

## **Sleep Assessment in a Population-Based Study of Chronic Fatigue Syndrome**

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**ABSTRACT** (298 words)

**Background** Chronic fatigue syndrome (CFS) is a disabling condition that affects approximately 800,000 adult Americans. The pathophysiology remains unknown and there are no diagnostic markers or characteristic physical signs or laboratory abnormalities. Most CFS patients complain of unrefreshing sleep and many of the postulated etiologies of CFS affect sleep. Conversely, many sleep disorders present similarly to CFS. Few studies characterizing sleep in unselected CFS subjects have been published and none have been performed in cases identified from population-based studies.

**Methods.** The study included 339 subjects (mean age 45.8 years, 77% female, 94.1% white) identified through telephone screen in a previously described population-based study of CFS in Wichita, Kansas. They completed 2 self-administered sleep questionnaires. Scores for five sleep factors (insomnia/hypersomnia, non-restorative sleep, excessive daytime somnolence, sleep apnea, and restlessness) in the Centre for Sleep and Chronobiology's Sleep Assessment Questionnaire<sup>®</sup> (SAQ<sup>®</sup>) were dichotomized based on threshold. The Epworth Sleepiness Scale score was used as a continuous variable.

**Results.** 81.4% of subjects had an abnormality in at least one SAQ<sup>®</sup> sleep factor. Subjects with sleep factor abnormalities had significantly lower wellness scores but statistically unchanged fatigue severity scores compared to those without SAQ<sup>®</sup> abnormality. CFS subjects had significantly increased risk of abnormal scores in the non-restorative (adjusted odds ratio [OR] = 28.1; 95% confidence interval [CI]= 7.4-107.0) and restlessness (OR = 16.0; 95% CI = 4.2-61.6) SAQ<sup>®</sup> factors compared to non-fatigued, but not for factors of sleep apnea or excessive daytime somnolence. This is consistent with studies finding that, while fatigued, CFS subjects are not

sleepy. A strong correlation (0.78) of Epworth score was found only for the excessive daytime somnolence factor.

**Conclusions.** SAQ<sup>®</sup> factors describe sleep abnormalities associated with CFS and provide more information than the Epworth score. Validation of these promising results will require formal polysomnographic sleep studies.

## INTRODUCTION

Chronic Fatigue Syndrome (CFS) is a disabling condition affecting an estimated 142 to 560 per 100,000 adults in the United States.<sup>1,2</sup> The pathophysiology remains unknown, and infectious etiologies, immune dysfunction, stress, dysautonomias, and abnormalities in the hypothalamic-pituitary axis are among current hypotheses being investigated. Of course none of these hypotheses are mutually exclusive as known and postulated pathways inter-relate and integrate these diverse physiologic processes.

Sleep physiology may be central to understanding CFS. Unrefreshing sleep is the most prevalent of the 8 CFS case-defining symptoms, being endorsed by 88-95% of cases identified in population-based studies<sup>1,3</sup> and 70-80% of cases in clinic-based studies.<sup>4,5</sup> Most of the postulated etiologies of CFS affect sleep, e.g. infection, cytokines, stress, and hormones. Sleep deprivation or experimental disruption of sleep is known to produce many of the features of CFS, including fatigue, impaired cognition, and even joint pain and stiffness.<sup>6-10</sup>

While sleep problems figure prominently in CFS symptoms, primary sleep disorders, such as sleep apnea and narcolepsy, are exclusionary conditions for the diagnosis under the current research case definition.<sup>11</sup> According to DSM-IV classification, primary sleep disorders are those not related to known etiologies of sleep pathology, e.g. mental disorders (most commonly depression or anxiety), medical conditions, and substance use (including alcohol, caffeine, medications and illegal drugs).<sup>12</sup> Clearly primary sleep disorders must be considered in the differential diagnosis of CFS, as most patients with these conditions will respond to therapy. However, at some level, including sleep abnormalities as both a case defining symptom and an exclusionary diagnosis introduces confusion into CFS diagnosis, management and research.

Is CFS a condition that explains sleep disturbance, or could an underlying sleep pathology result in or contribute to development of CFS? Accurately identifying the relationship of sleep abnormalities to CFS requires as a start, characterizing sleep in persons with CFS. Formal sleep studies require all-night polysomnography and a multiple sleep latency test under standardized environmental conditions. Polysomnography records brain, muscle, heart, eye, and respiratory activity as well as oxygen saturation throughout the night. Results define sleep architecture, duration and timing of sleep, respiratory obstruction and abnormal limb movements. Interpretation requires expertise and judicious interpretation. The multiple sleep latency test is a measure of how quickly subjects will fall asleep when asked to do so while lying down and monitored in a quiet dark room. The subject's brain activity is monitored with electrodes during the four or five 20-minute nap opportunities given at two-hour intervals over the course of the day. The time from starting the nap to the onset of sleep defined by the brain electrical activity (sleep latency) detects whether there is a predisposition to daytime sleepiness.

Because of the complexity and expense of formal sleep testing, few studies characterizing sleep in unselected CFS subjects are available, and none have been performed in cases identified from population-based studies. Inefficient sleep (i.e. more time in bed awake) has been consistently documented.<sup>4, 13 16</sup> Several studies have also described an alpha electroencephalogram (EEG) arousal disturbance during non-rapid eye movement sleep.<sup>17, 18</sup> The reported prevalence of undiagnosed primary sleep disorders (sleep apnea, narcolepsy, and restless leg syndrome/periodic limb movements in sleep) varies from 0% to 50% of CFS patients.<sup>4,5,13,14,16,19,20</sup> This no doubt reflects differences in case ascertainment as well as selection criteria, and emphasizes the importance of excluding a treatable primary sleep disorder when evaluating patients with unexplained fatigue.

The purpose of this study was to begin the process of accurately describing sleep characteristics of persons with CFS identified in the general population of Wichita, Kansas.<sup>2</sup> We used two brief self-administered questionnaires to screen and profile sleep abnormalities; the Epworth Sleepiness Scale<sup>21</sup> and the Centre for Sleep and Chronobiology's Sleep Assessment Questionnaire<sup>®</sup> (SAQ<sup>®</sup>).<sup>22-25</sup> We correlated results with subject variables potentially associated with sleep abnormalities (age, sex, neck circumference, and body mass index [BMI]) and with measures of wellness and fatigue. If validated by formal sleep studies, simple screening tools like the SAQ<sup>®</sup> have the potential to improve the accuracy of case ascertainment in population-based epidemiologic studies and to facilitate the identification of treatable primary sleep disorders in patients presenting with clinically unexplained fatigue.

## METHODS

### Study Design

Details of the population-based study developed to estimate the prevalence and incidence of CFS are published.<sup>2</sup> In brief, a random digit-dialing telephone survey screened 56,146 people, interviewed in detail 3,528 who reported fatigue of at least 1 month's duration and 3,634 randomly selected non-fatigued people. The detailed interview was structured to detect exclusionary medical and psychiatric diagnoses and identify criteria specified in the 1994 research case definition of CFS.<sup>11</sup> At baseline all subjects meeting criteria for CFS on the telephone and randomly selected non-fatigued subjects were invited to clinic for further medical and psychiatric evaluation. In accordance with CFS case definition, subjects endorsing sleep apnea or narcolepsy in the telephone interview or during the clinical evaluation were excluded. However other potential primary sleep disorders were not specifically addressed with targeted questions. In the second year of the study all subjects previously evaluated at the clinic, and newly identified fatigued subjects fulfilling criteria for CFS were invited to clinic. Subjects evaluated in clinic during the second year completed the SAQ<sup>®</sup> and Epworth Sleepiness Scale described below. This study adhered to human experimentation guidelines of the U.S. Department of Health and Human Services. All participants were volunteers who gave informed consent.

### Fatigue groups

Data from both the baseline and second year study visits were used to classify subjects into one of 6 mutually exclusive fatigue groups:

1] Never fatigued. Those who did not report fatigue at either baseline or year two, and are without medical or psychiatric exclusions;

2] Not currently fatigued but fatigued at baseline. Those who reported fatigue at baseline but were not classified as CFS, and who report no fatigue at year two and are without medical or psychiatric exclusions;

3] Insufficient symptoms or fatigue. Fatigued subjects without exclusionary diagnoses but with insufficient symptoms or fatigue severity to be classified as CFS at either visit;

4] Medical or psychiatric exclusions. Subjects with current medical or psychiatric conditions that could explain fatigue and are exclusions for the diagnosis of CFS;

5] Chronic fatigue syndrome in remission. Subjects classified as CFS at baseline who were fatigued at year two, do not have medical or psychiatric exclusions, but lack number of symptoms or fatigue severity for current diagnosis of CFS;

6] CFS. Subjects currently meeting all criteria of the 1994 CFS research case definition.<sup>11</sup>

### Sleep Questionnaires

The SAQ<sup>®</sup> was developed to screen for primary sleep disorders and sleep abnormalities in epidemiologic studies.<sup>22-25</sup> The questionnaire includes 17 items scored on a 5 point Likert scale from 1 (never) to 5 (always). Data from questionnaires completed by subjects referred for formal sleep testing at the Sleep Disorders Clinic of the Centre for Sleep and Chronobiology as well as 30 healthy volunteers similarly evaluated as controls were used to define the performance of the questionnaire. Principal component analysis identified 6 factors labeled (i) insomnia/hypersomnia, (ii) non-restorative sleep, (iii) sleep schedule disorder, (iv) excessive daytime somnolence, (v) sleep apnea, and (vi) restlessness. Threshold values for detection of an abnormality in each factor were selected to optimize sensitivity and specificity using receiver operator characteristic curves to distinguish factor scores from subjects with validated primary

sleep disorders and controls. The insomnia/hypersomnia factor (insomnia) factor was normed based on data from 56 subjects with a diagnosis of psychophysiological or idiopathic insomnia. The non-restorative sleep factor score threshold was determined based on data for 81 CFS or fibromyalgia patients with alpha EEG arousal disturbance during non-rapid eye movement sleep. The excessive daytime somnolence factor score threshold was determined based on data from 32 subjects with narcolepsy or idiopathic hypersomnolence. The threshold for the sleep apnea score was determined from data on 450 subjects with obstructive or central sleep apnea, and that for the restlessness factor based on data from 109 subjects with restless leg syndrome or periodic involuntary limb movements in sleep. Thresholds for the sleep schedule factor score have not been determined so this factor was not included in the current study. Factor scores above threshold indicate the presence of a sleep abnormality characteristic of the primary sleep disorder used to norm the score. Factor scores above threshold had sensitivities varying between 79-100% and specificities between 68-96% for detection of abnormality in the respective primary sleep disorder group.<sup>26</sup> Completed SAQs<sup>®</sup> were sent to the Sleep Disorder Clinic of the Centre for Sleep and Chronobiology for blind scoring.

The Epworth Sleepiness Scale was designed to distinguish the daytime sleepiness experienced by narcoleptic patients from that of normal subjects. It consists of eight questions asking the respondent to rate the potential for falling asleep in sedentary situations on a 4-point Likert scale from 0 (never) to 3 (high chance).<sup>21</sup> The total of the responses (0-24) is the Epworth score. Using a cut-off of >10, the Epworth scores had 93.5% sensitivity and 100% specificity for distinguishing narcoleptic subjects from controls.<sup>27</sup> We used the score as a continuous variable.

### Statistical Analyses

We used F-tests, t-tests, or Kruskal-Wallis tests to compare groups with respect to

continuous variables and  $\chi^2$  or Fisher-exact tests for categorical data. Pairwise comparisons were performed using the Bonferroni adjustment. BMI was categorized according to NIH clinical guidelines (<18.5 underweight, 18.5 to 24.9 normal, 25.0 to 29.9 overweight, 30.0 to 39.9 obese,  $\geq 40$  extreme obesity).<sup>28</sup> Men with neck circumference  $\geq 43.18$ cm (17 inches) and women with neck circumference  $\geq 40.64$ cm (16 inches) were classified as having large neck sizes, a correlate of sleep apnea.<sup>29</sup> Univariate logistic regression models estimated odds ratios and 95% confidence intervals for the associations between SAQ<sup>®</sup> factors above threshold, age, sex, BMI, neck circumference, fatigue severity (measured by the Fatigue Assessment Instrument<sup>30</sup>) and self-reported wellness scores (assessed from the question: “During the past 4 weeks, where would you place yourself in terms of energy, wellness, and ability to complete your every day activities on a scale from 1 to 100?”). Epworth scores were correlated with SAQ<sup>®</sup> factor scores, age, BMI, neck circumference, fatigue severity and wellness scores. Because we were primarily interested in the association between sleep abnormalities and fatiguing illnesses, and because of the correlations among the potential predictors of sleep disorders, we used a forward selection process to determine multivariate models. We included the fatigue groups first, and then selected from the remaining pool of variables. We used the Hosmer and Lemeshow statistic to evaluate how well the data fit the final logistical model.<sup>31</sup> All tests were 2-sided and p-values were considered significant if they did not exceed 0.05. All analyses were performed using SAS version 8.1 (SAS Institute, Inc., Cary, NC).

## RESULTS

### Sample characteristics

One subject attending the clinic was dropped from analysis because missing data did not permit scoring of any factor in the SAQ<sup>®</sup>. Demographic and clinical characteristics of the remaining 339 subjects in the sample are shown in Table 1 along with the distribution of these characteristics by fatigue group. Over half the fatigued subjects (145/277, 52.3%) as well as one not fatigued subject had exclusionary medical or psychiatric conditions identified during the clinical evaluation. Medical exclusions identified during the clinic visit included abnormal blood or urine tests, abnormal Romberg test, adrenal insufficiency, bladder tumor, BMI = 47, cerebral palsy, chronic hepatitis, emphysema, heart disease within 2 years of evaluation, hypertension, hypothyroidism, inflammatory bowel disease, kidney cancer, lupus, melanoma, uncontrolled diabetes, rheumatoid arthritis, self-reported sleep apnea and narcolepsy, and major surgery within the past year. Psychiatric disorders included anorexia or bulimia nervosa, bipolar disorder, delusional disorder, and major depressive disorder with melancholic features.

Age, sex, race, education, income and mean neck circumference were similar across groups, as was duration of fatigue. The groups differed significantly with respect to BMI ( $P = 0.0157$ ). Never fatigued subjects were significantly less obese than subjects who had ever been fatigued (mean = 25.3, standard deviation [SD] = 4.7, and mean = 28.9, SD = 6.4, respectively,  $P < 0.0001$ ). The mean wellness scores were significantly higher in never fatigued and subjects not currently reporting fatigue than in any of the currently fatigued groups ( $P < .0017$ ). Fatigue severity was evaluated only in currently fatigued subjects. The mean scores differed across the fatigue groups, with lowest value reported in the ISF group and highest in CFS. Interestingly,

the CFS-remission and CFS groups had statistically indistinguishable mean wellness and fatigue severity scores.

### Abnormalities in SAQ<sup>®</sup> factor scores

Abnormalities in each of the 5 SAQ<sup>®</sup> sleep factors dichotomized according to score above or below threshold are summarized in Table 2. Sample sizes varied slightly (n = 331 to 339) because of missing data for individual sleep factor scores. The never fatigued group served as reference when assessing the association between fatiguing illnesses and abnormalities in SAQ<sup>®</sup> factors of sleep apnea, restlessness and excessive daytime somnolence. For the insomnia and excessive daytime somnolence factors, the never and not currently fatigued groups were combined as reference because insufficient numbers of never fatigued subjects scored positive for these factors.

Overall, 81.4% of study subjects scored positive in at least one sleep factor. Those with at least one abnormal sleep factor had significantly lower wellness scores (mean = 48.9, SD = 20.9) than those without any (mean = 71.7, SD = 20.9),  $P < 0.0001$ ). However fatigue severity scores were not significantly different in these two groups. Restricting analysis of wellness scores to those currently fatigued showed a similar effect; those with one or more abnormal sleep factors had lower wellness scores (mean = 46.0, SD = 19.0) than those with no abnormalities (mean = 56.7, SD = 16.4),  $P = 0.006$ . Abnormalities in the sleep apnea and insomnia factors were identified least frequently (approximately 28% of sample) and restlessness most frequently (51.6%). The mean number of abnormal sleep factors per individual varied by fatigue status ( $P < 0.0001$ ), being highest in subjects with an exclusionary diagnosis (2.4) and lowest in those never fatigued (0.4).

Univariate odds ratios for demographic and fatigue group variables showed differences for each of the five SAQ<sup>®</sup> sleep factors. Women were almost half as likely as men to be positive for sleep apnea (OR = 0.57) and about twice as likely to be positive for the non-restorative sleep

and insomnia factors (OR = 2.26 and 2.09 respectively). Increased age was minimally associated only with non-restorative and insomnia factors. BMI as a continuous variable showed an increased association with the sleep apnea, restlessness and excessive daytime somnolence factors. Most of the BMI effect on sleep factors was concentrated in the obesity/extreme obesity stratum ( $\geq 30$ ; OR = 1.93, 2.62, and 2.52 respectively). The Pearson correlation between neck circumference and BMI was 0.55 (0.69 among men, 0.72 among women). Neck circumference as a continuous variable was only significantly associated with the sleep apnea factor.

For all sleep factors, fatigued subjects tended to have significantly increased odds ratios compared to non-fatigued. However there was considerable variation in the extent of this association. The sleep apnea and excessive daytime somnolence factors showed the least association with fatigue groups. Significantly increased odds ratios for the sleep apnea factor were noted only for insufficient symptoms/fatigue and exclusionary diagnoses groups (3.66 and 2.92, respectively). Increased odds ratios for excessive daytime somnolence were found only for insufficient symptoms/fatigue, exclusionary diagnoses and CFS-remission groups (5.15, 5.75 and 3.78 respectively). All fatigue groups showed significantly increased odds ratio for the insomnia factor, with the magnitude being greatest for the subjects with exclusionary diagnoses (12.73) and similar for CFS-remission and CFS groups (8.05 and 9.66 respectively). By contrast, while the odds ratios for the restlessness and non-restorative factors were also increased in all fatigue groups, the magnitude of the odds ratio was greatest for CFS (18.5 for restlessness and 24.16 for nonrestorative) and lowest in CFS-remission (5.89 for restlessness and 12.89 for nonrestorative).

Multivariate logistic regression models with forward selection estimated the additional effect of female sex, age, categories of BMI, and neck circumference in centimeters, after including the fatiguing illness subgroups. Again different predictors were associated with the

individual sleep factor abnormalities (Table 3). The model did not change the pattern or magnitude of the associations of fatigue groups with each sleep factor noted in the univariate analysis. The strongest association was between CFS and non-restorative sleep. CFS was also more strongly associated than any other fatigue category with the restlessness factor. In addition the CFS-remission group showed odds ratio only half that of CFS for the non-restorative factor and less than half that of CFS for restlessness. Subjects with medical or psychiatric exclusionary conditions showed the strongest association with insomnia and were second only to CFS in strength of association with non-restorative sleep and restlessness. As might be expected, larger neck circumference remained significantly associated with abnormalities in the sleep apnea factor after accounting for fatiguing illnesses. Having a BMI  $\geq 30$ , compared with normal BMI, predicted restlessness, and excessive daytime sleepiness, but not sleep apnea. Older current age was the only predictor of non-restorative sleep, after fatiguing illness was considered. No additional predictors entered the model for insomnia after including the fatigue groups.

Description of the Epworth scale, overall, by sex and by fatigue group is displayed in Table 4. Non-fatigued subjects had scores similar to those described in normal controls<sup>21</sup> and fatigued subjects had scores in the high normal range. Significant differences were found only for the comparison of the never fatigued and exclusionary diagnoses groups and the never fatigued and insufficient symptoms/fatigue groups ( $P < 0.0017$ ). Females had slightly higher mean scores than males, but the difference was not significant. Table 5 displays the Pearson correlation coefficients between the Epworth score and the SAQ<sup>®</sup> factor scores, age and clinical variables. The only correlation of note was with the excessive daytime somnolence factor (0.78).

## DISCUSSION

The vast majority of the study population (81.4%) had an abnormal score in at least one sleep factor. The prevalence of sleep abnormalities is lowest in the never fatigued group, but with nearly one-third (29.3%) scoring positive in one or more factors, the value is higher than might be expected. However the pattern of the sleep abnormalities in this control group (e.g. highest for excessive daytime somnolence and sleep apnea) is compatible with the poor sleep hygiene associated with the modern lifestyle as well as with unrecognized sleep apnea in subjects not complaining of sleep-related symptoms. Interestingly, fatigued subjects with sleep factor abnormalities had significantly lower wellness scores but statistically unchanged fatigue severity scores compared to those with no abnormalities. This suggests that the SAQ<sup>®</sup> measures of sleep abnormalities are more important for the over-all sense of well-being than for fatigue. Other studies have also found that measures of sleep pathology did not correlate with measures of function.<sup>15,16</sup>

Each sleep factor showed a rather characteristic risk profile that was consistent with the intended construct for that factor. For example, a decreased odds ratio for females and an increased odds ratio for increased neck size were found only for the sleep apnea factor, consistent with known risks for polysomnography validated sleep apnea. The non-restorative factor was normed based on CFS and fibromyalgia patients with the alpha EEG sleep disorder and subjects with CFS were 28 times more likely to have abnormalities in this factor compared to non-fatigued subjects. Interestingly, CFS subjects currently failing to meet CFS criteria because of a reduction in symptoms or fatigue (CSF-R) also had significantly reduced odds for scoring abnormal in this factor. These observations are encouraging and demonstrate the utility of the SAQ factors to characterize or profile sleep problems in fatigued subjects. Abnormalities

in the nonrestorative sleep factor may also predict the presence of the alpha EEG sleep disorder, a suggestion requiring polysomnographic studies for confirmation.

CFS subjects were also 16 times more likely than those never fatigued to screen positive for the restlessness factor. Again remission was associated with a reduction in the odds ratio for this factor. Abnormalities in this factor may relate to the inefficient sleep of CFS subjects.<sup>4, 13-16</sup>

Interestingly, abnormalities in the sleep apnea and excessive daytime somnolence factors were least associated with fatigue groups and neither was significantly associated with CFS. Again this is consistent with studies finding that, while fatigued, CFS subjects are not sleepy. The excessive daytime somnolence factor scores showed a strong correlation with the Epworth Sleepiness scale that was designed to detect pathologic sleepiness.

Second only to the CFS fatigue group, subjects with exclusionary medical or psychiatric conditions were significantly more likely than those not fatigued to have an abnormal score in the restlessness, non-restorative and insomnia sleep factors. The high prevalence of sleep abnormalities in this group could be expected based on the known impact of medications, psychiatric disease and medical illness on sleep.

The SAQ<sup>®</sup> was developed for epidemiologic screening of subjects to identify those to be referred for formal sleep testing. Cut-off values for the five separate sleep factors were established relative to specific primary sleep disorders versus healthy controls. Factor scores above threshold are intended to indicate the presence of a sleep abnormality characteristic of the primary sleep disorder used to norm the score. However factor scores do not map in a direct one-to-one fashion to a primary sleep disorder. For example, while the sleep apnea factor was normed to optimize sensitivity and specificity of a positive score in polysomnography validated

sleep apnea subjects, these subjects could also score positive in other factors. This is the first published exploration of SAQ<sup>®</sup> results in an epidemiologic study of fatigued subjects.

The primary limitation of this study is the lack of polysomnography and multiple sleep latency test results to correlate with SAQ<sup>®</sup> findings. In addition, in this initial exploration of sleep abnormalities in fatiguing illnesses we did attempt to control for medication. The cross-sectional study design cannot distinguish whether sleep abnormalities are a result or cause of CFS.

## CONCLUSIONS

Despite these limitations, our findings have importance for the clinical assessment of unexplained fatiguing illnesses as well as for research. Both sleep screening instruments were easy to administer and identified potential sleep abnormalities, however the SAQ<sup>®</sup> provided considerably more information than the Epworth Sleepiness Scale. The SAQ<sup>®</sup> sleep factors of non-restorative sleep and restlessness are particularly associated with CFS. Further study of the inter-relatedness of sleep pathology and chronic fatigue is warranted. We are planning to conduct formal sleep laboratory studies in this population to provide data that will clarify the limits of interpretation of the SAQ<sup>®</sup> and increase the clinical and research utility of this simple, relatively inexpensive screening questionnaire to detect and characterize treatable primary sleep disorders in the community.

**Competing interests**

No competing interests are declared

**Author's contributions**

ERU had primary responsibility for study design, interpretation of results and drafted the manuscript. RN carried out data analysis participated in interpretation, collaborated in study design, collaborated in data collection, and collaborated in preparing the manuscript. HM designed the sleep assessment questionnaire and scoring algorithms, participated in interpretation of results, and drafting of the manuscript. AC and CS carried out scoring and interpretation of the sleep assessment questionnaire and participated in drafting the manuscript. MR participated in the design of the study, data collection, and preparation of the manuscript. WCR is principal investigator of the study from which this data derived, participated in study design, data collection, interpretation of results, and drafting the manuscript. All authors read and approved the final manuscript.

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Table 1: Demographic and clinical characteristics overall and by fatigue group

	Overall	NF	NF F	ISF	M/P	CFS-R	CFS
No. (%)	339	41 (12.1)	21 (6.2)	90 (26.6)	145 (42.8)	18 (5.3)	24 (7.1)
Mean Age, years (SD)	45.8 (10.9)	46.9(13.0 )	40.6(8.2)	44.5(11.2)	47.3(10.5 )	46.4(7.5)	44.7(10.4)
Female (%)	77.0	63.4	71.4	74.4	83.5	72.2	79.2
White (%)	94.1	92.7	100.0	91.1	96.6	83.3	95.8
Education>High School(%)	65.5	80.5	66.7	62.2	63.5	55.6	70.8
Income > \$40,000/yr (%)	47.5	58.5	61.9	44.4	43.5	66.7	37.5
Mean BMI (SD)*	28.5 (6.3)	25.3(4.7)	28(5.7)	28.6(6.4)	29.5(6.7)	28.6(5.2)	28.2(6.0)
<18.5: Underweight (%)	3.6	7.3	4.8	2.2	2.8	0.0	8.3
18.5-24.9: Normal (%)	25.7	36.6	23.8	27.8	23.6	22.2	16.7
25-29.9: Overweight (%)	30.5	41.5	33.3	26.7	27.8	38.9	33.3
30-39.9: Obesity (%)	32.8	14.6	33.3	33.3	36.1	33.3	41.7
≥40: Extreme obesity (%)	7.4	0.0	4.8	10.0	9.7	5.6	0.0

Neck circumference (cm) Mean (SD)	36.4 (3.8)	35.7 (3.9)	36.4 (3.7)	36.8 (4.1)	36.4 (3.8)	36.3 (2.6)	36.3 (3.3)
≥43.18 cm in males (%)	12.8	0.0	16.7	17.4	20.8	0.0	0.0
≥40.64 cm in females (%)	6.3	7.7	0.0	12.1	4.2	7.7	0.0
Years fatigued, median (Range)	6.8 (0.3-55.5)	-----	-----	5.9 (0.5-40.8)	7.2 (0.3-55.5)	8.6 (2.1- 39.7)	6.5 (1.4-47.8)
Mean Wellness score (SD) <sup>†</sup>	53.0 (22.7)	85.5(14.9 )	70.5(17.2 )	51.9 (17.0)	44.0 19.3)	56.4 19.2)	39.8 (18.3)
Fatigue severity score Mean (SD) <sup>†</sup>	5.4 (1.0)	-----	-----	5.0 (0.9)	5.5 (1.0)	5.6 (0.8)	6.0 (0.6)

\*P=0.0157; <sup>†</sup>P<0.0001

NF - never fatigued; NF|F – baseline fatigue currently not fatigued; ISF – insufficient symptoms or fatigue for CFS;  
M/P – medical or psychiatric exclusion; CFS-R – baseline CFS currently remission; CFS – currently CFS

Table 2: Univariate odds ratio for abnormality in SAQ<sup>®</sup> factors by subject characteristics

Abnormality in SAQ <sup>®</sup> Factor: Scores Above Threshold									
	Any factor			Sleep apnea			Restlessness		
	%	No.	OR (95% CI)	%	No.	OR (95% CI)	%	No.	OR (95% CI)
Total	81.4	339		27.8	331		51.6	337	
Fatigue group*									
NF	29.3	41	1.0	12.2	41	1.0	9.8	41	1.0
NF F	67.7	21	<b>4.83(1.56,14.95)</b>	33.3	21	3.60(0.98,13.25)	57.1	21	<b>12.33(3.21,47.37)</b>
ISF	86.7	90	<b>15.71(6.34,38.89)</b>	33.7	86	<b>3.66(1.30,10.33)</b>	48.9	90	<b>8.85 (2.91,26.88)</b>
M/P	93.1	145	<b>32.62(12.87,82.68)</b>	28.9	142	<b>2.92 (1.07,7.97)</b>	63.6	143	<b>16.19(5.46,47.97)</b>
CFS-R	88.9	18	<b>19.33 (3.84,97.34)</b>	27.8	18	2.77(0.69,11.14)	38.9	18	<b>5.89 (1.45,23.89)</b>
CFS	87.5	24	<b>16.91 (4.24,67.51)</b>	21.7	23	2.00 (0.51,7.81)	66.7	24	<b>18.5 (4.86,70.36)</b>
Males	74.4	78	1.0	36.8	76	1.0	49.4	77	1.0
Females	83.5	261	1.75 (0.96,3.20)	25.1	255	<b>0.57 (0.33,0.99)</b>	52.3	260	1.13 (0.68,1.87)
Age (years)			1.02 (0.99,1.04)			1.00 (0.97,1.02)			1.00 (0.98,1.02)
BMI(continuous)			<b>1.09 (1.04,1.15)</b>			<b>1.05 (1.01,1.09)</b>			<b>1.05 (1.02,1.09)</b>
<18.5	75.0	12	1.08 (0.27,4.33)	8.3	12	0.34 (0.04,2.84)	50.0	12	1.56 (0.46,5.23)
18.5-24.9	73.6	87	1.0	20.9	86	1.0	39.1	87	1.0
25-29.9	77.7	103	1.25 (0.64,2.43)	27.5	102	1.43 (0.73,2.81)	47.6	103	1.41 (0.79,2.52)
≥30	89.7	136	<b>3.13 (1.51,6.50)</b>	33.9	130	<b>1.93 (1.03,3.64)</b>	62.7	134	<b>2.62 (1.50,4.56)</b>
Neck circ. (cm)			1.04 (0.97,1.13)			<b>1.13 (1.06,1.21)</b>			1.05 (0.99,1.11)
Small/normal	80.2	308	1.0	26.8	302	1.0	51.0	306	1.0
Large <sup>†</sup>	92.3	26	2.96 (0.68,12.87)	45.8	24	2.31 (1.00,5.36)	61.5	26	1.54 (0.68,3.50)

\* NF and NF|F reference for non-restorative sleep and insomnia; NF reference for all other SAQ Factors

<sup>†</sup> males ≥43.18, females ≥ 40.64 cm. OR = Odds ratios, CI = 95% confidence interval

NF - never fatigued; NF|F – baseline fatigue currently not fatigued; ISF – insufficient symptoms or fatigue for CFS;  
 M/P – medical or psychiatric exclusion; CFS-R – baseline CFS currently remission; CFS – currently CFS  
 Table 2 (cont'd.): Univariate odds ratio for abnormality in SAQ<sup>®</sup> factors by subject

characteristics

Abnormality in SAQ <sup>®</sup> Factor: Scores Above Threshold									
	Non-restorative sleep			Insomnia			EDS		
	%	No.	OR(95%CI)	%	No.	OR(95%CI)	%	No.	OR (95% CI)
Total	40.1	337		28.2	333		46.6	335	
Fatigue Status*									
NF	2.4	41	1.0	0.0	40	1.0	17.5	40	1.0
NF F	14.3	21	1.0	14.3	21	1.0	33.3	21	2.36 (0.70,7.98)
ISF	25.6	90	<b>4.98(1.63,15.23)</b>	24.4	90	<b>6.25(1.78,21.96)</b>	52.2	90	<b>5.15(2.07,12.86)</b>
M/P	59.0	144	<b>20.89(7.19,60.66)</b>	39.7	141	<b>12.73(3.80,42.63)</b>	54.9	142	<b>5.75(2.38,13.85)</b>
CFS-R	47.1	17	<b>12.89(3.21,51.76)</b>	29.4	17	<b>8.05 (1.69,38.34)</b>	44.4	18	<b>3.77(1.10,12.99)</b>
CFS	62.5	24	<b>24.16(6.54,89.32)</b>	33.3	24	<b>9.66 (2.30,40.69)</b>	37.5	24	2.83(0.89,9.03)
Males	26.0	77	1.0	18.0	78	1.0	42.3	78	1.0
Females	44.2	260	<b>2.26 (1.29,3.98)</b>	31.4	255	<b>2.09 (1.11,3.95)</b>	47.9	257	1.25 (0.75,2.09)
Age (years)			<b>1.05 (1.02, 1.07)</b>			<b>1.03 (1.01,1.06)</b>			1.01 (0.99,1.03)
BMI(continuous)			1.00 (0.97,1.04)			1.02 (0.98,1.06)			<b>1.07 (1.03,1.11)</b>
<18.5	58.3	12	1.98 (0.58,6.75)	8.3	12	0.23 (0.03,1.84)	50.0	12	1.93(0.57,6.52)
18.5-24.9	41.4	87	1.0	28.7	87	1.0	34.1	85	1.0
25-29.9	33.3	102	0.71 (0.39,1.28)	24.0	100	0.78 (0.41,1.50)	43.6	101	1.49(0.82,2.71)
≥30	42.2	135	1.04 (0.60,1.79)	32.3	133	1.19 (0.66,2.14)	56.6	136	<b>2.52 (1.44,4.42)</b>
Neck circ. (cm)			0.96 (0.91,1.02)			0.99 (0.93,1.05)			1.06 (1.00,1.12)
Small/normal	40.5	306	1.0	28.4	303	1.0	46.1	304	1.0
Large	34.6	26	0.78 (0.34,1.80)	28.0	25	0.98 (0.40,2.43)	46.2	26	1.00 (0.45,2.24)

\* NF and NF|F reference for non-restorative sleep and insomnia; NF reference for all other SAQ Factors

† males  $\geq 43.18$ , females  $\geq 40.64$  cm. OR = Odds ratios, CI = 95% confidence interval

NF - never fatigued; NF|F – baseline fatigue currently not fatigued; ISF – insufficient symptoms or fatigue for CFS;

M/P – medical or psychiatric exclusion; CFS-R – baseline CFS currently remission; CFS – currently CFS

Table 3: Adjusted odds ratios and 95% confidence intervals for abnormalities in SAQ factors

using logistic regression models with forward selection

Variable*	Sleep Apnea	Restlessness	Non-restorative	Insomnia	Excessive Daytime Sleepiness
Fatigue group					
NF	1.0	1.0	1.0	1.0	1.0
NF F	3.50	<b>11.13(2.86,43.26)</b>	1.0	1.0	2.13(0.62,7.32)
ISF	(0.93,13.16)	<b>7.91(2.57,24.34)</b>	<b>5.37 (1.73,16.67)</b>	<b>6.25(1.78,21.96)</b>	<b>4.80(1.89,12.21)</b>
M/P	<b>3.50</b>	<b>14.19(4.73,42.55)</b>	<b>21.50(7.30,63.38)</b>	<b>12.73(3.80,42.63)</b>	<b>5.26(2.14,12.94)</b>
CFS-R	<b>(1.22,10.01)</b>	<b>5.23(1.27,21.57)</b>	<b>13.63 (3.33,55.81)</b>	<b>8.05 (1.69,38.34)</b>	3.48(0.99,12.25)
CFS	<b>2.83</b>	<b>16.02(4.17,61.55)</b>	<b>28.10</b>	<b>9.66 (2.30,40.69)</b>	2.41(0.74,7.82)
	<b>(1.02,7.83)</b>		<b>(7.38,106.99)</b>		
	2.74				
	(0.67,11.18)				
	2.06				
	(0.52,8.23)				
Female	---	---	---	---	---
Age (years)	---	---	<b>1.05 (1.02,1.07)</b>	---	---
BMI	---	---	---	---	---
<18.5		1.76(0.45,6.84)			2.57(0.70,9.35)
18.5-24.9		1.0			1.0
25-29.9		1.44(0.78,2.68)			1.60(0.86,2.98)
$\geq 30$		<b>2.18(1.21,3.91)</b>			<b>2.26(1.27,4.04)</b>
Neck circumference (cm)	<b>1.13</b>	---	---	---	---
	<b>(1.05,1.20)</b>				
Goodness-of-fit P <sup>†</sup>	0.9244	0.7933	0.0701	1.0000	0.6676

\*Fatigue groups were included in all models; other variables entered the models using a forward selection method

†Hosmer-Lemeshow statistic

---: variable did not satisfy forward selection algorithm

NF and NF|F reference for non-restorative sleep and insomnia; NF reference for all other SAQ Factors

NF - never fatigued; NF|F – baseline fatigue currently not fatigued; ISF – insufficient symptoms or fatigue for CFS;

M/P – medical or psychiatric exclusion; CFS-R – baseline CFS currently remission; CFS – currently CFS

Table 4: The Epworth scale by sex and fatigue group

	Mean (SD)	Median (Range)
All subjects	10.2 (5.3)	11.0 (0-23)
Male	9.6 (5.5)	9.0 (0-22)
Female	10.4 (5.3)	11.0 (0-23)
Fatigue groups*		
NF	6.0 (4.3)	5.0 (1-17)
NF F	8.4 (4.9)	7.0 (1-18)
ISF	11.1 (5.0)	11.0 (1-23)
M/P	11.3 (5.3)	12.0 (0-22)
CFS-R	9.8 (6.4)	8.5 (1-22)
CFS	9.4 (4.5)	9.5 (2-18)

\* P <0.0001

NF - never fatigued; NF|F – baseline fatigue currently not fatigued; ISF – insufficient symptoms or fatigue for CFS; M/P – medical or psychiatric exclusion; CFS-R – baseline CFS currently remission; CFS – currently CFS

Table 5: Correlation of Epworth scales with SAQ<sup>®</sup> factor scores, age, BMI, neck circumference, fatigue and wellness scores.

	Pearson correlation
SAQ <sup>®</sup> Factor	
Sleep Apnea	0.26
Restlessness	0.23
Non-restorative	0.22
Insomnia	0.11
<b>EDS</b>	<b>0.78</b>
Age	0.05
BMI	0.23
Neck circumference	0.10
Wellness score	-0.26
Fatigue severity score	0.02