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Fatigue: The forgotten symptom of sleep apnea

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Abstract

Objective: The present investigation was designed to explore the role and implications of both daytime sleepiness and fatigue in obstructive sleep apnea syndrome with respect to sleep, perceived health quality, and psychological functioning. **Methods:** Our participants consisted of two groups: 124 older community volunteers who completed a polysomnographic sleep study and were diagnosed with sleep apnea, and 19 healthy controls. All participants completed self-report measures of sleepiness, fatigue, sleep quality, health quality, and psychological functioning. **Results:** The apnea sample was divided according to clinically relevant cut-offs on sleepiness and fatigue. When those with mid-range scores were ruled out, the following groups remained: low sleepiness/low fatigue (LL, *n*=23), high sleepiness/high fatigue (HH, *n*=28), high sleepiness/low fatigue (HS, *n*=10) and low sleepiness/high fatigue (HF, *n*=13). The respiratory disturbance index did not differ significantly among these groups and only the two highly fatigued groups (HH and HF) experienced significantly lower average oxygen saturation than the control group. Analyses revealed that the HH group was significantly worse than the LL and control groups on most sleep, health quality, and psychological measures. On these same measures, the groups for whom fatigue was low (LL and HS), regardless of sleepiness, were similar to controls. **Conclusion:** When patients with sleep apnea are classified into different sleepiness/fatigue categories, the results show that high fatigue is associated with more severe dysfunction than high sleepiness. The current debate on whether to treat apnea patients with low sleepiness needs to consider the impact of fatigue.

Keywords: Fatigue; Sleepiness; Sleep apnea; Symptom

Introduction

Daytime sleepiness has long been known to be a prominent aspect of obstructive sleep apnea (OSA) [1]. Only recently have studies indicated that fatigue may be an important symptom of sleep apnea as well [2]. Because fatigue has been understudied, the present investigation was designed to explore the role and implications of both daytime sleepiness and fatigue in OSA syndrome.

Studies using experimentally induced sleep deprivation indicate that sleepiness is physiologically based and dependent on both the length of prior wakefulness and circadian rhythm status [3]. Sleep apnea, which restricts or disrupts sleep, tends to result in substantial sleepiness. In clinical practice, screening and referral for sleep apnea are typically centered on the evaluation of sleepiness, employing the self-report Epworth Sleepiness Scale [1,4] and/or the Multiple Sleep Latency or Maintenance of Wakefulness tests [5–8] to evaluate the extent of sleep

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propensity. Moreover, there has traditionally been a focus on driving accidents as an index of impairment, rather than on more widespread impact on quality of life, health and well-being.

It is notable that there is a substantial segment of the sleep apnea population who do not complain of the expected daytime sleepiness symptoms. Little is known about the characteristics of such individuals, and optimal treatment for them continues to be debated [9,10]. The dialogue over whether to treat has focused on sleepiness as measured by the Epworth Sleepiness Scale and has tended to ignore other subjectively reported symptoms.

Fatigue, on the other hand, appears more related to perceived depletion of physical and/or mental energy [11]. Experimentally, it has been operationalized as exercise tolerance [12], though this does not appear to take into account the many aspects of subjectively experienced fatigue [11]. The International Classification of Sleep Disorders [13] lists exhaustion among other complaints such as sleepiness and insomnia as part of the minimal criteria required to make a diagnosis of obstructive sleep apnea syndrome. It includes symptoms of loss of libido and morning headaches but does not mention the term "fatigue" specifically. It is commonly taught in medical education that a complaint of excessive daytime sleepiness raises the possibility of sleep disorder, while complaints of fatigue, tiredness, and lack of energy tend to suggest psychiatric and other medical diagnoses (e.g., depression, hypothyroidism) [4].

Basic research has already established the important link between insomnia and fatigue [14–18], but recognition of fatigue in sleep apnea is relatively recent [2,4,19]. Interestingly, when sleep apnea patients themselves were asked to choose among assorted descriptors, including sleepiness, tiredness, fatigue, and lack of energy to describe their most prominent symptom, 40% chose lack of energy, and only 22% chose sleepiness [4].

In a recent study, Hossain et al. [2] reported that fatigue was a common complaint in their sleep clinic sample of individuals referred for possible sleep apnea. Notably, they found substantial numbers of patients with various combinations of sleepiness and fatigue: high ratings of both, either one symptom or the other alone, or neither symptom. They found that high fatigue was associated with greater depression and illness impact. However, since they did not compare those with and without an apnea diagnosis, we cannot be sure that the presence of fatigue is a specific feature of sleep apnea.

One major problem in the whole area of daytime sleepiness and fatigue has been the overlap in definition between the concepts, both in the research literature as well as in clinical practice [20]. To address this problem, in a recent study, we examined commonly used sleepiness and fatigue questionnaires and identified those items in the measures that were related to each of the two constructs, but not to each other (i.e., unconfounded items evaluating either sleepiness or fatigue) [21]. The results revealed that the two symptoms were most clearly distinct when sleepiness is defined by sleep propensity and fatigue is defined as diminished energy or weakness.

The goal of the present study was to evaluate the presence and correlates of fatigue and sleepiness in a sample of older individuals diagnosed with sleep apnea using the distinct Empirical Sleepiness and Fatigue measures [21]. In addition, we examined the descriptive features and characteristics of individuals with high and low levels of sleepiness and fatigue, particularly those who experience high levels of both compared to those who are relatively uncomplaining. We included a healthy comparison sample to evaluate the specific link between sleep apnea, sleepiness/fatigue symptoms, and their contribution to different aspects of functioning. We expected to replicate the findings of Hossain et al. [2] as well as to clarify the association between sleep apnea and fatigue.

Specifically, the study was designed to answer the following questions:

- How do patterns of sleepiness and fatigue in individuals with sleep apnea compare with those in healthy individuals?
- What are the implications of constellations of high sleepiness/high fatigue and of low sleepiness/low fatigue?
- When daytime sleepiness and fatigue are measured as distinct entities, which is the more important symptom of sleep apnea?

Method

Participants

Community sample with apnea

These were older volunteers who were recruited from the community with posters and at "golden age" meetings who endorsed daytime fatigue or sleepiness or sleep problems at night. Selection criteria were as follows: aged 50 and over, community resident, and sufficient cognitive and language skills to complete the measures in English or French (the two official languages used in Montreal). Exclusion criteria included a prior diagnosis of primary sleep disorder, major illness (i.e., any illness which would account for daytime fatigue and sleepiness) or drug use known to cause daytime fatigue, sleepiness, or insomnia, current clinically significant psychological or psychiatric disorder, dementia, parasomnias, or severe sleep phase disorder.

Of 188 participants who began the study, 10 were excluded due to major illness and 32 dropped out before completion of the protocol. A total of 146 participants completed the Questionnaire Battery and underwent nocturnal PSG. The 124 individuals (59 males and 65 females, mean age=63.02, S.D.=11.40) who were diagnosed with apnea comprised the present sample.

Control sample

A convenience sample of 19 volunteers comprised the control sample (5 males and 14 females, mean age=42.0, S.D.=9.21). They were first screened to be without obesity or symptoms of sleep apnea and subsequently tested to ensure that they did not have apnea either by PSG exam (n=10) or, when this was not feasible, with the SnoreSat home screening device (n=9). The exclusion criteria were otherwise the same as for the community sample.

Measures

Empirical sleepiness and fatigue scales [21]

These were developed by correlation and factor analysis of all items from four questionnaires purporting to measure sleepiness and fatigue: Stanford Sleepiness Scale [22], Epworth Sleepiness Scale [23], Fatigue Severity Scale [24], Chalder Fatigue Scale [25]. The two Empirical scales represent different constructs that are only minimally correlated with each other and that have distinctive patterns of associations. The Empirical Sleepiness Scale consists of six items from the Epworth Sleepiness Scale while the Empirical Fatigue Scale consists of one item from the Fatigue Severity Scale and two from the Chalder Fatigue Scale. The Stanford Sleepiness Scale was found to be highly correlated with fatigue items and was not included in the final scales. Both scales have excellent test–retest reliability and internal consistency as well as good validity. The Empirical Fatigue scale scores range from 3 to 18, and Empirical Sleepiness scores range from 0 to 18. Higher scores indicate greater sleepiness or fatigue.

Questionnaire battery

This consisted of an extensive, 2-h battery of questionnaires on sleep, health, quality of life and psychological adjustment. Included in the present investigation are the SF-36 Health Survey [26] and individual items, subscale scores, or overall test scores from the following measures: Sleep Questionnaire—a modified version of the retrospective questionnaire used in previous investigations [27]; the Spielberger State-Trait Anxiety Inventory-Form Y2 [28]; and the Beck Depression Inventory Primary Care Subscale [29]. To reduce the number of items used for analysis from the large number of items in these questionnaires, in a previous study [30], we selected a subset of 21 items and distilled them into manageable factors. Because the different items had an assortment of measurement properties, scores were standardized so that they could be added together. Factor analysis revealed a five-factor structure: QSleep Disorder, QFatigue, QSleepiness, QInsomnia, QPsychological. For the present analyses, only the QSleep Disorder, QInsomnia, and QPsychological subscales were employed because the QFatigue and the QSleepiness subscales contain the Empirical Fatigue and Sleepiness measures, respectively. Table 1 presents the items comprising the three Q subscales as well as their factor loadings.

Laboratory PSG assessment

Participants were monitored in a supervised sleep laboratory from 10 p.m. to 7 a.m. Monitoring included three leads EEG, EOG, bilateral anterior tibialis and chin EMG, ECG, pulse oximetry, nasal and oral airflow with nasal pressure cannulae and thermistor, and respitrace bands for measurement of respiratory effort [31]. All signals were acquired on a digital data management system (Sandman, Nellcor-Puritan Bennett & Tyco, Ottawa, Canada). A certified polysomnographic technologist with at least 10 years of experience manually scored the studies blind to the results of symptom assessments. Sleep stages were first scored in 30-s epochs according to standard criteria [32]. Next, EEG arousals were scored according to standard current consensus criteria [33]. An apnea event was scored when there was a cessation of breathing for 10 or more seconds. A hypopnea was defined a priori as an event lasting at least 10 s with an airflow decrease of >50% from a baseline in the amplitude compared to the mean of the largest

Table 1
Subscale items derived from a large questionnaire battery submitted to factor analysis

Subscale	Factor loading
QPsychological subscale	
Beck Depression Inventory: PCI subtotal	0.830
Spielberger State Trait Anxiety Inventory: total	0.826
SF-36: Mental Health (subscale)	0.804
QInsomnia subscale	
Do you have insomnia? Yes/No	0.763
At bedtime, how long does it usually take you to fall asleep? (hours)	0.675
I wake up too early in the morning and cannot get back to sleep. (Check if yes)	0.663
I have difficulty falling asleep at bedtime. (Check if yes)	0.632
Generally, how many times per night do you wake up and use the bathroom? (frequency)	0.357
QSleep Disorder subscale	
Do you snore? (Yes/No)	0.623
Do you wake up in the middle of the night feeling unable to breathe? (Yes/No)	0.610
Have you noticed that parts of your body jerk at night? (Yes/No)	0.581
Do you wake up with a dry mouth? (Yes/No)	0.422

three breaths over the previous four epochs, or a lesser reduction in airflow signal amplitude accompanied by either at least a 3% oxygen desaturation or an EEG arousal [34]. Leg movements, apnea events and associated arousals were scored manually according to scoring rules established by the Atlas Task Force of the American Sleep Disorders Association [35]. The cutoff criterion for defining a case with significant apnea/hypopnea as well as periodic limb movements is 10 or more events per hour of EEG sleep.

Home PSG assessment

Home sleep period recording to screen for the presence of sleep apnea was performed with a SnoreSat Recorder (SegaTech Electronics, Calgary, Canada). This device records pulse oximetry, nasal airflow with nasal pressure cannulae, microphone for snoring, and respitrace bands for measurement of respiratory effort. This device has been compared to overnight PSG, providing similar apnea indices (r=.97), though lacking EEG recording to detect sleep arousals. Sensitivity and specificity for OSA in a sample of patients with suspected OSA were high, .98 and .88, respectively, using a cutoff criterion of 15 [36]. Records underwent automated scoring which was validated by visual inspection of the raw data disclosed in 10-min epochs. Respiratory disturbance indices were adjusted for any time spent with invalid recording or persistent movement suggesting wakefulness.

Procedure

Both samples were recruited with prior approval of the ethics review boards of McGill University (FWA00004545, May, 2003) and Mount Sinai Hospital Center in Montreal. Participants signed a consent form advising them of all aspects of the study, including the right to withdraw at any time.

Participants completed the 2-h questionnaire battery at the Jewish General Hospital and underwent polysomnography (PSG) assessment in an accredited sleep laboratory. Control participants who underwent home monitoring were instructed in the afternoon about the use of the device and returned home with written instructions. All were paid a small honorarium for their participation and were refunded for travel and parking expenses.

All participants were provided information about the results of their assessment. Those receiving a sleep disorder diagnosis were offered appropriate treatment and/or referral to a sleep specialist.

Results

Data treatment and configuration of the sample

In general, the data analyses to examine group differences consisted of multivariate (MANOVA) followed by univariate analysis of variance (ANOVA) and post hoc t tests [least significant difference (LSD)]. The Empirical Sleepiness and Fatigue measures [21] were used to establish low and high fatigue and sleepiness groupings for the sample of participants with apnea. For the Empirical Sleepiness Scale (maximum score=18), cutoff scores of 4 and under and 8 and over were used to establish Low Sleepiness (n=45) and High Sleepiness (n=50) groupings. This left 29 individuals who fell in the Medium Sleepiness category. The sample was also divided into groups of Low Fatigue (score of 9 or less, n=44) and High Fatigue (score of 12 or more of a maximum score of 18, n=55) groups. This left 25 individuals in the Medium Fatigue group. These cut-off scores were consistent with scores obtained for clinical groups (chronic fatigue syndrome, narcolepsy) and normal controls [21]. A breakdown (by number and percentage of the total apnea sample) of participants who fell into the various Low, High, and Medium sleepiness and fatigue groups is presented in Table 2. This shows that a substantial percentage of the apnea sample was either low or high on both symptom dimensions: low sleepiness/ low fatigue (LL), high sleepiness/ high fatigue (HH), high sleepiness/ low fatigue (HS), low sleepiness/ high fatigue (HF). A Chi-square test of association based on 4 cells (LL, HH, HS, HF) was significant, χ^2 (df=1,75)=11.11, P<.001. The following analyses were conducted on these four groups and the control group (CL).

Table 3 shows univariate analysis of variance comparisons (ANOVA) and post hoc test results as well as mean scores on the Fatigue Scale, the Sleepiness Scale, age and body mass index (BMI) for participants in the five groups of interest (LL, HH, HS, HF, CL). The mean Fatigue score for the CL group was below the cut-off for the Low Fatigue category, although 6 participants (31.6%) were classified as High Fatigue. The mean Sleepiness Scale score for the CL group fell between the apnea sample's Low and High Sleepiness scores. Overall, the CL group was significantly younger than all of the apnea groups. The CL group had a lower mean BMI than any of apnea groups, though these scores were unavailable for about half the sample. The LL group had a significantly lower BMI than the HH group.

Group comparisons

Further analyses compared the four apnea groups (LL, HH, HS, HF) and the CL. Because the mean age was

Table 2
Breakdown of apnea sample in to Low, Medium, and High categories according to Sleepiness and Fatigue measure cutoff scores

Fatigue n (%)					
		Low	Medium	High	Total
Sleepiness	Low	23 (18.5)	9 (7.3)	13 (10.5)	45 (36.3)
	Med	11 (8.9)	5 (4.0)	13 (10.5)	29 (23.4)
	High	10 (8.1)	11 (8.9)	29 (23.4)	50 (40.3)
	Total	44 (35.5)	25 (20.2)	55 (44.4)	124 (100.0)

Table 3
Means, standard deviations, univariate ANOVAs, and post-hoc tests (LSD) for Sleepiness and Fatigue measures, age and BMI for four apnea subgroups and control group

	Group	Mean	S.D.	*F*	*df*	*P*	Post hoc
Fatigue measure	LL	6.91	1.70	43.46	4,88	<.001	CL, LL, HS<HH, HF
	HH	14.36	1.95				
	HS	7.10	1.85				
	HF	13.85	2.19				
	CL	7.79	4.13				
Sleepiness measure	LL	1.70	1.40	84.08	4,88	<.001	LL,HF<CL<HH,HS
	HH	10.92	2.25				
	HS	11.20	2.90				
	HF	1.38	1.71				
	CL	4.21	2.95				
Age	LL	65.48	11.04	16.52	4,88	<.001	CL<LL,HH,HS,HF
	HH	59.53	10.84				HH<HF
	HS	62.20	11.75				
	HF	67.62	10.81				
	CL	42.00	9.21				
BMI	LL	25.75	3.99	5.22	4,77	<.001	CL<HS,HH,HF
	HH	30.72	6.90				LL<HH
	HS	27.88	3.85				
	HF	29.63	7.68				
	CL*	21.66	2.13				

n: Total=93; LL=23; HH=28; HS=10; HF=13; CL=19 (*CL=8).
Higher scores indicate more fatigue or sleepiness.

significantly lower for CL than for the other groups, all ANOVAs described below were also carried out with age as a covariate. The pattern of results from the analyses of covariance (ANCOVAs) did not differ from the ANOVA findings, and are not reported here.

To compare scores of these five groups on polysomnograpic variables [Respiratory Disturbance Index (RDI) and oxygen saturation (Spo_2)], a MANOVA was carried out. There was a significant main effect for Group, $F(8,170)=4.92$, $P<.001$. Table 4 presents the ANOVA (*F* statistic) and post hoc (least significant difference, LSD) results as well as means and standard deviations for each group for both measures. As expected, all four apnea groups had significantly higher RDI scores than the CL group. No significant differences were found among the four apnea groups. The HH and HF groups had significantly lower mean Spo_2 than the CL group and the HF group had significantly lower mean Spo_2 that either the LL or HS groups.

We examined group differences in perceived functioning in eight physical and mental health domains as measured by the SF-36 Health Survey. A MANOVA was carried out comparing scores of the five groups on the Physical Functioning, Physical Role, Body Pain, General Health, Vitality, Social Functioning, Emotional Role, and Mental Health subscales. There was a significant main effect for group, $F(32,324)=1.79$, $P<.01$. Univariate ANOVA comparisons showed significant group differences for all 8 subscales. Table 5 presents the ANOVA (*F* statistic) and post hoc (least significant difference, LSD) results as well as means and standard deviations for each group on each subscale. The CL and LL groups were not statistically different from each other and, with the exception of the Mental Health subscale, both had significantly higher functioning scores than the HH and HF groups. The HH and HF groups, which also did not differ from each other, had the lowest scores on all eight subscales, but were

Table 4
Means, standard deviations, univariate ANOVAs, and post hoc tests (LSD) for RDI and Spo_2 measure of four apnea subgroups and control group

	Group	Mean	S.D.	*F*	*df*	*P*	Post hoc
Respiratory	LL	28.77	1.40	6.99	4,85	<.001	CL<LL, HH, HS, HF
Disturbance Index	HH	25.43	2.25				
	HS	27.84	2.90				
	HF	35.29	1.71				
	CL	3.64	2.95				
Spo_2 (%)	LL	96.56	1.33	4.91	4,85	<.01	HH, HF<CL
	HH	95.35	2.03				HF<LL, HS
	HS	96.76	1.72				
	HF	94.48	4.43				
	CL	97.66	1.22				

Table 5
Means, standard deviations, univariate ANOVAs, and post hoc tests (LSD) for 8 subscales of the SF-36 health functioning measure for four apnea subgroups and control group

	Group	Mean	SD	F	df	*P*	Post-hoc
Physical Functioning	LL	84.09	12.50	7.34	4,85	<.001	CL, LL, HS >HH, HF
	HH	59.44	25.01				
	HS	77.00	27.41				
	HF	53.75	29.47				
	CL	86.32	22.73				
Role physical	LL	77.27	33.55	10.39	4,85	<.001	CL, LL>HH, HF
	HH	34.26	42.83				CL>HS
	HS	50.00	42.49				
	HF	18.75	32.20				
	CL	86.84	32.66				
Body pain	LL	77.27	23.47	4.38	4,85	<.01	CL, LL>HH, HF
	HH	52.37	28.76				HS>HH
	HS	73.00	25.15				
	HF	53.25	29.78				
	CL	76.68	25.60				
General health	LL	71.64	19.07	5.56	4,85	<.01	CL, LL, HS> HH, HF
	HH	60.06	19.51				
	HS	75.20	16.20				
	HF	57.75	19.68				
	CL	81.63	13.98				
Vitality	LL	62.04	15.25	8.37	4,85	<.001	CL, LL>HH, HF
	HH	38.52	18.54				
	HS	49.50	22.42				
	HF	33.33	19.58				
	CL	61.58	22.97				
Social functioning	LL	84.66	18.87	7.95	4,85	<.001	CL, LL>HH, HF
	HH	62.04	28.69				HS>HF
	HS	75.00	25.00				
	HF	47.92	27.09				
	CL	87.50	16.67				
Role emotional	LL	77.27	31.57	3.46	4,85	<.01	CL, LL>HH, HF
	HH	53.09	43.62				
	HS	63.33	45.68				
	HF	38.89	42.24				
	CL	82.46	34.01				
Mental health	LL	81.82	13.56	4.75	4,85	<.01	CL, LL>HF
	HH	66.96	15.56				LL>HH
	HS	69.00	17.62				
	HF	56.33	25.15				
	CL	76.21	20.46				

n: Total=90; LL=22; HH=27; HS=10; HF=12; CL=19.

significantly lower on seven. Taken together, it appears that those with low fatigue and sleepiness scores report health functioning similar to that of healthy controls, while the lowest scores on health functioning were reported by those groups with high fatigue.

In order to examine group differences in other self-reported symptom domains, a MANOVA test was carried out comparing the three Questionnaire Battery factor scores [30]: QSleep Disorders, QPsychological and QInsomnia. There was a significant main effect for group, $F(12,204)=4.40$, $P<.001$. Univariate ANOVA tests show that there were significant group differences on all three factors (Table 6). The CL group had the lowest score on all three comparisons. On the QPsychological subscale, the CL and LL groups did not differ significantly and had significantly lower scores than the HH and HF groups. On the QSleep Disorders subscale, the four apnea groups did not differ from each other in reported symptoms. On the QInsomnia subscale, all apnea groups experienced more insomnia symptoms than the healthy controls and the HF group reported more than the LL group.

A discriminant analysis was carried out to predict group membership for three groups: LL, HH, and CL. The predictor variables included in the step-wise analysis were: RDI, Spo_2, all eight SF-36 subscale scores, as well as the three Q-factors: QPsychological, QInsomnia, and QSleep Disorder. We found that a discriminant function, including RDI, QSleep Disorder, SF-36 Vitality, and QInsomnia as predictors, could discriminate among the three groups at the .001 level of significance with a canonical correlation of 0.785 accounting for 61.6% of the variance. Using this function, the classification accuracy for the three groups was

Table 6
Means, standard deviations, univariate ANOVAs, and post-hoc tests (LSD) for 3 factor subscales of the questionnaire battery for four apnea subgroups and control group

	Group	Mean	SD	F	df	*P*	Post-hoc
QPsychological	LL	28.15	1.56	7.78	4,72	<.001	CL, LL<HH, HF
	HH	30.29	2.02				HS<HF
	HS	29.66	1.62				
	HF	32.92	3.96				
	CL	28.59	2.58				
QInsomnia	LL	49.89	3.19	6.00	4,72	<.001	CL<LL, HH, HS, HF
	HH	50.83	3.37				LL<HF
	HS	50.74	3.87				
	HF	53.60	5.91				
	CL	46.82	2.24				
QSleepDisorder	LL	39.65	2.00	5.79	4,72	<.001	CL<LL, HH, HS, HF
	HH	41.08	2.64				
	HS	39.61	2.37				
	HF	40.54	2.99				
	CL	37.60	1.52				

n: Total=73; LL=17; HH=21; HS=9; HF=9; CL=17.

74% overall, with the LL group membership at 58%, HH at 71%, and CL at 100% accuracy.

Finally, regression analyses were carried out to predict fatigue and sleepiness severity from the above independent variables for the apnea groups (LL, HH, HS, HF, *n*=56). Regression equations for predicting fatigue and sleepiness scores were significant and presented in Table 7. The prediction equation for the Fatigue Scale, including SF-36 Physical Functioning, Spo_2, and SF-36 Vitality appears robust, accounting for 55% of the variance. Only one predictor variable (RDI) was found for the Sleepiness Scale, and this was comparatively weak.

Discussion

Patterns of sleepiness/fatigue and their implications

Similar to the Hossain et al. study [2], we identified four apnea subgroups characterized by combinations of high and low levels of sleepiness and fatigue. In the present study, among participants with sleep apnea, a substantial number (23%) presented with high levels of both daytime fatigue and sleepiness, while, counterintuitively, 19% were relatively asymptomatic on both. Of equal interest is the presence of those groups who experienced high fatigue only (10%) as well as low fatigue and high sleepiness (8%). Clearly, sleep apnea not only has several symptom presentations, but our findings underline the importance of fatigue as a symptom of sleep apnea, both in the presence and absence of sleepiness. More research is needed to understand the pathophysiological association between fatigue and sleep apnea.

The present study is one of the very few to show that highly fatigued individuals with sleep apnea not only have impaired daytime functioning, but such fatigue-related impairments may be even more profound than those associated with sleepiness. Despite having similar levels of apnea severity, as measured by the RDI, the groups were very different in their functioning. Notably, the groups with high fatigue tended to report diminished quality of life and less adaptive psychological functioning, while the groups with low levels of sleepiness and fatigue were not

Table 7
Regression equation beta weights for predicting Fatigue and Sleepiness for apnea groups (LL, HH, HS, HF, *n*=56)

	Unstandardized coefficients		Standardized coefficients		
	B	Std. error	Beta	t	*P*
Fatigue Scale [a]					
Constant	89.868	19.916		4.512	<.001
SF-36 Physical Functioning	−.068	.017	−.421	−4.019	<.001
Mean O_2% during sleep	−.742	.208	−.330	−3.567	<.01
SF-36 Vitality	−.062	.020	−.319	−3.041	<.01
Sleepiness Scale [b]					
Constant	8.947	1.154		7.751	<.001
Sleep RDI	−.069	.031	−.284	−2.197	<.05

[a] R^2=.55, $F(3,53)$=21.71, P<.001.
[b] R^2=.08, $F(1,55)$=4.83, P<.05.

significantly different from the healthy controls. Of equal interest, another objective measure associated with sleep apnea, mean Spo_2, was lower in high fatigue individuals. In addition, mean Spo_2 was a significant predictor for fatigue but not for sleepiness. This suggests that this particular apnea index may distinguish fatigue and sleepiness in this population. Interestingly, low mean Spo_2 is a disease characteristic found in another patient population, severe chronic obstructive lung disease, where fatigue is also a prominent feature of disability [37–39].

Implications

Our findings support the observation made in other studies that a surprising number of individuals with sleep apnea have few daytime sleepiness/fatigue complaints. The present study also adds new information to the current debate about whether it is appropriate to treat people with sleep apnea who are not sleepy [9]. The LL group was not only low on reported sleepiness and fatigue but also on numerous other indices of poor functioning. In fact, in many cases the group with high sleepiness but with low fatigue was quite similar to the LL group, including at least one recognized index of sleep apnea severity: mean Spo_2. Studies have shown that treating patients with apnea who do not complain of excessive daytime sleepiness with Continuous Positive Airway Pressure (CPAP) does not change arterial blood pressure, suggesting that such patients could be at less risk for the adverse cardiovascular consequences of untreated sleep apnea [9,40]. Our findings extend the "low risk" profile by suggesting that even high levels of sleepiness, provided that there is a low level of fatigue, may be associated with reduced risk from the consequences of sleep apnea. Future research should evaluate this possibility empirically. On the other hand, the present study indicates that an important and problematic group is the one with low sleepiness but high fatigue (and a whole gamut of other complaints), suggesting that highly fatigued people should not be overlooked for apnea treatment simply because they are not sleepy.

Limitations

Limitations of the present study include the fact that the control sample was somewhat sleepy and fatigued. Possibly these symptoms are prevalent in well-functioning, non-complaining people, but not with the same frequency or impact as in people with sleep apnea. In addition, the control sample was younger. While controlling for the age difference through ANCOVAs revealed a very similar pattern of findings, it is not entirely possible to dismiss the possible impact of age. Thus, despite the inclusion of a control sample, we still cannot definitively say that fatigue is clearly a consequence of sleep apnea. In addition, we did not have objective measures of sleepiness or fatigue and did not evaluate participants' cardiovascular health or their response to CPAP treatment. Future research should address these limitations.

The present sample consisted of community volunteers who had moderately severe sleep apnea, many of whom also had substantial daytime complaints. All were recruited for a study of individuals with daytime sleepiness, fatigue, or sleep related concerns. Thus, the low fatigue and low sleepiness groups may have been under-represented. In addition, none were previously diagnosed with sleep apnea, suggesting the need for replication of the present results in a clinical sample. The fact that participants' sleep apnea was discovered through a research study, and not through medical consultation, highlights the need for better case-finding methods for primary care health professionals to identify candidates for polysomnographic evaluation [41].

Finally, another limitation of the study is that two of the groups had small sample sizes (HF and HS). Sample sizes in this study were sufficient to detect large effect sizes of .6–.7 S.D. between means at an α=.05 and β=.2. Increased sample sizes would allow detection of smaller between-group differences.

Conclusions

We believe that the present study, in which a newly diagnosed sample of individuals with sleep apnea was compared to a non-clinical, control sample without apnea, strengthens the case that fatigue is associated with sleep apnea at least as closely, if not more so, as is sleepiness. If more widely recognized, the presence of fatigue as a symptom of sleep apnea could increase appropriate referrals to sleep clinics.

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References

[1] Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. Chest 1993;103:30–6.
[2] Hossain JL, Ahmad P, Reinish LW, Kayumov L, Hossain NK, Shapiro C. Subjective fatigue and subjective sleepiness: Two independent consequences of sleep disorders? J Sleep Res 2005;14:245–53.
[3] Dinges D. An overview of sleepiness and accidents. J Sleep Res 1995; 4:4–14.
[4] Chervin RD. Sleepiness, fatigue, tiredness, and lack of energy in obstructive sleep apnea. Chest 2000;118:372–9.
[5] Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 1986;9:519–24.
[6] Reynolds CF, Coble PA, Kupfer DJ, Holzer BC. Application of the multiple sleep latency test in disorders of excessive sleepiness. Electroencephalogr Clin Neurophysiol 1982;53:443–52.
[7] Roth T, Hartse KM, Zorick F, Conway W. Multiple naps and the evaluation of daytime sleepiness in patients with upper airway sleep apnea. Sleep 1980;3:425–39.

[8] Arand D, Bonnet M, Hurwitz T, Mitler M, Rosa R, Sangal RB. The clinical use of the MSLT and MWT. Sleep 2005;28:14–5.
[9] Barbe F, Mayoralas LR, Duran J, Masa JF, Maimo A, Montserrat JM, et al. Treatment with continuous positive airway pressure is not effective in patients with sleep apnea but no daytime sleepiness. Ann Int Med 2001;134:1015–23.
[10] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–5.
[11] Libman E, Creti L, Rizzo D, Jastremski M, Bailes S, Fichten CS. Descriptors of fatigue in Chronic Fatigue Syndrome. J Chronic Fatigue Syndr 2007;14:37–45.
[12] Saito Y, Iemitsu M, Otsuki T, Maeda S, Ajisaka R. Gender differences in brachial blood flow during fatiguing intermittent handgrip. Med Sci Sports Exerc 2008;40:684–90.
[13] American Sleep Disorders Association. International Classification of Sleep Disorders: Diagnostic and Coding Manual (ICSD-2). American Academy of Sleep Medicine, 2005.
[14] Fichten CS, Creti L, Amsel R, Brender W, Weinstein N, Libman E. Poor sleepers who do not complain of insomnia: myths and realities about psychological and lifestyle characteristics of older good and poor sleepers. J Behav Med 1995;8:189–223.
[15] Marchini EJ, Coates TJ, Magistad JG, Waldum SJ. What do insomniacs do, think, and feel during the day? A preliminary study. Sleep 1983;6:147–55.
[16] Martin BJ. Sleep loss and subsequent exercise performance. Acta Phys Scand 1988;133:28–32.
[17] Shepard JW. Sleep, biorhythms and human performance. Sports Med 1984;1:11–37.
[18] Stepanski E, Koshorek G, Zorick F, Glinn M, Roehrs T, Roth T. Characteristics of individuals who do or do not seek treatment for chronic insomnia. Psychosomatics 1989;30:421–7.
[19] Lichstein KL, Means MK, Noe SL, Aguillard RN. Fatigue and sleep disorders. Behav Res Ther 1997;35:733–40.
[20] Pigeon WR, Sateia MJ, Ferguson RJ. Distinguishing between excessive daytime sleepiness and fatigue: Toward improved detection and treatment. J Psychonom Res 2003;54:61–9.
[21] Bailes S, Libman E, Baltzan M, Amsel R, Schondorf R, Fichten CS. Brief and distinct empirical sleepiness and fatigue scales. J Psychosom Res 2006;60:605–13.
[22] Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC. Quantification of sleepiness: a new approach. Psychophysiology 1973;10:431–7.
[23] Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14:540–5.
[24] Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121–3.
[25] Chalder T, Berelowitz G, Pawlikowska T, Watts L, Wessely S, Wright D, et al. Development of a fatigue scale. J Psychosom Res 1993;37: 147–53.
[26] Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 Health Survey: Manual and Interpretation Guide. Lincoln (R.I.): QualityMetric Incorporated, 1993.
[27] Fichten CS, Libman E, Creti L, Amsel R, Tagalakis V, Brender W. Thoughts during awake times in older good and poor sleepers: the Self-Statement Test: 60+. Cog Ther Res 1998;22:1–20.
[28] Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. Manual for the State-Trait Anxiety Inventory (Form Y). Palo Alto (Calif): Consulting Psychologists Press, 1983.
[29] Beck A, Steer R, Brown G. BDI-II: Beck Depression Inventory manual. 2nd ed. San Antonio: The Psychological Corporation, Harcourt Brace & Company, 1996.
[30] Bailes S, Baltzan M, Rizzo D, Fichten CS, Amsel R, Creti L, et al. Fatigue, psychological distress, insomnia, sleep disorder, and sleepiness: Discriminant validity of 5 subscales from a lengthy sleep questionnaire battery. Presentation at the Canadian Psychological Association annual convention, Ottawa. Abstracted in Canadian Psychology, 48(2a), 2007. p. 118–9. Abstract #37.
[31] American Thoracic Society. Indications and standards for cardiopulmonary sleep studies. Am Rev Respir Dis 1989;139:559–68.
[32] Rechtschaffen A, Kales A, editors. A manual of standardized terminology, techniques, and scoring system for sleep stages of human subjects. Washington, DC: National Institute of Health, Publication 204, U.S. Government Printing Office, 1968.
[33] ASDA (American Sleep Disorders Association) Sleep Disorders Task Force. EEG arousals: scoring rules and examples. Sleep 1992;15: 173–84.
[34] American Academy of Sleep Medicine Task Force (AASM). Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667–89.
[35] ASDA Atlas Task Force of the American Sleep Disorders Association. Recording and scoring leg movements. Sleep 1993;16:749.
[36] Vazquez JC, Tsai WH, Flemons WW, Masuda A, Brant R, Hajduk E, et al. Automated analysis of digital oximetry in the diagnosis of obstructive sleep apnea. Thorax 2000;55:302–7.
[37] Baghai-Ravary R, Quint JK, Golding JJP, Hurst JR, Donaldson GC, Wedzicha JA. Determinants and impact of fatigue in patients with chronic obstructive disease. Resp Med 2009;103:216–23.
[38] Breslin E, van der Schans C, Bruekink BS, Meek P, Mercer K, Volz W, et al. Perception of fatigue and quality of life in patients with COPD. Chest 1998;114:958–64.
[39] Kappela M, Larson JL, Patel MK, Covey MK, Berry JK. Subjective fatigue, influencing variables and consequences in chronic obstructive pulmonary disease. Nurs Res 2006;55:10–7.
[40] Kapur VK, Resnick HE, Gottlieb DJ. Sleep disordered breathing and hypertension: does self-reported sleepiness modify the association? Sleep 2008;31:1127–32.
[41] Bailes S, Baltzan M, Rizzo D, Fichten CS, Grad R, Wolkove N, et al. Sleep disorder symptoms are common and unspoken in Canadian general practice. Fam Pract 2009;26:294–300.