
likelihood ratio test; BLRT= Bootstrapped likelihood ratio test, *p<0.05.

Table 3. Indicators and unadjusted predictors means by symptom cluster profile

	High Subjective Wakefulness	**Mild Insomnia**	**Insomnia-related Distress**
	n=46 (26.3%)	n=79 (45.1%)	n=50 (28.6%)
Indicators			
Insomnia Severity Index	18.6 (4.8)	14.4 (6.8)	20.9 (6.1)
Glasgow Sleep Effort Scale	7.1 (3.5)	5.2 (5.5)	9.5 (3.8)
Fatigue Severity Scale	32.6 (13.2)	30.5 (17.4)	44.4 (14.3)
Beliefs and Attitudes about Sleep	113.9 (50.0)	106.4 (46.9)	156.9 (62.7)
Epworth Sleepiness Scale	10.2 (5.6)	8.5 (5.0)	10.0 (7.3)
Pre-sleep Arousal Scale	33.0 (10.5)	29.4 (10.4)	40.4 (19.4)
Sleep Onset Latency	63.0 (50.1)	26.0. (21.7)	51.8(60.5)
Wake After Sleep Onset	144.4 (56.3)	51.9 (32.4)	52.1 (40.5)
Sleep Efficiency	56.3 (12.3)	83.3 (9.2)	77.6 (16.4)
PSG Total Sleep Time	364.8 (73.9)	388.6 (54.9)	378.3 (74.9)
Predictors			
Age, years	53.9 (14.4)	47.8 (13.1)	45.7 (12.3)
Gender, %female	71.7	54.4	68.0
Race, %Caucasian	46.7	56.4	55.1
Education, years	16.1 (3.4)	15.8 (3.1)	16.0 (3.2)

Ethnicity, Hispanic	4.5	6.4	16.3
BMI Category, % Normal Weight	43.5	38.0	30.0
Overweight	23.9	26.6	36.0
Obese	32.6	35.4	34.0
OSA Severity, % No OSA	47.8	30.4	48.0
Mild	19.6	26.6	28.0
Moderate	19.6	25.3	14.0
Severe	13.0	17.7	10.0

PSG=Polysomnography; BMI=Body mass index; OSA=Obstructive sleep apnoea; AHI=Apnoea hypopnea in

Table 4. Unstandardized odds ratios for symptom cluster membership

	Mild Insomnia vs. High Subjective Wakefulness		**Mild Insomnia vs. Insomnia-related Distress**		**High Subjective Wakefulness vs. Insomnia-related Distress**	
	OR (95% CI)	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Covariates						
Age	**0.956 (0.926-0.986)**	**0.019***	1.005 (0.977-1.034)	0.763	**1.052 (1.013-1.092)**	**0.025***
Gender	0.665 (0.310-1.428)	0.38	0.698 (0.316-1.541)	0.455	1.049 (0.447-2.459)	0.927
Education	0.981 (0.875-1.101)	0.786	0.948 (0.845-1.064)	0.448	0.967 (0.851-1.097)	0.659
Race	0.968 (0.763-1.228)	0.82	1.072 (0.843-1.362)	0.636	1.108 (0.839-1.462)	0.545
Ethnicity	1.138 (0.225-5.749)	0.896	0.351 (0.102-1.206)	0.163	0.309 (0.065-1.471)	0.216
AHI Category	**1.639 (1.088-2.467)**	**0.047***	**1.869 (1.209-2.891)**	**0.018***	1.141 (0.704-1.848)	0.653
BMI Category	0.868 (0.586-1.285)	0.552	**0.554 (0.384-0.801)**	**0.008***	0.639 (0.421-0.971)	0.078

OR=Odds Ratio; CI= Confidence Intervals; AHI=Apnoea Hypopnea Index; BMI=Body Mass Index, *p<0.05.

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