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Fatigued but not sleepy? An empirical investigation of the differentiation between fatigue and sleepiness in sleep disorder patients in a cross-sectional study

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ABSTRACT

Objective: Sleepiness and fatigue are common complaints among individuals with sleep disorders. The two concepts are often used interchangeably, causing difficulty with differential diagnosis and treatment decisions. The current study investigated sleep disorder patients to determine which factors best differentiated sleepiness from fatigue.

Methods: The study used a subset of participants from a multi-site study ($n = 606$), using a cross-sectional study design. We selected 60 variables associated with either sleepiness or fatigue, including demographic, mental health, and lifestyle factors, medical history, sleep questionnaires, rest-activity rhythms (actigraphy), polysomnographic (PSG) variables, and sleep diaries. Fatigue was measured with the Fatigue Severity Scale and sleepiness was measured with the Epworth Sleepiness Scale. A Random Forest machine learning approach was utilized for analysis.

Results: Participants' average age was 47.5 years (SD 14.0), 54.6% female, and the most common sleep disorder diagnosis was obstructive sleep apnea (67.4%). Sleepiness and fatigue were moderately correlated ($r = 0.334$). The model for fatigue (explained variance 49.5%) indicated depression was the strongest predictor (relative explained variance 42.7%), followed by insomnia severity (12.3%). The model for sleepiness (explained variance 17.9%), indicated insomnia symptoms was the strongest predictor (relative explained variance 17.6%). A *post hoc* receiver operating characteristic analysis indicated depression could be used to discriminate fatigue (AUC = 0.856) but not sleepiness (AUC = 0.643).

Conclusions: The moderate correlation between fatigue and sleepiness supports previous literature that the two concepts are overlapping yet distinct. Importantly, depression played a more prominent role in characterizing fatigue than sleepiness, suggesting depression could be used to differentiate the two concepts.

1. Introduction

Sleepiness and fatigue are common complaints among sleep disorder patients in clinical settings. The two concepts are often used interchangeably, which can cause difficulty and confusion in making a differential diagnosis and patient care. Sleepiness is usually defined as an "increased propensity of falling asleep" [1] or feeling drowsy accompanied by decreased alertness. In contrast, fatigue is generally defined as having low energy, feeling exhausted and lethargic, weary and weak, with impaired physical or cognitive function [1,2]. Sleepiness has been studied more extensively in the context of sleep, and associated with increased homeostatic sleep drive prior to the onset of sleep. In contrast, fatigue is more general and exhibits non-specific presentation and symptomatology, stemming from diverse factors such as physical, physiological, and psychological causes that have not been studied in-depth. Typically, fatigue manifests as a pervasive sense of tiredness and exhaustion.

In addition, sleep disorders may lead to independent consequences of

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both sleepiness and fatigue, and may differ across various sleep disorders [3,4]. For example, insomnia patients may experience sleep disturbance, but report mainly fatigue symptoms and not necessarily sleepiness, which yields different clinical presentations compared to other sleep disorders such as hypersomnia and obstructive sleep apnea (OSA). Thus, accurate differentiation between sleepiness and fatigue is crucial for developing effective intervention strategies in sleep disorders characterized by fatigue and/or sleepiness [5].

Although there have been previous attempts to theoretically differentiate the two concepts [1,2,6] by focusing on different assessment tools and biological systems, there has been no clear consensus as to what constitutes the experience of sleepiness or fatigue. This poses an important challenge, especially for sleep disorder patients whose diagnosis and treatment often hinge upon the differentiation of the two concepts. For example, an emphasis on fatigue instead of sleepiness in general medical clinics may lead to a lower likelihood of referrals to a sleep clinic, leading to underdiagnosis of disorders such as obstructive sleep apnea (OSA). In fact, several studies have noted a high prevalence of undiagnosed OSA, with up to approximately 90% of individuals with OSA not being diagnosed [7–9]. Furthermore, implementing stimulus control therapy as a part of cognitive-behavioral therapy for insomnia recommends that one should go to bed only when they feel sleepy but not fatigued, which is often a vague distinction for clinicians and their patients.

One main reason for the lack of differentiation is that very few empirical studies have compared sleepiness and fatigue in tandem. One study investigating both sleepiness and fatigue in sleep disorder patients noted only a weak correlation ($r = 0.180$) between fatigue and sleepiness [3]. In that study, an overwhelming majority of participants reported having clinical fatigue without excessive daytime sleepiness, while very few reported having excessive daytime sleepiness without overlapping clinical fatigue. This suggests that sleepiness and fatigue may be independent consequences of sleep disorders. Nevertheless, a closer investigation of both sleepiness and fatigue using empirical data to differentiate the two concepts is warranted.

One of the problems in separating the conceptual basis of 'sleepiness' and 'fatigue' is that many factors may contribute to the individual experience of both sleepiness and fatigue. Standard regression analysis may be insufficient in separating these two similar concepts as this statistical method is prone to overfitting when many variables are entered. Machine learning algorithms, including Random Forest, may offer a solution as these algorithms are robust to overfitting and can handle a variety of both parametric and non-parametric variables [10].

The current study was an exploratory study aimed to empirically investigate the differentiation between sleepiness and fatigue in a sample of sleep disorder patients. We did not establish pre-determined hypotheses due to limited empirical studies on the topic in this sample, making it challenging to derive robust hypotheses. We used Random Forest regression analyses to examine a large number of subjective and objective variables that have been shown to be associated with either sleepiness or fatigue, including demographic factors, mental health, lifestyle and behavioral factors, medical history, sleep questionnaires, multiday rest-activity rhythms using actigraphy, polysomnography (PSG), and sleep diaries.

2. Methods

The Stanford Technology Analytics and Genomics in Sleep (STAGES) study was used for this study (data available at www.sleepdata.org [11]). The STAGES study was a cross-sectional, multi-site study involving 11 data collection sites from six sleep centers across the USA and Canada, including Stanford University, Bogan Sleep Consulting, Geisinger Health, Mayo Clinic, MedSleep, and St. Luke's Hospital, and was conducted between 2018 and 2020. Data collection included online sleep/medical history (459 variables derived using the Alliance Sleep Questionnaire [12]), one night in-lab nocturnal PSG data, actigraphy over two weeks, sleep diaries, and data from electronic medical records. A subset of variables relevant to fatigue and sleepiness were selected for this study (Table 1).

Inclusion criteria for the STAGES study were: (1) individuals age 19 and over; and (2) received an in-lab PSG study to diagnose a sleep disorder such as OSA, restless legs syndrome (RLS), insomnia, or other less common sleep disorders or receiving follow-up care that required a PSG to be collected meeting the following criteria: (a) full diagnostic PSG with a minimum of two hours of total sleep time, or (b) a split night study with a minimum of two hours total sleep time. Exclusion criteria included: (1) being unable to read and/or understand English; (2) unable or unwilling to complete all study requirements; (3) undergoing a PSG conducted exclusively for treatment purposes (*e.g.*, full-night PAP titration, oral appliance evaluation); (4) not having a smartphone to pair with actigraphy; (5) presence of an acute unstable medical condition; (6) presence of an acute behavioral or psychiatric disorder, including active suicidal ideation; and (7) any medical condition or surgical history that could affect the safety of the participant or might interfere with the study. The exclusion criteria was primarily based on electronic medical records to evaluate conditions that met critiera, or was under the investigator discretion.

2.1. Procedures (temporal overview)

Participants learned about the study from personnel (staff members at the sleep clinic, fellows, or other clinical staff) at each individual sleep clinic or through materials such as new patient packet, study brochures, or video advertisements in the clinic waiting room, or an automatic appointment reminder system. The study was approved by each institution's IRB ethics committee (Stanford 39550, Bogan 1245030, Geisinger 2018–0191, Mayo 17–007077, MedSleep Pro00023705, and St. Luke's 2018.001). All participants consented to participating in the study. Screening and enrollment were conducted by assessing eligibility based on chart review and/or contacting potential subjects *via* email or phone prior to the sleep study or in person during a scheduled PSG.

Each participant spent approximately 1–2.5 h completing questionnaires and associated baseline measurements. In addition, participants were asked to wear an actigraph for two weeks at home following the visit. Actigraphy was started prior to the beginning of the PSG for all participants. PSG was conducted as a standard care procedure for all participants visiting the sleep clinic. All participants provided informed consent. IRB approval was obtained from each institution where data were collected.

2.2. Measures

2.2.1. Alliance sleep questionnaire (ASQ)

The ASQ is a comprehensive online questionnaire comprised of validated measures and questions developed for the instrument to collect subjective data related to the participant's sleep and medical history and current symptoms [13]. Topics in the ASQ included current sleep symptoms, medical history, medications, previous treatments for sleep disorders, sleep habits/schedule, and symptoms of sleep disorders, anxiety and depression. Standardized questionnaires included in the ASQ and used for this study were Insomnia Severity Index (ISI) [14], revised Morningness-Eveningness Questionnaire (rMEQ) [15], Patient Health Questionnaire (PHQ-9) [16], and Generalized Anxiety Disorder-7 (GAD-7) Questionnaire [17]. The ISI is a self-report questionnaire that assesses the severity of insomnia symptoms experienced over the past month, and was used to measure insomnia symptoms in this study. It consists of seven items, each rated on a 5-point Likert scale (0–4), resulting in a total score ranging from 0 to 28. Internal consistency (Cronbach's alpha) was 0.85 in this sample.The rMEQ is a reduced scale of Morningness-Eveningness Questionnaire (MEQ) that consists of five items. It has total scores ranging from 4 to 26, with higher scores indicating morning chronotype. Internal consistency (Cronbach's alpha)

Table 1
Variables selected as predictors for sleepiness or fatigue.

Category	Variable	Description
Demographics	nsrr_sex	Participant sex
	nsrr_race	Participant race
	nsrr_ethnicity	Participant ethnicity
	modified_dem_0110	Participant age
	nsrr_bmi	Body mass index (BMI)
	bthbts_0100	Bed partner or roommate
Mental Health	gad_0800	Generalized Anxiety Disorder-7 questionnaire
	phq_1000	Patient Health Questionnaire (PHQ-9)
Lifestyle and Behavioral health	cir_0100	Routinely travel to other time zones
	sedentary	Sedentary lifestyle (exercise rarely or never)
	alcohol1	Alcohol consumption (never or rarely, monthly, weekly)
	alcohol2	Alcohol consumption (number of servings per day)
	bthbts_0500	Number of people living in your household
	smokingstatus	Never smoker, former smoker, current smoker
	packyears	Packs per day * years smoked
	caffeine1	Caffeine consumption (rarely or never)
Medical History (self-report)	mdhx_5700	Hypertension
	mdhx_5710	Congestive heart failure
	mdhx_5720	Cardiovascular problem, other
	mdhx_5800	Asthma
	mdhx_5810	Chronic obstructive pulmonary disease
	mdhx_5820	Pulmonary problem, other
	mdhx_5900	Allergies or sinus problems
	mdhx_5910	Tonsillectomy or adenoidectomy
	mdhx_5920	Nasal, jaw, or apnea surgery
	mdhx_5950	Ear, nose, and throat problem or surgery, other
	mdhx_6000	Dental problems
	mdhx_6100	Gastrointestinal problem or surgery
	mdhx_6200	Neurologic problem
	mdhx_6300	Hypercholesterolemia
	mdhx_6310	Type 2 diabetes
	mdhx_6320	Endocrine or metabolic problem
	mdhx_6400	Urologic or kidney problem
	mdhx_6500	Pain or fatigue
	mdhx_6600	Psychiatric or mental health problem
	mdhx_6700	Medical problem or surgery, other
Sleep Questionnaire	cir_0700	Revised Morningness-Eveningness Questionnaire total score
	ess_0900	Epworth Sleepiness Scale total score
	index_4	Multivariate Apnea Prediction Index 4: narcolepsy-like symptoms score
	index_1	Multivariate Apnea Prediction Index 1: apnea score
	isi_score	Insomnia Severity Index total score
	map_0200	Frequent awakenings
	map_0500	Frequent tossing, turning, thrashing
	map_0800	Morning Headache
	sched_2600	Self-reported sleep quality for irregular work, current shift
	sched_4100	Self-reported sleep quality for weekend nights, non-school nights, non-work nights or days
Actigraphy	IS	Intradaily Stability
	IV	Interdaily Variability
	RA	Relative Amplitude
	L5	Lowest average activity (5 h)
	L5_starttime	Time of L5 start
	M10	Highest average activity (10h)
	M10_starttime	Time of M10 start
PSG	AHI	Apnea Hypopnea Index
Sleep Diary (7-d average)	BT_diary	Bedtime
	SOL_diary	Sleep onset latency
	NWAK_diary	Number of awakenings
	WT_diary	Wake time
	quality_of_sleep_diary	Sleep quality
	TIB_diary	Time in bed

was 0.67 in this sample. The PHQ-9 composed of nine questions that correspond to the nine diagnostic criteria for major depressive disorders in the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM–IV). We used this questionnaire to measure depression in this study. Each item is rated on a 4-point Likert scale (0–3), resulting in a total score ranging from 0 to 27. Internal consistency (Cronbach's alpha) was 0.86 in this sample. The GAD-7 is a self-report anxiety questionnaire consisting of seven items. It asked how often seven symptoms were experienced on a 4-point Likert scale, ranging from 0 = "never", 1 = "several days", 2 = "more than half the days", 3 = "almost every day", resulting in a total score ranging from 0 to 21. Internal consistency (Cronbach's alpha) was 0.91 in this sample.

Additional scales included the Fatigue Severity Scale (FSS) [18] and Epworth Sleepiness Scale (ESS) [19]. The FSS is a 9-item self-report questionnaire used to assess fatigue. Each item is scored from 1 (strongly disagree) to 7 (strongly agree), with the overall FSS score calculated as an average score of the nine items. Higher scores indicate greater fatigue, with a score of >3 indicating a clinically relevant level of fatigue [3]. Internal consistency (Cronbach's alpha) was 0.94 in this sample.The ESS is an 8-item self-reported questionnaire used to assess daytime sleepiness. Each item is scored from 0 to 3 on a Likert-like scale, with the overall ESS score calculated as a total score of the eight items. A higher total score indicates excessive sleepiness, and a score of 10 or more indicates a clinical level of sleepiness [20,21]. Internal consistency (Cronbach's alpha) was 0.86 in this sample.

2.2.2. Actigraphy

Actigraphy is a wrist-worn accelerometer used as a non-invasive method of assessing sleep-wake patterns. In this study, a consumer actigraph (Amazfit Arc, Huami), which has been validated against PSG [22], was worn on the non-dominant wrist. The same device hardware and firmware (version frozen by Huami) were used throughout the study. Raw activity data were recorded in 1-min epochs and made directly available to the STAGES research team. For each participant, the seven days with the least missing data were selected, and data gaps were imputed [23]. Actigraphy data were used to derive non-parametric descriptions of 24-h activity patterns. Interdaily variability (IV) estimates the fragmentation of rest-activity rhythms and is calculated by the ratio of the mean squares of the difference between the first derivative and population variance and reflects the transitions between rest and activity [24,25]. Intradaily stability (IS) estimates the consistency of the rest-activity rhythms between days and is calculated as the ratio between the variance of the average 24-h around the mean and population variance [26]. L5 is the lowest average activity of five consecutive hours and reflects movement during sleep and nighttime arousals. M10 is the highest average activity of ten consecutive hours and reflects activity during the most active time of the day. L5 start time is the onset of the least active sequence, and M10 start time is the onset of the highest active sequence. RA is the normalized difference between M10 and L5 and represents the amplitude of activity patterns, with higher RA indicating a stronger rhythm.

2.2.3. PSG

Polysomnography (PSG) objectively assesses sleep and its associated physiology through the recording of brain wave activity (electroencephalography), eye movements (electro-oculography), muscle activity

(electromyography), cardiac function (electrocardiography), breathing patterns, limb movements, and oxygen levels [26]. All PSGs included in this study were conducted as part of standard of care and followed the clinical protocol of each site. For the purposes of this study, only the apnea-hypopnea index (AHI) was used.

2.2.4. Sleep diary

An electronic daily sleep diary was collected for two weeks. The sleep diary included self-reported sleep parameters such as sleep onset latency, number of awakenings, wake time, quality of sleep, and time in bed.

2.2.5. Electronic Medical Record (EMR)

Approximately six months after enrollment in the study, a qualified study staff member or clinician obtained diagnostic information from each participant's medical record including final physician diagnosis and results from the PSG.

2.3. Statistical analysis

Of the 453 variables in the complete database, 60 were selected as possible predictors of sleepiness or fatigue based on previous associations with sleepiness or fatigue. R (R Core Team, version: 4.1.2), using the most recent shell of RStudio (version: 2022.07.2, RStudio, Boston, MA) was used for all data analysis. Using the R package "nparACT" [27], we derived IV, IS, L5, and M10 [28]. The R package "RandomForest" (version:4.7–1.1) was used to predict sleepiness and fatigue. In all RF models, the number of trees was set to 500, and the "tuneRF" function selected the minimum out-of-bag error. RF training data sets comprised 30% of the complete data set, after which the model was tested on the remaining 70%.

In addition to Random Forest analyses, we used receiver operating characteristics (ROC) curve analysis to characterize differences in sleepiness and fatigue. Area under the curve (AUC), sensitivity, and specificity were calculated for the strongest predictor that emerged from the Random Forest results (R package "ROCit", "PRROC") to discriminate between these two concepts. Youden's Index was used to assess the trade-off between sensitivity and specificity, with higher values indicating a stronger ability to accurately discriminate between sleepiness or fatigue based on a chosen predictor.

3. Results

3.1. Participants

The STAGES cohort consisted of patients visiting sleep clinics across the USA and Canada and was therefore not representative of the general population but rather enriched in sleep disorders. Of the 1775 individuals enrolled in the study, 606 cases were included for analysis in this study (Fig. 1). The main reason for excluding cases was incomplete data for questionnaires, actigraphy, PSG, or sleep diary.

The sample had a diverse range of age groups, with similar ratios for gender, and was predominantly white (Table 2). Approximately two-thirds of the cohort had OSA with approximately one-eighth having insomnia, hypersomnia, or sleep-related movement disorder (Table 2).

3.1.1. Prevalence of fatigue and sleepiness in sleep disorder patients

The proportion of clinical fatigue and excessive daytime sleepiness in our sample was 64.5% (n = 391) and 41.9% (n = 254), respectively. When sleepiness and fatigue were considered together, the sample was further divided into the four following groups based on cut-off points of both measures: No clinical fatigue or excessive daytime sleepiness, only

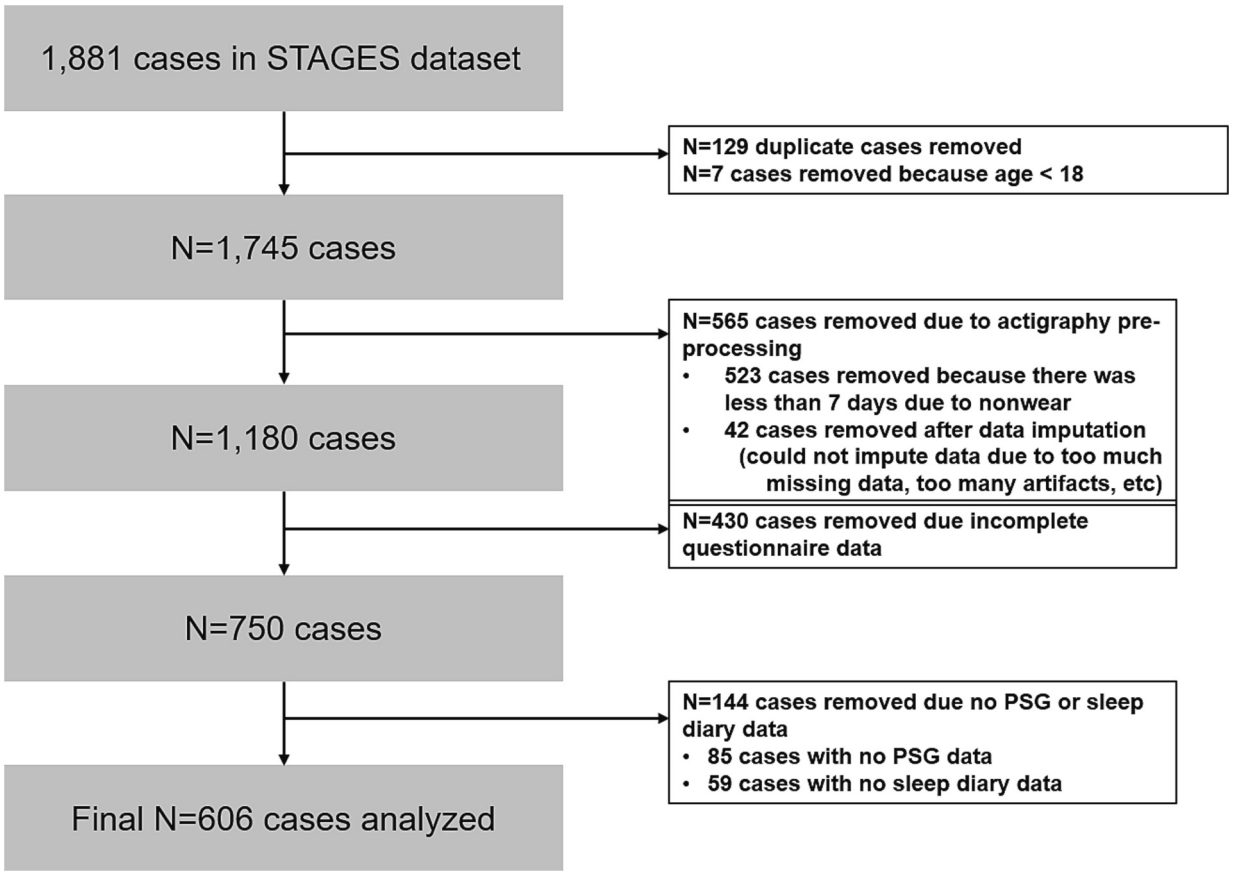

Fig. 1. Flowchart of final sample included for analysis. The complete dataset consisted of 606 individuals.

Table 2
Characteristics of the sample (n = 606).

Characteristics	Mean ± SD or n (%)
Age	
19–29	62 (10.2)
30–39	139 (22.9)
40–49	125 (20.6)
50–59	144 (23.7)
60–69	105 (17.3)
70+	31 (5.1)
Sex	
Male	275 (45.3)
Female	331 (54.6)
Race	
White	518 (85.4)
Black/African-American	24 (3.9)
Asian	2 (0.3)
Native Hawaiian or other Pacific Islander	35 (5.7)
Other	27 (4.4)
AHI	
AHI < 5	213(35.1)
5 ≤ AHI < 15	189 (31.2)
15 ≤ AHI < 30	111 (18.3)
AHI ≥ 30	93 (15.3)
ISI score ≥ 10	405 (66.8)
FSS score	3.789 ± 1.650
FSS score ≥ 3 (total sample)	391 (64.5)
OSA	409(58.6)
Insomnia	97 (65.9)
Hypersomnia	84 (85.7)
Sleep-related movement disorder	67 (73.1)
Others	23 (78.2)
ESS score	9.7 ± 5.1
ESS score ≥ 10 (total sample)	254 (41.9)
OSA	409 (41.5)
Insomnia	97 (32.9)
Hypersomnia	84(67.8)
Sleep-related movement disorder	67 (47.76)
Others	23 (34.78)
Sleep Disorder Diagnosis	
OSA	409 (67.4)
Insomnia	97 (16.0)
Hypersomnia	84 (13.8)
Circadian rhythm sleep disorder	2 (0.3)
Parasomnia	21 (3.4)
Sleep-related movement disorder	67 (11.0)

Note: a subset of individuals had multiple sleep disorder diagnoses, thus the n represent the number of individuals with the given diagnosis and the percent represents the fraction of the population (n = 606) with that diagnosis.
AHI = Apnea-Hypopnea Index; ISI = Insomnia Severity Index; FSS = Fatigue Severity Scale; ESS = Epworth Sleepiness Scale; OSA = Obstructive Sleep Apnea.

clinical fatigue, only excessive daytime sleepiness, and both clinical fatigue and excessive daytime sleepiness. Among the sample, 25.4% (n = 154) had neither excessive daytime sleepiness nor clinical fatigue, 32.6% (n = 198) had only clinical fatigue, 10.0% (n = 61) had only excessive daytime sleepiness, 31.8% (n = 193) had both clinical fatigue and excessive daytime sleepiness.

Among individual sleep disorders, clinical fatigue was most prevalent in hypersomnia (85.7%), followed by sleep-related movement disorders (73.1%), insomnia (65.9%) and OSA (58.6%). Excessive daytime sleepiness was most prevalent in hypersomnia (67.8%), followed by sleep-related movement disorder (47.7%), OSA (41.5%) and insomnia (32.9%). Information is presented in Table 2.

The association between FSS and ESS scores in this sample was r = 0.334 (p < .001). When correlation analysis were run separately for the OSA and insomnia group, the correlation was stronger between FSS and ESS for OSA patients (r = 0.30, p < .001), but lower and not significant for insomnia patients (r = 0.17, p = .08).

3.1.2. Predictors of fatigue vs. sleepiness

The RF model for fatigue (Fig. 2 A) yielded an explained variance of 49.5% (root mean squared error = 111.8). The strongest predictor of fatigue was severity of depressive symptomatology (PHQ-9 scores), which explained 42.7% of the model variance. Other variables explaining at least 5% of the variance were insomnia severity (ISI scores; 12.3% of the model variance) and age (6.9% of the model variance).

The RF model for sleepiness (Fig. 2 B) yielded an explained variance of 17.9% (root mean squared error = 21.67). The strongest predictor of sleepiness was insomnia severity (ISI scores), which explained 17.6% of the model variance. Other variables explaining at least 5% of the variance were sleep onset latency as assessed by sleep diary (13.2%), depressive symptomatology (PHQ-9 scores; 11.0%), morning headaches (6.3%), narcolepsy like symptoms (Index 4 on the MAP; 5.2%) and self-reported sleep quality for weekend nights or non-work or non-sleep days (5.0%). Explained variance for both fatigue and sleepiness predictors can be found in Fig. 2.

3.1.3. Significance of predictors for fatigue and sleepiness

A general linear model (GLM) was performed on both fatigue and sleepiness separately using the top predictors with at least 5% explained variance of the model to establish significance and valence of each predictor. Depression (ß = 1.35, η^2 = 0.14), insomnia severity (β = 0.56, η^2 = 0.03) and age (β = -0.12, η^2 = 0.01) were significantly associated with fatigue (ps < 0.0001). Insomnia severity, (ß = 0.15, η^2 = 0.01, p < .0001), sleep onset latency based on sleep diaries (ß = -0.02, η^2 = 0.01, p < .0001), depression (ß = 0.14, η^2 = 0.01, p < .001), morning headaches (ß = 0.67, η^2 = 0.02, p < .0001), narcolepsy-like symptoms (ß = 0.61, η^2 = 0.01, p < .001), and self-reported sleep quality for weekend nights or non-work or non-sleep days (ß = 0.49, η^2 = 0.005, p < .05) were significantly associated with sleepiness.

3.1.4. ROC analysis differentiating fatigue vs. sleepiness

An ROC curve analysis using depression severity (PHQ-9 scores) was conducted to differentiate fatigue and sleepiness. ROC curve analysis indicated depression severity can be used to differentiate individuals with and without fatigue, with the optimal cut-off point of PHQ-9 = 5 (area under the curve = 0.856, sensitivity = 0.676, specificity = 0.882; Youden's index = 0.550; Fig. 3). In contrast, depression severity was inadequate in differentiating those with and without sleepiness (area under the curve = 0.643, Youden's index = 0.220; Fig. 3). In other words, if an individual had a PHQ-9 score at or above 5 (n = 367), they had an 86.6% chance of having clinical fatigue (318 of 367) and only a 51.7% chance of having clinical sleepiness (190 of 367).

4. Discussion

The current study utilized a machine learning approach to discern the distinctions between sleepiness and fatigue in a sample of individuals with sleep disorders. Our findings shed light on the factors that underlie these two related yet distinct concepts. One key observation from our study was that fatigue was more closely linked to depression. The explanatory values for depression was higher for fatigue (42.7%), compared to sleepiness (11%). A separate GLM analysis confirmed this finding, showing a positive and significant association between depression and fatigue. This suggests that individuals with sleep disorders and fatigue may harbor underlying mental health issues, notably depression, which may intensify their sense of exhaustion.

There were also differences found in individual sleep disorders, with hypersomnia showing the highest rates of clinical fatigue and excessive daytime sleepiness among all the different sleep disorders. When

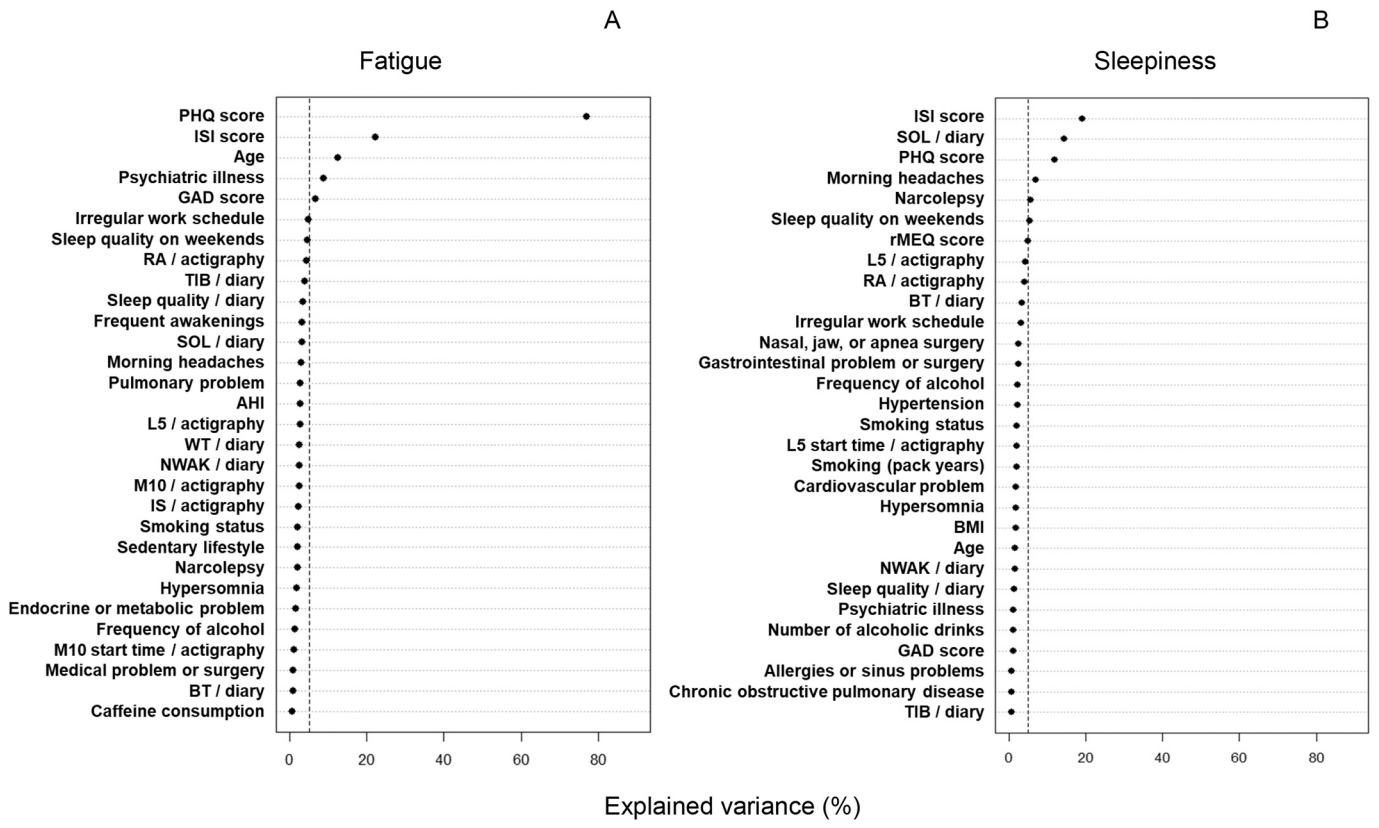

Fig. 2. Variance of importance output of the Random Forest regression of the sample ($n = 606$). Separate models were run to predict fatigue (A) and sleepiness (B). The x-axis represents the percent of the total model variance explained.
PHQ = Patient Health Questionnaire; ISI = Insomnia Severity Index; GAD = Generalized Anxiety Disorder-7 questionnaire; RA = Relative Amplitude; TIB = Time In Bed; SOL = Sleep Onset Latency; AHI = Apnea Hypopnea Index; L5 = Lowest average activity; WT = Wake Time; NWAK = Number of Awakenings; M10 = Highest average activity; IS = Intradaily Stability; M10 start time = Time of M10 start; BT = Bedtime; rMEQ = revised Morningness-Eveningness Questionnaire; L5 start time = Time of L5 start; BMI = Body Mass Index.

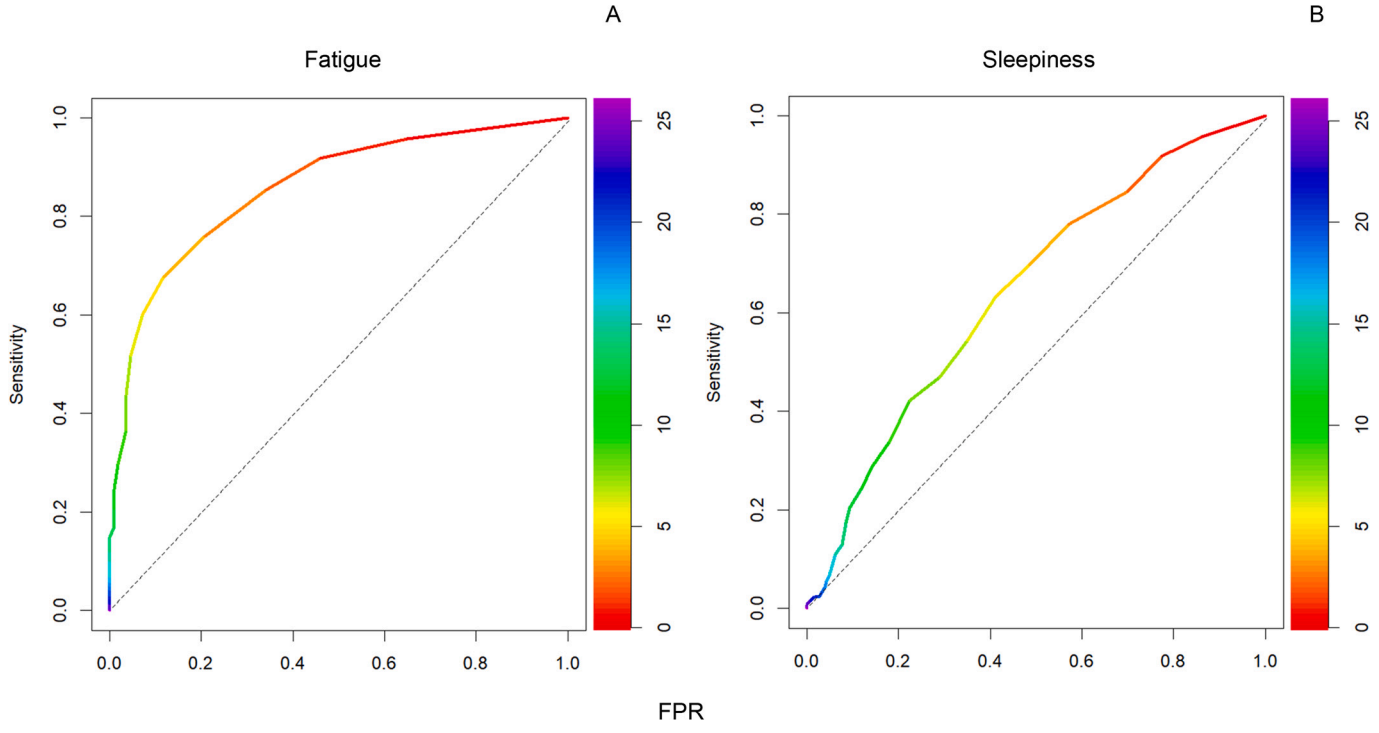

Fig. 3. Receiver operating characteristic (ROC) curves for differentiating the presence or absence of fatigue (A) and sleepiness (B) using the degree of depressive symptomatology (PHQ-9 scores). The Area Under the Curve (AUC) was 0.856 for fatigue and 0.643 for sleepiness.

comparing OSA and insomnia, which consist of the majority of sleep disorders, clinical fatigue was more prevalent in insomnia (65.9%) than OSA (58.6%). This is consistent with the literature that depression has a stronger association with insomnia than OSA. Conversely, excessive daytime sleepiness was more prevalent in OSA (41.5%) compared to insomnia (32.9%). Our study provides further insight into the nuanced differences between sleepiness and fatigue, especially in different sleep disorders, which, despite their similarities, are separable concepts.

4.1. Fatigue and Sleepiness as independent constructs for sleep disorder patients

Fatigue and sleepiness were prevalent in this sample of patients from sleep disorder clinics, with a higher prevalence of fatigue (64.5%) than sleepiness (41.9%). Among our sample, only 10.0% reported excessive sleepiness without overlap of fatigue, while 32.6% reported clinical fatigue without overlap with sleepiness. Our findings are consistent with a previous study by Hossein et al. [3], who found a 64% prevalence of clinical fatigue in sleep disorder patients, with 17% of the sample reporting excessive sleepiness and 4% reporting excessive sleepiness without overlap of fatigue. This may especially be the case for those with OSA, as previous studies found that OSA patients more frequently report problems with feeling fatigued or tired or lack of energy compared to sleepiness [29].

The correlation between sleepiness and fatigue was moderate ($r = 0.334$) in our study. Previous studies have found weak to moderate correlations of sleepiness and fatigue based on various samples, from sleep disorder patients to chronically ill patients [3,30,31]. Our findings support the literature that sleepiness and fatigue have partial overlap but are not identical and can be independent consequences of sleep disorders.

In additional support of this idea, a recent study investigating how individuals perceive the semantic meanings of the words “sleepy”, “fatigued”, “tired” and “drowsy” differently found that individuals construed these words as distinct concepts. Individuals especially found the largest difference in the words “sleepy” and “fatigued”, indicating the importance of clearly defining these clinical concepts and being cautious not to use these words interchangeably [32].

4.2. Depression and mental health factors strongly influence fatigue vs. sleepiness

The current variables used in the study were selected based on previous findings on their associations with sleepiness and fatigue. Nevertheless, the selected factors were better at explaining fatigue compared to sleepiness (explained variance 49.5% *vs.* 17.9%, respectively). It is possible that the inclusion of additional variables could increase explanatory power, especially for sleepiness, though we were unable to identify such factors from PSG in a recent study of community-based individuals [33]. Future studies utilizing unsupervised machine learning will become increasingly valuable, eliminating the need for arbitrary selection of variables.

In our study, fatigue was more strongly explained by mental health factors, especially depression, compared to sleepiness. More specifically, the severity of depressive symptoms was the strongest predictor of fatigue and not a meaningful predictor of sleepiness, suggesting depression could be used to differentiate the two concepts. Previous studies investigating the difference in sleepiness and fatigue in sleep disorder patients have suggested that clinical fatigue may be more strongly influenced by depressive symptoms or other mental health factors [3,34]. In fact, one study found that fatigue in OSA patients was driven by depressive symptoms, explaining 42.3% of the variance after controlling for disease severity [34]. Considering the high prevalence of depression in OSA patients, with one study finding 15.5% of untreated OSA patients meeting the criteria for dysthymia and 6% meeting the criteria for major depression [35], complaints of fatigue in OSA patients may warrant additional screening for depression. Depressive symptoms are also highly prevalent in individuals with insomnia, with up to 20% of individuals with insomnia experiencing depression [36]. The literature also suggests a bidirectional relationship between insomnia and depression, and that having insomnia was associated with a 2.1 times higher risk of developing depression [37]. Nevertheless, while it is probable that depression could be misconstrued as fatigue in individuals with sleep disorders, further investigation is necessary to determine the clinical utility of using depression to differentiate the two concepts. Future studies are needed to explore whether depression-specific interventions targeting fatigue can help alleviate fatigue symptoms, but not sleepiness.

Results from ROC analysis in our study also found that the optimal cut-off point for the PHQ-9 in differentiating those with and without fatigue was 5. Typically, a cut-off point of 10 or higher is used to determine a diagnosis of major depressive disorder [38]. A PHQ-9 score of 5 indicates only mild symptoms (below 5 is considered minimal depressive symptomatology). The lower cut-off point found in our study suggests that sleep disorder patients with even subclinical symptoms of depression may frequently complain about fatigue. Our findings are consistent of those of Fava and colleagues [39], who found that fatigue was one of the most common prodromal symptoms in depressed patients.

Several explanations may be able to clarify why fatigue is more strongly associated with mental health factors such as depression compared to sleepiness. Fatigue is often a symptom of depression, and the FSS includes items that are also common with depressive symptoms. This may have resulted in an increase of loading of the PHQ-9 onto the FSS. Additionally, fatigue is often conceptualized and divided into subtypes, such as physical and mental fatigue. The former term, physical fatigue, is often defined as the diminution of muscular strength, as opposed to mental fatigue, an inner sensation often assessed through self-reported questionnaires consistent with this study. Fatigue can also be distinguished from fatigability, which refers to “decrements in motor or cognitive performance over time” and lack of stamina to meet performance goals, and differs from the self-reported sensation of fatigue [6]. Psychologically, low motivational affective states (*e.g.*, anhedonia, reluctance to initiate social interactions or physical activity) can be reflected in fatigue compared to sleepiness. Biologically, there is considerable overlap in the neuromodulators, such as norepinephrine, dopamine, and serotonin, that regulate mood and wake regulation. In addition, the hypothalamic-pituitary-adrenal (HPA) axis has been implicated in the experience of fatigue. Stress often accompanies or precipitates sleep disturbance [40], with prolonged stress activating the HPA axis, a complex system that regulates stress response and energy metabolism and secretes cortisol, a stress hormone. Increased cortisol levels can lead to sleep disturbance, with elevated cortisol levels at night interfering with the ability to sleep. Prolonged stress can cause hyperactivation of the HPA axis and lead to depression, enhancing the sensation of fatigue.

In summary, results from our study indicate that depression plays a more prominent role in characterizing fatigue than it does in sleepiness. While fatigue and sleepiness share similarities, the presence of depression as a distinguishing factor underscores the need for comprehensive mental health assessments in sleep clinics, which can aid in more accurate diagnosis and address underlying issues associated with fatigue and sleepiness in sleep disorder patients.

4.3. Limitations

This study has limitations. First, our study population was drawn from sleep clinics in North America. Thus, the interpretation of these results are limited to sleep disorder patients and may not extrapolate to the general public, especially those without clinically disruptive sleep problems. Furthermore, all participants completed the questionnaires in English. How these terms of ‘fatigue’ and ‘sleepiness’ might translate to

other languages or have a bearing on cultural influences is unknown. Second, while we had not previously detected an association between PSG measures and ESS scores [33], further or novel analyses of PSG data beyond our current use of AHI might reveal trait-like characteristics indicative of fatigue or sleepiness. Additionally, the correlation between FSS and ESS yielded a significant correlation of 0.334 in the whole sample. However, when analyzed separately in the OSA and insomnia samples, the correlation was high for FSS and ESS in OSA patients, but non-significant and low for the insomnia patients. Since the large majority of the sample were mainly OSA patients and both sleepiness and fatigue are associated with OSA, this may have inflated the correlation between the two variables. Third, the study was exploratory in nature without predetermined hypotheses; thus, there is a need to follow-up and replicate the results in an independent dataset. Fourth, we used a subset of a larger sample for analysis. The main reason was because of missing data, and the analysis used in this study required inclusion of a comprehensive set of variables. Nevertheless, there is a chance that significant bias may have been introduced in the study. Thus, further analyses with larger independent datasets are needed to replicate the findings in this study.

Finally, it should be noted that while some analyses were conducted for individual sleep disorders based on physician diagnosis and electronic medical charts, there is a possibility that individuals had multiple sleep disorders. For example, physician-based diagnosis reported 12% had insomnia diagnosis, but our sample found 67% of individuals were above the cut-off on the Insomnia Severity Index. While sleep diagnostics in our sample were primarily based on PSG, OSA was most likely the most common primary sleep disorder diagnosis. This underreporting of insomnia is also not surprising considering insomnia is often commonly underdiagnosed in OSA patients, which is reflected in this large discrepancy.

5. Conclusions

This study employed a machine learning approach in a sample of sleep disorder patients to differentiate between sleepiness and fatigue using factors previously established as correlates of these two concepts. Fatigue was more strongly associated with mental health factors, especially depression, compared to sleepiness. This suggests that individuals with sleep disorders and fatigue may harbor underlying mental health issues, notably depression, which may intensify their sense of exhaustion. In contrast, sleepiness was more strongly associated with sleep factors, such as insomnia severity and sleep onset latency. Our findings have implications for developing more precise diagnostic and treatment strategies in individuals with sleep disorders who present with complaints of fatigue and/or sleepiness.

Statement of significance

Sleepiness and fatigue are common complaints among sleep disorder patients, and these terms are often used interchangeably. This can cause difficulty and confusion in making a differential diagnosis and providing optimal patient care. The current study investigated factors associated with sleepiness and fatigue in a large sample of sleep disorder patients using a machine learning approach to determine which factors best-differentiated sleepiness from fatigue. Fatigue and sleepiness were moderately correlated, suggesting the concepts were overlapping yet distinct. Fatigue was better characterized by depression than sleepiness, suggesting depression could be used to differentiate the two concepts.

CRediT authorship contribution statement

Sooyeon Suh: Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Renske Lok:** Writing – review & editing, Methodology, Formal analysis, Data curation, Conceptualization. **Lara Weed:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Ayeong Cho:** Writing – review & editing, Writing – original draft, Formal analysis. **Emmanuel Mignot:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition. **Eileen B. Leary:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition. **Jamie M. Zeitzer:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

None. The authors have no competing interests to report.

Data availability

The data used in this article are available in the National Sleep Research Resource repository at *https://sleepdata.org/*.

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