Sleep Medicine 64 (2019) 71–76

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Identifying subtypes of Hypersomnolence Disorder: a clustering analysis

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ARTICLE INFO

Article history:
Received 18 February 2019
Received in revised form
18 June 2019
Accepted 19 June 2019
Available online 4 July 2019

Keywords:
Hypersomnolence
Hypersomnolence disorder
Depression
Clustering

ABSTRACT

Background: Patient heterogeneity is problematic for the accurate assessment and effective treatment of Hypersomnolence Disorder. Clustering analysis is a preferred approach for establishing homogenous subclassifications. Thus, this investigation aimed to identify more homogeneous subclassifications of Hypersomnolence Disorder through clustering analysis.
Methods: Patients undergoing polysomnography (PSG) and multiple sleep latency test (MSLT) assessment for hypersomnolence were recruited as part of a larger investigation. A sample of patients with Hypersomnolence Disorder was determined based on a post hoc chart review protocol. After removing persons with missing data, 62 participants were included in the analyses. Self-report total sleep time, Epworth Sleepiness Scale (ESS) score, and Sleep Inertia Questionnaire (SIQ) score were chosen as clustering variables to mirror Hypersomnolence Disorder diagnostic traits. A statistically-driven clustering process produced two clusters using Ward's D hierarchical approach. Clusters were compared across characteristics, self-report measures, PSG/MSLT results, and additional objective measures.
Results: The resulting clusters differed across a variety of hypersomnolence-related subjective metrics and objective measurements. A more severe hypersomnolence phenotype was identified in a cluster that also had elevated depressive symptoms. This cluster endorsed significantly greater daytime sleepiness, sleep inertia, and functional impairment, while displaying longer sleep duration and worse vigilance.
Conclusions: These results provide growing support for a nosological reformulation of hypersomnolence associated with psychiatric disorders. Future research is necessary to solidify the conceptualization and characterization of unexplained hypersomnolence presenting with-and-without psychiatric illness.

1. Background

Hypersomnolence is broadly characterized by excessive daytime sleepiness (EDS) that often presents with prolonged sleep duration [1]. It is a common sleep complaint among the general population, with an estimated prevalence as high as 30% [2–4]. In many cases, secondary causes such as medical conditions, sleep disorders, medications, substance use, or insufficient sleep duration will account for a patient's hypersomnolence [5–7]. However, in some instances, patients do experience hypersomnolence without a conditional explanation, which the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) broadly classifies as Hypersomnolence Disorder [8].

Hypersomnolence Disorder diagnostic criteria focus on self-report of EDS that is frequent, impairing, and not better accounted for by another sleep disorder or medication [8]. Additionally, nonrestorative sleep and sleep inertia (impairment of alertness associated with sleep-wake transition) are characteristics emphasized within diagnostic features of the disorder [8]. These symptoms can widely differ among patients, which has resulted in phenotypic heterogeneity within the condition.

Notably, the DSM-5 acknowledges patient variation in the description of the disorder. Specifically, the DSM-5 highlights increased nocturnal sleep duration, daytime napping, and excessive sleep inertia as characteristics that may vary among patients [8]. Currently, patient heterogeneity complicates the reliable

Nonstandard Abbreviations: PST, Pupillographic Sleepiness Test; PST PUI, Pupillograhic Sleepiness Test Pupillary Unrest Index; PVT nLapsesT, Psychomotor Vigilance Task – Number of Lapses (Tukey Transformed); SIQ, Sleep Inertia Questionnaire; HSI, Hypersomnia Severity Index.

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https://doi.org/10.1016/j.sleep.2019.06.015
1389-9457/

assessment and effective treatment of Hypersomnolence Disorder and has contributed to a poor understanding of the illness's etiology and pathophysiology [9–11]. Hence, addressing patient heterogeneity is critical for improving the assessment, treatment, and classification of persons experiencing unexplained hypersomnolence.

Phenotypic heterogeneity is a common problem for many scientific and medical domains. Data-driven, computational subtyping has been recognized as a means of resolution [12–15]. When considering the subdivision of clinical populations, the predominant approach has been to utilize statistical or machine learning strategies, with a clear preference for employment of unsupervised clustering among the existing scientific literature [12,16]. In principal, clustering has demonstrated an efficient ability to stratify clinical disorders, resulting in more homogenous subdivisions.

Thus, this investigation aimed to identify more homogeneous subclassifications of Hypersomnolence Disorder through unsupervised clustering analysis, in order to address the problematic patient heterogeneity occurring in the disorder.

2. Material and methods

2.1. Participants

The data utilized in this investigation were acquired from a larger study evaluating multidimensional assessments of hypersomnolence. As part of this larger investigation, patients referred for polysomnography (PSG) and a multiple sleep latency test (MSLT) to evaluate hypersomnolence at Wisconsin Sleep, the sleep lab and clinic of the University of Wisconsin–Madison, were recruited. From this patient pool, 75 individuals were selected for inclusion in these analyses based on a post hoc chart review protocol. Selection was dependent upon the presentation of hypersomnolence without a conditional explanatory diagnosis (eg, narcolepsy, sleep apnea, insufficient sleep syndrome, periodic limb movement disorder, or a circadian rhythm disorder), with these exclusionary diagnoses determined by the treating clinician.

Patients provided informed consent on the night of their evaluation and the parent study was approved by the Health Sciences Institutional Review Board of the University of Wisconsin–Madison.

2.2. Data collection

2.2.1. Demographics and self-report metrics

Patients completed a battery of questionnaires during their clinical assessment that included demographic information as well as the Epworth Sleepiness Scale (ESS) [17], Sleep Inertia Questionnaire (SIQ) [18], Functional Outcomes of Sleep Questionnaire – 10 item (FOSQ-10) [19], Pittsburgh Sleep Quality Index (PSQI) [20], Hypersomnia Severity Index (HSI) [21], and Inventory of Depressive Symptomatology – Self-Report (IDS-SR) [22].

2.2.2. Objective measures

PSG data were collected following American Academy of Sleep Medicine (AASM) parameters using a standard six-channel electroencephalographic montage paired with other recording sensors including electrooculogram, submental electromyogram, electrocardiogram, bilateral tibial electromyogram, respiratory inductance plethysmography, pulse oximetry, and a position sensor (Alice Sleepware; Phillips Respironics, Murrysville, Pennsylvania, United States) [23]. A registered sleep technologist staged all PSG recordings using 30-second epochs according to AASM criteria [23]. PSG was performed ad libitum, with participants remaining minimally disturbed throughout the night and not awakened at a prescribed time the following morning. A daytime MSLT was conducted upon completion of nocturnal PSG. Sleep macrostructure variables were compiled from the PSG evaluation and MSLT mean sleep onset latency was calculated from daytime nap opportunities.

Additional objective measures previously utilized for the assessment of hypersomnolence, the pupillographic sleepiness test (PST) [24,25] and psychomotor vigilance task (PVT) [26,27], were administered after MSLT naps one and three. Average PST pupillary unrest index (PUI), PVT mean reaction time, and PVT number of lapses (Tukey transformed) were tabulated for each participant.

2.3. Clustering variables

The DSM-5 emphasizes endorsements of “excessive quantity of sleep (eg, extended nocturnal sleep or involuntary daytime sleep), deteriorated quality of wakefulness (ie, sleep propensity during wakefulness as shown by difficulty awakening or inability to remain awake when required), and sleep inertia (ie, a period of impaired performance and reduced vigilance following awakening from the regular sleep episode or from a nap)” within the diagnostic criteria for Hypersomnolence Disorder [8]. The variables utilized for clustering were selected to mirror these diagnostic characteristics. Specifically, self-report total sleep time (acquired from the fourth item on the PSQI), ESS score, and SIQ score were selected for clustering.

2.4. Clustering process and comparisons

Initially, outlier analysis was conducted on the self-report total sleep times, ESS scores, and SIQ scores that were utilized for clustering. Then, these data were z-score transformed to account for unit differences across variables [28]. Finally, the clustering process was executed using open-source packages available in R Studio (The R Foundation; Boston, MA). This statistically-driven process determined the appropriate clustering technique as well as the optimal number of clusters [28,29]. Ultimately, Ward's D hierarchical technique was employed to fit two clusters from this dataset. Prior to clustering, cluster tendency was calculated (Hopkins Statistic = 0.46). However, because clustering variables were selected a priori based on DSM-5 Hypersomnolence Disorder criteria, pre-defined thresholds were not utilized that would terminate the planned cluster analysis.

After performing the clustering, the resulting two clusters were compared across demographics, self-report metrics, and objective measures using independent samples Student's *t*-test. All statistical comparisons were performed in JMP© Pro 14 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Full sample demographics, self-report metrics, and objective measures

The final sample included 62 individuals after 13 were excluded due to missing data. On average, the final sample was young-to-middle aged (mean = 31.2 ± 10.2 years), predominantly female (90.3%), and endorsed clinically significant excessive daytime sleepiness (Mean ESS = 14.4 ± 4.2), difficulty with sleep inertia (Mean SIQ = 66.4 ± 16.8), and moderately severe depressive symptomatology (Mean IDS-SR = 25.3 ± 13.3). Consistent with the clinical nature of the sample, nearly half (N = 29; 46.8%) of the sample were taking psychotropic medications at the time of assessment. Average self-reported sleep duration was 464 ± 96.5 min. A complete summary of the full sample's demographics and self-report metrics is presented in Table 1.

On objective measures, the sample demonstrated prolonged sleep duration (Mean PSG Total Sleep Time, TST = 543 ± 109 min) and normative sleep continuity (Mean PSG Sleep Efficiency = 87.4 ± 7.3%), along with no indication of sleep-disordered breathing (Mean PSG Apnea-Hypopnea Index = 0.8 ± 1.4) or periodic limb movement disorder (Mean PSG Periodic Limb Movement Arousal Index = 0.54 ± 0.9). Average daytime sleep propensity on the MSLT was 11.8 ± 4.7 min. Two sleep onset REM (SOREM) periods occurred across the entire sample. One participant had a nocturnal SOREM without MSLT SOREM; one participant had a single MSLT SOREM. Mean values from PST and PVT variables were consistent with those obtained from previous investigations on patients with disorders associated with hypersomnolence [24–27]. A complete summary of the full sample's results on the objective measures is presented in Table 2.

3.2. Cluster comparisons

The clustering process produced two clusters: Cluster A (N = 32) and Cluster B (N = 30). The following paragraphs present differences across demographics, self-report metrics, and objective measures (PSG, MSLT, PVT, and PST) for these two clusters. A complete summary of cluster comparisons across demographics and self-report metrics is presented in Table 3, whereas the cluster comparisons across objective measures are presented in Table 4.

The two clusters did not significantly differ in age, body mass index, or self-report total sleep time. However, significant differences were identified across all other self-report metrics. Specifically, Cluster A endorsed greater subjective daytime sleepiness (ESS mean difference = 3.36; $p = 0.001$), difficulty with sleep inertia (SIQ mean difference = 28.2; $p < 0.0001$), hypersomnia severity (HSI mean difference = 3.76; $p = 0.0004$), functional impairment related to sleep (FOSQ-10 mean difference = −2.68; $p = 0.0006$), and depressive symptomatology (IDS-SR mean difference = 14.6; $p < 0.0001$), as well as worse overall sleep quality (PSQI mean difference = 2.93; $p = 0.0002$). Additionally, psychotropic medication use at the time of assessment was more common among patients in Cluster A compared to Cluster B (X^2 (1, N = 62) = 4.27; $p = 0.04$).

Furthermore, in regards to the objective measures, the resulting clusters significantly differed in PSG time in bed (TIB), TST, sleep efficiency (SE), wake after sleep onset (WASO), duration of N2 sleep (N2), and duration of rapid eye movement sleep (REM). Specifically, Cluster A displayed longer TIB (mean difference = 73.0 min; $p = 0.006$), TST (mean difference = 98.8 min; $p = 0.0002$), N2 (mean difference = 44.9 min; $p = 0.007$), and REM (mean difference = 27.5 min; $p = 0.04$), with greater SE (mean difference = 5.47%; $p = 0.003$) and less WASO (mean difference = −25.4 min; $p = 0.01$). Notably, the two clusters demonstrated comparable MSLT mean sleep onset latency results.

Moreover, the clusters did not significantly differ in PVT mean reaction time or PST pupillary unrest index, but Cluster A did display significantly more impaired vigilance on the PVT based on Tukey transformed number of lapses (PVT nLapsesT mean difference = 1.11; $p = 0.03$).

Table 1
Full sample: Demographics and self-report metrics.

Full Sample: Demographics	
Sample Size (N)	62
Female (%)	90.3
Psychotropic Medication Use (%)	46.8
Age (years)	31.2 ± 10.2
Body Mass Index (kg/m^2)	26.9 ± 5.39
Full Sample: Self-Report Metrics	
Epworth Sleepiness Scale	14.4 ± 4.20
Self-Report Total Sleep Time (minutes)	464 ± 96.5
Sleep Inertia Questionnaire	66.4 ± 16.8
Inventory of Depressive Symptomatology – Self-Report	25.3 ± 13.3
Functional Outcomes of Sleep Questionnaire – 10 item	12.5 ± 3.17
Pittsburgh Sleep Quality Index	7.53 ± 3.19
Hypersomnia Severity Index	23.4 ± 5.77

Results across demographics and self-report metrics are provided for the full sample. Values are presented as means ± standard deviations where appropriate.

Table 2
Full sample: Objective measures.

PSG	
Time in Bed (min)	620 ± 108
Total Sleep Time (min)	543 ± 109
Sleep Efficiency (%)	87.4 ± 7.34
Sleep Onset Latency (min)	17.3 ± 19.2
Wake After Sleep Onset (min)	60.0 ± 39.0
Awakenings (N)	25.1 ± 10.4
Arousal Index (N/hr)	11.1 ± 5.49
Apnea-Hypopnea Index (N/hr)	0.8 ± 1.41
Periodic Limb Movements Arousal Index (N/hr)	0.54 ± 0.86
N1 (min)	25.6 ± 25.2
N1 (%)	4.91 ± 4.94
N2 (min)	308 ± 66.9
N2 (%)	57.2 ± 9.24
N3 (min)	81.5 ± 52.6
N3 (%)	14.7 ± 7.87
REM (min)	129 ± 53.9
REM (%)	23.2 ± 7.06
REML (min)	134 ± 88.6
MSLT	
Mean Sleep Onset Latency (min)	11.8 ± 4.72
PVT	
Mean Reaction Time (ms)	256 ± 88.9
Number of Lapses – Tukey Transformed (N)	3.02 ± 2.03
PST	
Pupillary Unrest Index	7.78 ± 4.86

Objective measurement results from polysomnography (PSG), multiple sleep latency test (MSLT), psychomotor vigilance task (PVT), and pupillographic sleepiness test (PST) are provided for the full sample. Values are presented as mean ± standard deviation.

4. Discussion

Patient heterogeneity complicates the assessment and treatment of persons who endorse hypersomnolence without a conditional explanation. This investigation was designed to address this problem by using clustering analysis on data acquired from a clinical sample of persons with Hypersomnolence Disorder.

The primary results of this investigation identified two distinct clusters that differed across a variety of hypersomnolence-related self-report metrics and objective measurements. Specifically, Cluster A endorsed more problematic daytime sleepiness, sleep inertia, and functional impairment, while displaying longer sleep duration and worse vigilance. Notably, this more severe hypersomnolence phenotype associated with significantly greater depression severity, which indicates a positive relationship between hypersomnolence and depression symptomatology. These results reflect the intimate relationship shared between hypersomnolence and psychiatric illness, as well as highlight the deleterious impact of comorbidity on patient well-being [1,30–32].

Additionally, these results have importance when considering the nosological conceptualization of unexplained hypersomnolence and its association with psychiatric disorders Currently, a disconnect exists between the DSM-5 and the International Classification of Sleep Disorders – Third Edition (ICSD-3) in the classification and characterization of unexplained hypersomnolence presenting with-and-without psychiatric illness. The DSM-5 uses a

Table 3
Cluster comparisons: Demographics and self-report metrics.

Demographics	Cluster A	Cluster B	Mean Difference	*P* Value
Cluster Comparisons: Demographics				
Sample Size (N)	32	30		
Female (%)	93.8	86.7		
Psychotropic Medication Use (%)	59.4	33.3		0.04
Age (years)	29.8 ± 6.5	32.6 ± 13.0	−2.75	–
Body Mass Index (kg/m^2)	27.6 ± 5.8	26.0 ± 4.9	1.58	–
Cluster Comparisons: Self-Report Metrics				
Epworth Sleepiness Scale	16.1 ± 3.7	12.7 ± 4.0	3.36	0.001
Self-Report Total Sleep Time	451 ± 99.2	479 ± 93.0	−28.5	–
Sleep Inertia Questionnaire	80.1 ± 9.7	51.8 ± 8.4	28.2	<0.0001
Inventory of Depressive Symptomatology – Self-Report	32.2 ± 13.3	17.8 ± 8.4	14.6	<0.0001
Functional Outcomes of Sleep Questionnaire – 10 item	11.2 ± 2.7	13.9 ± 3.1	−2.68	0.0006
Pittsburgh Sleep Quality Index	8.97 ± 3.3	6.03 ± 2.3	2.93	0.0002
Hypersomnia Severity Index	25.8 ± 5.0	20.8 ± 5.4	3.76	0.0004

Cluster means ± standard deviations are provided for demographics and self-report metrics, where appropriate. Mean differences (Cluster A – Cluster B) between clusters are also presented. *P* values for significant comparisons have been included, with a hyphen (–) indicating a nonsignificant comparison.

single classifier (Hypersomnolence Disorder) for unexplained hypersomnolence presenting with-and-without psychiatric illness [8]. Furthermore, the DSM-5 recognizes that persons with Hypersomnolence Disorder "have a good sleep efficiency (>90%)," and this characterization is maintained when the condition presents along with psychiatric illness [8]. Contrastingly, the ICSD-3 taxonomically segregates unexplained hypersomnolence (Idiopathic Hypersomnia) from unexplained hypersomnolence cooccurring with psychiatric illness (Hypersomnia Associated with a Psychiatric Disorder) [32]. The ICSD-3 describes sleep efficiency as a distinguishing characteristic between the two conditions, whereby Hypersomnia Associated with a Psychiatric Disorder is characterized by low sleep efficiency, with such patients spending too much time in bed (ie, clinophilia) [32]. However, results from a recently conducted prospective investigation with concurrent meta-analysis suggest that this distinction may not be accurate. In this study, persons with comorbid hypersomnolence and depression objectively demonstrated increased sleep duration and similar sleep efficiency relative to healthy comparison participants [33]. The results from our current investigation corroborate these findings, as Cluster A demonstrated notably high sleep efficiency on PSG, as well as increased depressive symptoms. Given these findings, as well as the taxonomic inconsistencies across sleep and psychiatric nosologies, future work aimed at solidifying the conceptualization and characterization of unexplained hypersomnolence presenting with-and-without psychiatric illness is warranted.

The limitations of the MSLT as the gold standard measurement for EDS is also another major complication for the assessment of hypersomnolence. Both the DSM-5 and ICSD-3 consider a MSLT

Table 4
Cluster comparisons: Objective measures.

Cluster Comparisons: Objective Measures				
Variable	Cluster A	Cluster B	Mean Difference	*P* Value
PSG				
Time in Bed (min)	655 ± 113	582 ± 88.9	73.0	0.006
Total Sleep Time (min)	591 ± 109	492 ± 85.0	98.8	0.0002
Sleep Efficiency (%)	90.0 ± 5.24	84.6 ± 8.24	5.47	0.003
Sleep Onset Latency (min)	17.1 ± 22.7	17.4 ± 15.0	−0.26	–
Wake After Sleep Onset (min)	47.7 ± 29.7	73.1 ± 43.7	−25.4	0.01
Awakenings (N)	25.5 ± 9.3	24.7 ± 11.7	0.87	–
Arousal Index (N/hr)	10.6 ± 5.2	11.8 ± 5.8	−1.21	–
Apnea-Hypopnea Index (N/hr)	0.77 ± 1.4	0.83 ± 1.4	−0.06	–
Periodic Limb Movements Arousal Index (N/hr)	0.58 ± 1.0	0.50 ± 0.8	0.08	–
N1 (min)	27.5 ± 30.5	23.5 ± 18.1	4.00	–
N1 (%)	5.00 ± 5.8	4.81 ± 3.9	0.19	–
N2 (min)	330 ± 68.8	285 ± 57.3	44.9	0.007
N2 (%)	56.1 ± 8.6	58.3 ± 9.9	−2.22	–
N3 (min)	92.3 ± 60.5	70.1 ± 40.6	22.2	–
N3 (%)	15.3 ± 8.6	14.0 ± 7.1	1.35	–
REM (min)	142 ± 61.6	114 ± 40.6	27.5	0.04
REM (%)	23.6 ± 8.2	22.9 ± 5.7	0.67	–
REML (min)	123 ± 84.5	146 ± 92.7	−22.6	–
MSLT				
Mean Sleep Onset Latency (min)	11.2 ± 5.2	12.6 ± 4.0	−1.42	–
PVT				
Mean Reaction Time (ms)	263 ± 64.9	248 ± 110	14.7	–
Number of Lapses – Tukey Transformed (N)	3.56 ± 2.4	2.45 ± 1.4	1.11	0.03
PST				
Pupillary Unrest Index	7.93 ± 4.0	7.61 ± 5.7	0.33	–

Cluster means ± standard deviations are provided for objective results derived from polysomnography (PSG), multiple sleep latency test (MSLT), psychomotor vigilance task (PVT), and pupillographic sleepiness test (PST). Mean differences between clusters (Cluster A – Cluster B) are also presented. *P* values for significant comparisons have been included, with a hyphen (–) indicating a nonsignificant comparison.

mean sleep onset latency of <8 min as an objective indication of EDS [8,32]. However, there are major concerns surrounding the MSLT's ability to reliably capture subjective EDS as well as differentiate between disordered and healthy populations [1,11]. Furthermore, its capability to reliably segregate disorders of hypersomnolence, outside of type 1 narcolepsy, has also been questioned [34,35]. The results from this investigation further illustrate the insufficiency of the MSLT to reliably capture EDS as well as differentiate between severity of hypersomnolence. Neither of the resulting clusters displayed a MSLT mean sleep onset latency of pathological duration. Furthermore, Cluster A's more severe hypersomnolence, including a significantly greater endorsement of subjective EDS, was indistinguishable from Cluster B on this objective measure. As such, this investigation provides further support for consideration of expanding the objective measurement of EDS beyond the MSLT to improve the reliability and accuracy of hypersomnolence assessment.

A noteworthy finding in this investigation is that while there was an observed difference between the two identified clusters in total sleep time measured using ad libitum PSG, the two clusters did not differ on habitual self-reported sleep duration on the PSQI. While speculative, this suggests the possibility that patients in Cluster A may have been habitually sleeping less than their individual physiological sleep need, which could theoretically contribute to their overall more severe phenotype (eg, worse subjective sleepiness, sleep inertia, depression, etc.) relative to Cluster B. However, in the absence of longitudinal objective measures of sleep duration prior to testing across all participants, it is also possible that there were systematic differences between perceived and actual sleep times between Cluster A and Cluster B in the field prior to sleep testing in the laboratory. Regardless, these findings highlight the absence of an available, standardized method to measure individual sleep need. Additionally, it is critical for the field to more carefully consider interindividual differences in sleep requirement when assessing hypersomnolence.

There are limitations of this investigation that must be acknowledged. The relatively small sample size may have limited the utility of cluster analysis, as this methodology is most practical for larger datasets. This is likely reflected by the marginal Hopkins statistic for these data. As such, future research is warranted to perform clustering analysis on a larger sample of persons with Hypersomnolence Disorder. Moreover, the convenience sample resulted in a sex distribution that may not fully represent the Hypersomnolence Disorder population. Although female predominance is recognized as a characteristic of Hypersomnolence Disorder [36], it is likely that the sex distribution of this sample is disproportionately skewed towards females. Given this, future attempts at establishing subclassifications of Hypersomnolence Disorder should strive for a more equal sex distribution within their investigation sample. Patients within the convenience sample also varied in terms of psychotropic medication use at time of assessment, which potentially could have influenced the objectively captured outcomes. Further, there is the possibility that collection of multiple hypersomnolence measures within a singular testing session, that included ad libitum overnight sleep recording, may have affected results and contributed to the absence of observed differences between clusters on objective tests of daytime sleep propensity and drowsiness (ie, MSLT and PST). Additionally, although not necessarily a limitation, this investigation utilized self-report metrics mirroring DSM-5 Hypersomnolence Disorder diagnostic criteria which were selected a priori. Future subclassification efforts could consider additional hypersomnolence-related subjective and objective components, as well as measures not captured by this investigation such as EDS course/chronicity and night-to-night variability of sleep-wake patterns. Given the results of this investigation, future investigations that focus on objective measures currently described by the ICSD as distinguishing idiopathic hypersomnia from hypersomnolence related to psychiatric illness (eg, sleep efficiency) may prove beneficial for clarifying and refining the existing nosological inconsistencies. Finally, depressive symptomatology was determined using self-report measures rather than gold-standard diagnostic interviews. Thus, the relationships between specific psychiatric diagnoses (eg, major depressive disorder, dysthymia, etc.) and hypersomnolence variables could not be distinguished by this investigation.

In summary, this investigation identified two distinct subclassifications of clinical patients with Hypersomnolence Disorder that were distinguishable by the absence or presence of more significant depressive symptoms. Additionally, these results highlighted an important relationship between hypersomnolence symptoms and depression severity, whereby increased depression endorsement was associated with greater subjective and objective hypersomnolence symptomatology. Overall, these results reflect the complex relationship between unexplained hypersomnolence and psychiatric symptoms, provide evidence that sleep continuity is increased, rather than decreased, in unexplained hypersomnolence cooccurring with psychiatric illness, and indicate a need for future work aimed at solidifying the conceptualization and characterization of unexplained hypersomnolence presenting with-and-without psychiatric illness.

Funding

This research was support by a grant from the American Sleep Medicine Foundation Strategic Research Award (138-SR-16) to Dr. Plante.

Acknowledgements

We thank the American Sleep Medicine Foundation for funding the collection of these data through a Strategic Research Award (138-SR-16) to Dr. Plante. Furthermore, we greatly appreciate the staff and patients of Wisconsin Sleep for their involvement. Additionally, we would like to acknowledge Erika Dallmann, Megan Sippy, Lydia Leavitt, Mike Prairie, Sahand Eftekari, and Sara Khan for their assistance in collecting and organizing the data utilized in this investigation.

Conflict of interest

Dr. Rumble currently receives grant support from Merck and has previously received grant support from NIH, both of which are unrelated to the current study. Dr. Plante has received grant support from the National Institute of Mental Health, the National Institute on Aging, Brain and Behavior Research Foundation, University of Illinois at Chicago Occupational and Environmental Health and Safety Education and Research Center/National Institute for Occupational Safety and Health, and the Madison Education Partnership; and has served as a consultant to Teva Australia and Jazz Pharmaceuticals, unrelated to the current study.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.05.019.

References

[1] Plante DT. Hypersomnia in Mood Disorders: a rapidly changing landscape. Curr Sleep Med Rep 2015;1(2):122–30. https://doi.org/10.1007/s40675-015-0017-9.

[2] Dauvilliers Y, Lopez R, Ohayon M, et al. Hypersomnia and depressive symptoms: methodological and clinical aspects. BMC Med 2013;11:78. https://doi.org/10.1186/1741-7015-11-78.
[3] Fernandez-Mendoza J, Vgontzas AN, Kritikou I, et al. Natural history of excessive daytime sleepiness: role of obesity, weight loss, depression, and sleep propensity. Sleep 2015;38(3):351–60. https://doi.org/10.5665/sleep.4488.
[4] Ohayon MM. From wakefulness to excessive sleepiness: what we know and still need to know. Sleep Med Rev 2008;12(2):129–41. https://doi.org/10.1016/j.smrv.2008.01.001.
[5] Barateau L, Lopez R, Franchi JA, et al. Hypersomnolence, hypersomnia, and mood disorders. Curr Psychiatr Rep 2017;19(2):13. https://doi.org/10.1007/s11920-017-0763-0.
[6] Berkowski JA, Shelgikar AV. Disorders of excessive daytime sleepiness including narcolepsy and idiopathic hypersomnia. Sleep Med Clin 2016;11(3):365–78. https://doi.org/10.1016/j.jsmc.2016.04.005.
[7] Khan Z, Trotti LM. Central disorders of hypersomnolence: focus on the narcolepsies and idiopathic hypersomnia. Chest 2015;148(1):262–73. https://doi.org/10.1378/chest.14-1304.
[8] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington, VA: American Psychiatric Association; 2013.
[9] Evangelista E, Lopez R, Dauvilliers Y. Update on treatment for idiopathic hypersomnia. Expert Opin Investig Drugs 2018;27(2):187–92. https://doi.org/10.1080/13543784.2018.1417385.
[10] Mignot EJ. A practical guide to the therapy of narcolepsy and hypersomnia syndromes. Neurotherapeutics 2012;9(4):739–52. https://doi.org/10.1007/s13311-012-0150-9.
[11] Plante DT. Sleep propensity in psychiatric hypersomnolence: a systematic review and meta-analysis of multiple sleep latency test findings. Sleep Med Rev 2017;31:48–57. https://doi.org/10.1016/j.smrv.2016.01.004.
[12] Marquand AF, Wolfers T, Mennes M, et al. Beyond lumping and splitting: a review of computational approaches for stratifying psychiatric disorders. Biol Psychiatry Cogn Neurosci Neuroimaging 2016;1(5):433–47. https://doi.org/10.1016/j.bpsc.2016.04.002.
[13] Paulus MP, Huys QJ, Maia TV. A roadmap for the development of applied computational psychiatry. Biol Psychiatry Cogn Neurosci Neuroimaging 2016;1(5):386–92. https://doi.org/10.1016/j.bpsc.2016.05.001.
[14] Šonka K, Šusta M, Billiard M. Narcolepsy with and without cataplexy, idiopathic hypersomnia with and without long sleep time: a cluster analysis. Sleep Med 2015;16(2):225–31. https://doi.org/10.1016/j.sleep.2014.09.016.
[15] van Rooden SM, Colas F, Martínez-Martín P, et al. Clinical subtypes of Parkinson's disease. Mov Disord 2011;26(1):51–8.
[16] Mun EY, von Eye A, Bates ME, et al. Finding groups using model-based cluster analysis: heterogeneous emotional self-regulatory processes and heavy alcohol use risk. Dev Psychol 2008;44(2):481–95. https://doi.org/10.1037/0012-1649.44.2.481.
[17] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14(6):540–5.
[18] Kanady JC, Harvey AG. Development and validation of the sleep inertia questionnaire (SIQ) and assessment of sleep inertia in analogue and clinical depression. Cogn Ther Res 2015;39(5):601–12. https://doi.org/10.1007/s10608-015-9686-4.
[19] Chasens ER, Ratcliffe SJ, Weaver TE. Development of the FOSQ-10: a short version of the functional outcomes of sleep questionnaire. Sleep 2009;32(7):915–9.
[20] Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatr Res 1989;28(2):193–213.
[21] Kaplan KA, Plante DT, Cook JD, et al. Validation of the hypersomnia severity index (HSI). Sleep 2015;38(Abstract Suppl):A432.
[22] Trivedi MH, Rush AJ, Ibrahim HM, et al. The inventory of depressive symptomatology, clinician rating (IDS-C) and self-report (IDS-SR), and the quick inventory of depressive symptomatology, clinician rating (QIDS-C) and self-report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. Psychol Med 2004;34(1):73–82.
[23] Berry RB, Brooks R, Gamaldo CE, et al. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications, version 2.1. Illinois: Darien; 2014.
[24] McLaren JW, Hauri PJ, Lin SC, et al. Pupillometry in clinically sleepy patients. Sleep Med 2002;3(4):347–52. https://doi.org/10.1016/S1389-9457(02)00017-5.
[25] Prasad B, Choi YK, Weaver TE, et al. Pupillometric assessment of sleepiness in narcolepsy. Front Psychiatry 2011;2:35. https://doi.org/10.3389/fpsyt.2011.00035.
[26] Kim H, Dinges DF, Young T. Sleep-disordered breathing and psychomotor vigilance in a community-based sample. Sleep 2007;30(10):1309–16.
[27] Thomann J, Baumann CR, Landolt HP, et al. Psychomotor vigilance task demonstrates impaired vigilance in disorders with excessive daytime sleepiness. J Clin Sleep Med 2014;10(9):1019–24. https://doi.org/10.5664/jcsm.4042.
[28] Kassambara A. Practical guide to cluster Analysis in R: unsupervised machine learning. 1st ed. Create Space Independent Publishing Platform; 2017.
[29] Charrad M, Ghazzali N, Boiteau V, et al. NbClust: an R package for determining the relevant number of clusters in a data set. J Stat Softw 2014;61(6).
[30] Kaplan KA, McGlinchey EL, Soehner A, et al. Hypersomnia subtypes, sleep and relapse in bipolar disorder. Psychol Med 2015;45(8):1751–63.
[31] Soehner AM, Kaplan KA, Harvey AG. Prevalence and clinical correlates of co-occurring insomnia and hypersomnia symptoms in depression. J Affect Disord 2014;167:93–7. https://doi.org/10.1016/j.jad.2014.05.060.
[32] American Academy of Sleep Medicine. International classification of sleep disorders. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
[33] Plante DT, Cook JD, Goldstein MR. Objective measures of sleep duration and continuity in major depressive disorder with comorbid hypersomnolence: a primary investigation with contiguous systematic review and meta-analysis. J Sleep Res 2017;26(3):255–65.
[34] Johns MW. Sensitivity and specificity of the multiple sleep latency test (MSLT), the maintenance of wakefulness test and the epworth sleepiness scale: failure of the MSLT as a gold standard. J Sleep Res 2000;9(1):5–11.
[35] Lopez R, Doukkali A, Barateau L, et al. Test-retest reliability of the multiple sleep latency test in central disorders of hypersomnolence. Sleep 2017;40(12).zsx164.
[36] Leu-Semenescu S, Louis P, Arnulf I. Benefits and risk of sodium oxybate in idiopathic hypersomnia versus narcolepsy type 1: a chart review. Sleep Med 2016;17:38–44. https://doi.org/10.1016/j.sleep.2015.10.005.