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ORIGINAL ARTICLE

Sleepiness, fatigue, and risk of obstructive sleep apnea using the STOP-BANG questionnaire in multiple sclerosis: a pilot study

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Abstract
Purpose This study aims: (1) to identify patients with multiple sclerosis (MS) who are at high risk for obstructive sleep apnea (OSA) by utilizing the STOP-BANG questionnaire and (2) to evaluate the relationship between OSA risk as determined by the STOP-BANG questionnaire and self-reported sleepiness and fatigue using the Epworth Sleepiness Scale (ESS) and the Fatigue Severity Scale (FSS), respectively.
Methods A total of 120 consecutive patients presenting to the UC Davis Neurology MS Clinic were invited to participate in an anonymous survey. The exclusion criteria were: age <18 years, indefinite MS diagnosis, or incomplete survey.
Results There were 103 subjects included in our study: 42% of subjects (n=43) met the criteria for high-risk OSA, 69% of subjects (n=71) screened high for fatigue (FSS≥4), but only 24 subjects (23%) screened high for excessive daytime sleepiness (ESS>10). In males, 44% of the variation in ESS scores and 63% in FSS scores were explained by the STOP-BANG components. However, only 17% of the variation in ESS scores and 15% of the variation in FSS scores was explained by the STOP-BANG components in females.
Conclusions Over 40% of MS patients were identified as high risk for OSA based on the STOP-BANG questionnaire. The STOP-BANG questionnaire offers clinicians an efficient and objective tool for improving detection of OSA risk in MS patients.

Keywords Obstructive sleep apnea · Multiple sclerosis · Sleepiness · Fatigue

Abbreviations

AHI	Apnea–hypopnea index
BMI	Body mass index
EEG	Electroencephalography
ESS	Epworth Sleepiness Scale
FSS	Fatigue Severity Scale
OSA	Obstructive sleep apnea
MS	Multiple sclerosis
PSG	Polysomnography
UC	University of California

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Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system, affecting approximately 350,000 individuals in the USA and 2.5 million individuals worldwide [1]. More than 50% of patients with MS complain of a chronic sleep disturbance resulting in daytime sleepiness, worsening fatigue, depression, and a lowered pain threshold [2]. Of particular importance, fatigue is considered the most frequent and often the most disabling symptom of MS

[3–6], reported by at least 75% of patients at some point during their disease course [7].

Patients with obstructive sleep apnea (OSA) may have similar complaints to MS patients, such as fatigue, excessive daytime sleepiness, decreased concentration, mood changes, erectile dysfunction, and nocturia [8]. Symptomatic OSA occurs in 2–4% of adults in the general population [9] and is associated with increased cardiovascular and cerebrovascular morbidity and mortality, as well as decreased quality of life [10, 11].

Little is known regarding the predictive factors of OSA in MS patients. Studies have been limited by small sample sizes, varying methodologies, and inconsistent results [12]. Utilizing nocturnal oximetry to screen for OSA in 28 consecutive MS patients with subjective sleep complaints, Tachibana et al. found three patients to have significant oxygen desaturations and confirmed OSA in two of these patients on polysomnography (PSG) [13]. However, Wunderlin et al. found no evidence of sleep-related breathing disorders using portable cardiorespiratory studies in ten MS patients despite six patients scoring high on fatigue and sleepiness scales [14]. Utilizing formal PSG to screen for OSA, Ferini-Strambi et al. compared 25 consecutive MS patients to 25 healthy controls and found three of the MS patients had an apnea–hypopnea index (AHI) greater than 5 versus none of the controls [15]. However, Kaynak et al. found no subjects on PSG to have an AHI greater than 5 in their analysis of 27 MS patients with fatigue, 17 MS patients without fatigue, and 10 healthy controls [16]. In contrast, Veauthier et al. found that sleep-related breathing disorders were more common in fatigued MS patients (27%) than in non-fatigued MS patients (2.5%) in the largest sample to date by performing portable PSG with electroencephalography (EEG) on 66 MS patients (aged 20 to 66 years old) [17]. Additional studies involving large sample sizes are needed to clarify predictive factors of OSA in MS patients.

Similarly, little is known about the underlying causes of fatigue in MS. It has been hypothesized that fatigue in MS is multifactorial in origin: depression, pain, pro-inflammatory cytokines, and medications may all be contributing. It is noteworthy that the same somnogenic Th1 cytokine pattern seen in multiple sclerosis is also found in OSA patients, further pointing to the important role of inflammation in both diseases. [18–23].

Identifying sleep-related breathing disorders may be more difficult in MS patients because of the vague and overlapping symptoms associated with both diseases. Several screening questionnaires have been developed to identify individuals at high risk for OSA, including the checklist of the American Society of Anesthesiologists, the STOP questionnaire (*s*noring, *t*iredness, *o*bserved apnea, and high blood *p*ressure), the STOP-BANG questionnaire (STOP plus *B*MI, *a*ge, *n*eck circumference, *g*ender), the Wisconsin questionnaire, and the Berlin Questionnaire. The STOP-BANG questionnaire is a concise and easy-to-use, eight-point, dichotomized (yes/no) screening tool for OSA [24]. In a systematic review of screening questionnaires for OSA, the STOP-BANG questionnaire had the highest methodological quality and sensitivity [25]. Its use has been validated in different populations, including pre-operative patients [24, 26], hospitalized patients [27], and patients presenting to a sleep disorders unit [28]. However, it has not been validated in patients with MS to date.

Given the profound effect that both MS and OSA can have on daytime functioning, it is important to identify those MS patients who have OSA and institute early treatment in order to improve their overall health status and quality of life. The two major objectives of this study are to: (1) identify patients with MS presenting to an outpatient MS clinic who may be at high risk for OSA based on the STOP-BANG questionnaire and (2) evaluate the relationship between OSA risk based on the STOP-BANG questionnaire and self-reported sleepiness and fatigue using the Epworth Sleepiness Scale (ESS) [29, 30] and the Fatigue Severity Scale (FSS) [31], respectively.

Methods

A pilot study was conducted in which the first 120 patients presenting to the University of California Davis Neurology MS Clinic in a consecutive fashion between September 28, 2010 and January 25, 2011 were invited to participate in an anonymous survey. Subjects were excluded from the study if they refused participation (n=2), were under 18 years of age (n=1), did not report a diagnosis of MS (n=9), or incompletely filled out the survey (n=5), leading to the inclusion of 103 subjects. All data collected were self-reported by patients and considered anonymous, and thus confirmation of the disease status relied on self-report. Disease course and disability status could not be collected as the subjects' medical records were not accessed in view of this anonymous survey.

The study protocol was approved by the UC Davis Institutional Review Board. Patients were asked to complete the survey on their own in the presence of a trained clinical research coordinator in a confidential waiting room. The study coordinator was available if the subjects had any questions or needed assistance in filling out the questionnaire due to visual or motor impairment. The survey included MS status (yes, no, unsure), year diagnosed with MS, the STOP-BANG questions with neck circumference obtained (by clinical study coordinator) by measurement at the level of the cricothyroid membrane, the ESS, and the FSS. We

also noted whether patients reported having been tested for or previously diagnosed with OSA, though this was not a formal part of the questionnaire nor asked of all patients.

The STOP questionnaire consists of four yes/no questions, with one point given for each yes answer. A score of 2 or more positive responses out of a possible total score of 4 is considered high risk for OSA on the STOP questionnaire. The STOP-BANG questionnaire incorporates the STOP questions as well as assigns one point for each yes answer on the following: *B*MI>35, *a*ge>50 years, *n*eck circumference>40 cm, and *g*ender=male. A score of 3 or more positive responses out of a possible total score of 8 is considered high risk for OSA based on the STOP-BANG questionnaire. In the original validation study, sensitivities of this high-risk group were 83.6%, 92.9%, and 100% for detecting OSA as defined by AHI>5, >15, and>30, respectively [24].

ESS is the most commonly used measure of daytime sleepiness and involves asking the patient to rate the probability of dozing off or falling asleep (0=never, 1=slight chance, 2=moderate chance, 3=high chance) in eight different situations, with a total score greater than 10 out of 24 indicating possible excessive daytime sleepiness [29, 30]. We also considered a score of 16 or higher to indicate severe daytime sleepiness.

FSS is a commonly used instrument that evaluates aspects of fatigue in MS patients and contains nine statements whereby patients rate the severity of their fatigue symptoms using a Likert scale by circling a number from 1 (strongly disagree) to 7 (strongly agree) [31]. FSS is not strictly a measure of the physical aspect of fatigue but includes a question of motivation as well. Total scores can range from 9 to 63, and a cutoff value of 36 or greater (mean score across all questions of 4 or greater) is used to indicate individuals with fatigue [32]. FSS scores in this study are presented as a mean score across all questions for each subject (e.g., a score of 36 over nine questions is expressed as a mean of 4). We considered a mean score of greater than 5 to represent severe fatigue.

Statistical analysis

Descriptive statistics of subject characteristics and questionnaire outcomes were performed for the total sample, and *t*-tests were used to test for significant differences by gender, assuming unequal group variances. (Although certain variables were distributed nonparametrically, the sample size is sufficient to permit the use of *t*-tests.) STOP-BANG scores were correlated with FSS and ESS scores, which were analyzed as continuous scores and with scores dichotomized into high- and low-risk groups according to the diagnostic cutoff value for each questionnaire. A composite score of high FSS and high ESS was created and correlated with STOP-BANG score as well. Results are presented using *t*-tests, but chi-square tests yielded *p*-values within 0.01 of the *t*-test *p*-values. Mann–Whitney tests also yielded similar results. Bivariate associations between continuous variables were examined with Spearman's rank correlation due to ordinal rank values on STOP-BANG, FSS, and ESS questionnaires. An FSS >5 will be considered severe fatigue and an ESS ≥16 will be defined as severe excessive daytime sleepiness. We further analyzed the data to determine the relationship between STOP-BANG scores and these more severe thresholds of fatigue and sleepiness. We also estimated a multivariate regression to determine the extent to which the STOP-BANG components can explain the variation in ESS and FSS scores. To allow for a richer level of detail, we measure BMI, age, and neck circumference in their continuous forms rather than as dichotomous variables. We estimate models for the total sample and separately for each gender. All data analyses were conducted using Stata (Version 10.0).

Results

Seventeen patients were excluded, leaving a sample of 103 subjects that were 28% men and 72% women (Table 1). The STOP-BANG questionnaire yielded a mean score of 2.40 (Fig. 1) and classified 41.7% of our subjects as at high risk for OSA (Table 2). Three out of 103 subjects (2.9%) reported having undergone prior evaluation for OSA. Two subjects reported having been previously diagnosed with OSA: one screened as at high risk on the STOP-BANG questionnaire and the other screened negative, reporting resolution of OSA following surgery. One subject reported having had OSA ruled out 2 years ago with a sleep study and classified as at high risk on the STOP-BANG questionnaire.

The men in the sample had a significantly larger mean neck circumference and a significantly higher likelihood of being overweight (BMI >25 and≤30). The subjects most commonly reported positive responses on the STOP and STOP-BANG questionnaire components related to feeling tired, age over 50, loud snoring, and male gender (Table 3). More than 80% of subjects reported feeling tired, sleepy, or fatigued during the day.

When the ESS was administered, the subjects were most likely to report a moderate or high chance of dozing off while lying down to rest in the afternoon, followed by dozing off while watching TV or while sitting and reading (Table 4). More than 70% of subjects reported on the FSS that their motivation is lower when fatigued and that fatigue is among their three most disabling symptoms (Table 5).

With the use of the STOP questionnaire alone, the mean score was 1.45 and 37.9% of subjects screened as at high

Table 1 Subject characteristics (n=103)

Variable	Total sample, mean (SD)	Male (n=29), mean (SD)	Female (n=74), mean (SD)
Age (years)	45.78 (10.97)	44.72 (11.40)	46.19 (10.85)
Gender (%male)	28.16 (45.20)	100.00 (0.00)	0.00 (0.00)
BMI	28.02 (6.49)	27.30 (4.55)	28.30 (7.12)
% BMI >25 and≤30	33.01 (47.25)	51.72 (50.85)	25.68 (43.98)*
% BMI >30 and≤35	14.56 (35.45)	10.34 (30.99)	16.22 (37.11)
% BMI >35	15.53 (36.40)	6.90 (25.79)	18.92 (39.43)
Neck circumference (cm)	36.85 (4.24)	40.02 (4.31)	35.61 (3.53)**
Years since MS diagnosis	11.71 (8.88)	12.72 (10.11)	11.31 (8.39)

Years since MS diagnosis calculated as 2011 minus the year diagnosed

SD standard deviation, *MS* multiple sclerosis, *BMI* body mass index

*p<0.05; **p<0.01, comparing males and females

risk (Table 2). The difference in the proportion of patients determined to be at high risk for OSA using the STOP-BANG questionnaire compared with the STOP questionnaire was not statistically significant. Nonetheless, 18 of the subjects (17.5%) were classified as at high risk by one of these measures but not the other (11 for the STOP-BANG questionnaire and 7 for the STOP questionnaire). A correlation coefficient between the high risk classification of these two questionnaires is 0.64 (p<0.00001).

Analyzing gender differences on questionnaire outcomes, 76% of males screened as at high risk on the STOP-BANG questionnaire versus 28% of females, with males having a higher overall mean score of 3.48 versus 1.97 in females (p< 0.01). No significant gender differences occurred with scores on the STOP questionnaire, ESS, or FSS (Table 5).

Mean ESS in our sample was 7.33 with 23% of subjects (n=24) scoring higher than 10 on the ESS, suggestive of excessive daytime sleepiness. In our sample, 9% of subjects scored 16 or higher on the ESS, suggestive of severe daytime sleepiness. ESS score was not significantly correlated with age (r=0.12, p=0.23) or years since MS diagnosis (r=−0.11, p=0.26).

The mean FSS score was 4.6, with 69% of subjects (n= 71) screening high for fatigue. Only 53% of subjects scored greater than 5, indicating severe fatigue. FSS score was not significantly correlated with age (r=−0.05, p=0.61) or years since MS diagnosis (r=−0.10, p=0.29).

The mean ESS and FSS was not statistically different when STOP-BANG classification was categorized as high versus low (Table 6). Similarly, the percentage of high and severe ESS and FSS subjects was not statistically different depending on the dichotomized classification.

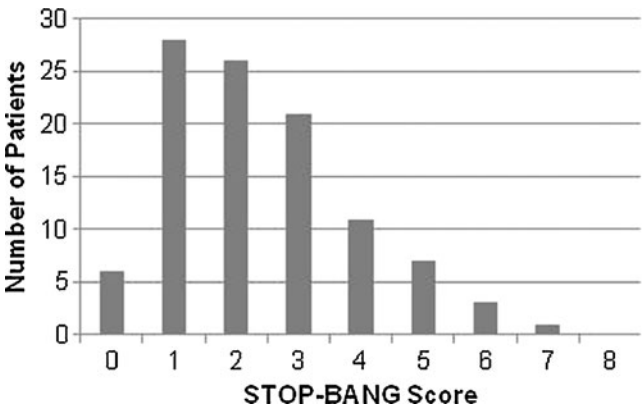

Fig. 1 Distribution of STOP-BANG scores (n=103)

Correlations between the STOP-BANG, ESS, and FSS scores

There was a statistically significant correlation between the ESS and the FSS (r=0.31, p<0.01). However, in the total sample, neither ESS nor FSS were statistically significantly correlated with the STOP-BANG score when analyzed both ordinally and by high or severe risk categories (Table 7; Figs. 2 and 3).

However, for males, the STOP-BANG score was statistically significantly correlated with the FSS (r=0.43, p= 0.02), the high and severe ESS categories (r=0.52, p= 0.004, and r=0.40, p=0.03, respectively), as well as the high risk category for both ESS and FSS measures (r= 0.52, p=0.04). For females, however, the STOP-BANG score was only correlated with the ESS (r=0.27, p=0.02) (Table 7).

Owing to the exploratory nature of the study, no adjustments for multiple comparisons were made.

Regression analysis

Consistent with the correlations presented above, the multivariate regressions indicate that the relationship between the STOP-BANG and the other surveys (ESS and FSS) is stronger for males than females. To allow for a richer level of detail, we measure BMI, age, and neck circumference in their continuous forms rather than as dichotomous variables. About 19% of the overall variation in the ESS scores can be explained by the eight components of the STOP-BANG questionnaire. However, if we estimate separate models for males and females, the explanatory power increases

Table 2 Summary of questionnaire outcomes for ordinal and dichotomous variables (n=103)

Outcome	Total sample, % (SD)	Male (n=29), % (SD)	Female (n=74), % (SD)
For ordinal variables			
STOP-BANG score	2.40 (1.52)	3.48 (1.45)	1.97 (1.33)**
STOP score	1.45 (1.00)	1.72 (1.13)	1.34 (0.93)
ESS	7.33 (4.83)	6.14 (4.80)	7.80 (4.79)
FSS	4.60 (1.58)	4.51 (1.60)	4.63 (1.58)
For dichotomous variables			
High STOP-BANG score	41.75 (49.56)	75.86 (43.55)	28.38 (45.39)**
High STOP Score	37.86 (48.74)	48.28 (50.85)	33.78 (47.62)
High ESS	23.30 (42.48)	17.24 (38.44)	25.68 (43.98)
Severe ESS	8.74 (28.38)	10.34 (30.99)	8.11 (27.48)
High FSS	68.93 (46.50)	65.52 (48.37)	70.27 (46.02)
Severe FSS	42.72 (49.71)	41.38 (50.12)	43.24 (49.88)
High ESS, High FSS score	21.36 (41.18)	17.24 (38.44)	22.97 (42.35)
Low ESS, Low FSS score	29.13 (45.66)	34.48 (48.37)	27.03 (44.71)
High ESS, Low FSS	1.94 (13.87)	0.00 (0.00)	2.70 (16.33)
Low ESS, High FSS	47.57 (50.19)	48.28 (50.85)	47.30 (50.27)

High STOP-BANG category is STOP-BANG≥3. High STOP category is STOP≥2. High ESS category is ESS>10. High FSS category is mean FSS≥4. Severe ESS category is ESS ≥16. Severe FSS category is mean FSS>5

SD standard deviation, *ESS* Epworth Sleepiness Scale, *FSS* Fatigue Severity Scale

**p<0.01

substantially for males. For this group, nearly 44% of the variation in the ESS scores can be explained by the STOP-BANG components. For females, only 17% of the variation can be explained by the STOP-BANG components.

For the total sample, the STOP-BANG components can explain about 22% of the variation in the FSS scores. As with the ESS model, when estimating separate models by gender, the STOP-BANG components explain a substantially greater share of FSS variation—63% for males. For females, only 15% of the variation can be explained by the STOP-BANG components.

Although it may not be surprising that the STOP-BANG item "tired" is the most consistently statistically significant predictor of ESS and FSS, themselves measures of being tired, a joint F-test of the remaining seven non-tired STOP-BANG elements was jointly significant at the 0.02 level for the male FSS model and the 0.09 level for the male ESS model (see Table 8). This result suggests that the other STOP-BANG elements are providing useful information.

"Years since MS diagnosis" also was added in the regression model to determine if such explained the variance in the ESS or FSS scores, yet it was not statistically significant nor did it change the basic results from the prior models.

Discussion

Our study reveals that a large proportion (42%) of MS patients may have a higher risk for OSA based on the STOP-BANG questionnaire. Given the profound effect that both MS and OSA can have on daytime functioning, it is important to identify those MS patients who are at risk for OSA so as to institute earlier treatment in order to improve their overall health status and quality of life. Lack of

Table 3 STOP-BANG components (n=103)

		Number of patients (%)
S:	Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?	30 (29.1)
T:	Do you often feel tired, fatigued, or sleepy during daytime?	84 (81.6)
O:	Has anyone observed you stop breathing during sleep?	13 (12.6)
P:	Do you have or are you being treated for high blood pressure?	22 (21.4)
	High risk based on STOP score≥2 responses	39 (37.9)
B:	BMI >35?	16 (15.5)
A:	Age >50?	34 (33.0)
N:	Neck circumference >40 cm?	19 (18.4)
G:	Gender male?	29 (28.2)
	High risk based on STOP-BANG score≥3 responses	43 (41.7)

All components are dichotomous variables

BMI body mass index

Table 4 Epworth Sleepiness Scale components ($n=103$)

Item	Description: likelihood of dozing off or falling asleep in the following situations	Mean score	Subjects rating ≥2 (%)
1	Sitting and reading	1.22	36.9
2	Watching TV	1.29	38.8
3	Sitting inactive in public place (e.g., a theater or a meeting)	0.57	16.5
4	As a passenger in a car for an hour without a break	1.09	30.1
5	Lying down to rest in the afternoon when circumstances permit	1.95	65.0
6	Sitting and talking to someone	0.19	3.9
7	Sitting quietly after a lunch without alcohol	0.83	22.3
8	In a car, while stopped for a few minutes in traffic	0.17	4.9

0 never, *1* slight chance, *2* moderate chance, *3* high chance

screening for OSA remains a common problem, and validated questionnaires offer an efficient method of improving detection, as Senthivel et al. have demonstrated in the primary care setting [33]. It is important to note that a positive STOP-BANG score does not necessarily equate to a diagnosis of OSA but rather being at risk for OSA as validation data with polysomnography is lacking.

The majority of subjects in our study were female (72%), as typically occurring in MS [1]. However, substantially more males than females were classified as at high risk (76% versus 28%) on the STOP-BANG questionnaire. As expected, males had a statistically larger neck circumference compared to females. Population-based studies have reported a two- to threefold greater risk for OSA in males compared to females [9–11]. Not only is the prevalence of being at risk for OSA more common in males but the severity of OSA is also worse in males compared to females. The gender difference may be explained by several factors including location of body fat distribution and anatomical airway differences [9–11]. Since the STOP-BANG questionnaire itself incorporates male gender among its criteria, one may expect that a larger amount of males have high STOP-BANG score questionnaire. However, in the original STOP-BANG validation study done in the pre-operative setting, an equal percentage (58%) of males and females were classified as at high risk using the STOP questionnaire. Details regarding the percentage at risk by gender using the STOP-BANG were not reported [24].

The STOP and STOP-BANG questionnaires have been applied in prior studies in select populations with variable results. In the original validation study by Chung et al., 27.5% of 2,467 pre-operative patients were classified as at high risk based on the STOP questionnaire [24] as opposed to a larger proportion (38%) in our study. Vasu et al. utilized the STOP-BANG questionnaire in 135 pre-operative patients undergoing elective surgery and found 41.5% to be at high risk for OSA [26], similar to the percentage of high-risk patients in our study. In contrast, the proportion of high-risk patients using the STOP-BANG questionnaire in our study is approximately half that reported in hospitalized patients [27] and in patients undergoing diagnostic PSG [28]. Specifically, in a survey of 195 hospitalized patients, Kumar et al. classified 65% as at high risk based on the STOP questionnaire and 80.5% based on the STOP-BANG questionnaire [27]. At the Sleep Disorders Unit of the Singapore General Hospital, 319 patients undergoing diagnostic PSG completed the STOP-BANG questionnaire, and 77.3% were classified as at high risk [28]. These patients

Table 5 Fatigue Severity Scale components ($n=103$)

Item	Description: choose a number from 1 to 7, based on how accurately it reflects your condition in the last week	Mean score	Subjects rating ≥5 (%)
1	My motivation is lower when I am fatigued	5.46	77.7
2	Exercise brings on my fatigue	3.65	32.0
3	I am easily fatigued	4.74	57.3
4	Fatigue interferes with my physical functioning	4.81	60.2
5	Fatigue causes frequent problems for me	4.32	50.5
6	My fatigue prevents sustained physical functioning	4.44	54.4
7	Fatigue interferes with carrying out certain duties and responsibilities	4.28	49.5
8	Fatigue is among my three most disabling symptoms	5.23	70.9
9	Fatigue interferes with my work, family, or social life	4.45	49.5

1 strongly disagree, *7* strongly agree

Table 6 Epworth Sleepiness Scale and Fatigue Severity Scale means by STOP-BANG category

	Low STOP-BANG, mean (SD)	High STOP-BANG, mean (SD)	*p*-value
ESS	7.42 (5.09)	7.21 (4.51)	0.83
FSS	4.52 (1.47)	4.7 (1.73)	0.59
% High ESS group	23.33 (42.65)	23.26 (42.75)	0.99
% High FSS group	70 (46.21)	67.44 (47.40)	0.79
% Severe ESS group	10 (30.25)	6.98 (25.78)	0.59
% Severe FSS group	38.33 (49.03)	48.84 (50.58)	0.29

High STOP-BANG category is STOP-BANG≥3. Low STOP-BANG category is STOP-BANG<3. High ESS category is ESS>10. High FSS category is mean FSS≥4. Severe ESS category is ESS ≥16. Severe FSS category is mean FSS>5. Although the table reports *p*-values for *t*-test, the *p*-values for chi-square test were nearly identical

ESS Epworth Sleepiness Scale, *FSS* Fatigue Severity Scale

had a higher pre-test probability of OSA than our population given that they had been selected for referral for PSG and Asian patients have a higher risk of OSA than Caucasians due to craniofacial factors [28].

When looking at different screening tools, the STOP and STOP-BANG questionnaires have not yet been applied in a large study in the general population, though we can draw parallels to results obtained with the Berlin Questionnaire. The Berlin Questionnaire has been commonly used for many years prior to the STOP and STOP-BANG questionnaires, though it is relatively less user-friendly and efficient to administer in a busy clinical setting but has similar components to the STOP-BANG questionnaire with questions related to snoring, fatigue, sleepiness, hypertension, and having a BMI>30) [34]. Furthermore, 35% of subjects who reported a chronic medical condition (such as diabetes, heart disease, and hypertension) during the 2005 National Sleep Foundation poll were classified as at high risk for OSA, similar to the proportion of high-risk patients in our study [36]. In addition, subsequent studies utilizing the Berlin Questionnaire have found a large proportion of patients with chronic medical conditions to be at high risk for OSA based on questionnaire positivity: 57% of 938 men with type 2 diabetes [37], 44% of 98 patients undergoing cardiac rehab [38], 53% of 121 acute stroke patients [39], and 46% of 249 patients with chronic wounds [40]. However, the authors also note that using the Berlin Questionnaires for OSA screening had several limitations as it was not adequately predictive of who should undergo sleep testing and, in addition, there was poor correlation with the polysomnography findings [35, 39, 40]. This caveat allows us to remind our reader the importance of separating being STOP-BANG-positive for OSA and having OSA.

Fatigue and sleepiness were common in our group of MS patients, with 69% scoring high on the FSS and 23% on the ESS. Stanton et al. had similar findings on the FSS and ESS in 60 outpatients with MS (64% and 32%, respectively) [4] as did Merkelbach et al. in 80 MS patients (58.75% and 27.5%, respectively) [41]. In our study, the most frequently elevated ESS component (65% of subjects) was the propensity to doze off lying down in the afternoon if circumstances permit. Stanton el al. similarly found that more than 70% of their patients reported taking an afternoon nap two or more days a week [4]. The majority of our subjects (78%) also reported that their motivation is negatively impacted by fatigue and that fatigue ranks among their three most disabling symptoms, a finding consistent with prior studies [4, 31, 32, 41].

Measures of fatigue and sleepiness were moderately correlated in our study (FSS vs ESS, r=0.31). Merkelbach et al.

Table 7 Spearman correlations of STOP-BANG with ESS and FSS (n=103)

Correlations	Total sample		Male (n=29)		Female (n=74)	
	r	*p*	*r*	*p*	*r*	*p*
STOP-BANG with ESS	0.132	(0.185)	0.196	(0.309)	0.271	(0.020)*
STOP-BANG with FSS	0.164	(0.099)	0.431	(0.020)*	0.154	(0.191)
STOP-BANG with both high ESS and high FSS	0.152	(0.126)	0.521	(0.004)**	0.141	(0.230)
STOP-BANG with high ESS	0.119	(0.233)	0.521	(0.004)**	0.117	(0.320)
STOP-BANG with severe ESS	0.090	(0.366)	0.403	(0.030)*	0.023	(0.847)
STOP-BANG with high FSS	0.056	(0.572)	0.209	(0.277)	0.087	(0.462)
STOP-BANG with severe FSS	0.171	(0.085)	0.335	(0.076)	0.169	(0.150)

High ESS category is ESS>10. High FSS category is FSS≥4. Severe ESS category is ESS ≥16. Severe FSS category is mean FSS>5

ESS Epworth Sleepiness Scale, *FSS* Fatigue Severity Scale

*p<0.05; **p<0.01

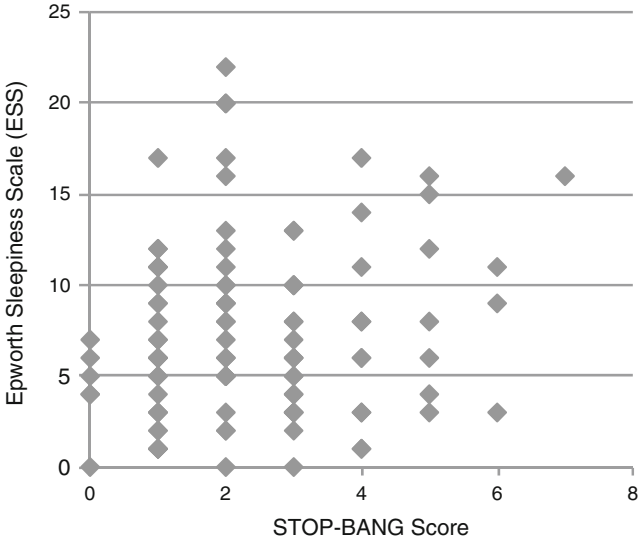

Fig. 2 ESS by STOP-BANG SCORE

similarly found a significant correlation between complaints of fatigue and sleepiness (FSS vs ESS, r=0.42) in 80 MS patients [41]. In their study, fatigue also correlated significantly with age (r=0.40) and disease duration (r=0.25) [41], whereas no statistically significant correlation was found in our study between these variables. Flachenecker et al. similarly did not find a statistically significant correlation between FSS and age or disease duration in a study involving 151 consecutive MS outpatients [32]. Mills and Young also did not find a relationship between age or disease duration versus fatigue, as measured by the Neurological Fatigue Index for MS Summary Scale, in a large cross-sectional survey of 635 respondents [42]. In our study, however, "years since MS diagnosis" was utilized instead of disease duration, leading to potential underestimation of the true duration of disease from symptom onset and limiting comparison between studies.

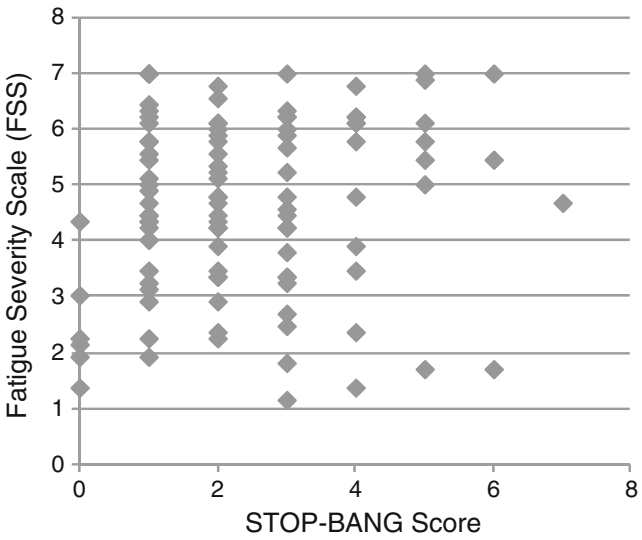

Fig. 3 FSS by STOP-BANG

Sleepiness alone did not appear to predict OSA risk as determined by the STOP-BANG questionnaire given that there was no significant correlation between the ESS and the overall STOP-BANG score. This suggests that clinicians might not discount the possibility of OSA in a patient who does not report excessive daytime sleepiness as indicated by the ESS. The ESS has been found in prior studies to be poorly reproducible [43] and a relatively insensitive (66% for AHI greater than 5) predictor of OSA [44]. However, in our study, further analysis by gender yielded significant findings. ESS score in females may bear greater relevance to OSA risk than in males as there was a positive correlation between ESS and STOP-BANG score (r=0.271, p=0.020).

For males, a composite score using a high ESS score combined with a high FSS score led to a statistically significant correlation (r=0.52, p=0.004) with STOP-BANG score, suggesting that males reporting excessive "sleepiness" and "fatigue" may be at a particularly high risk for OSA.

Fatigue alone also did not predict OSA risk as determined by the STOP-BANG questionnaire given the lack of a significant correlation between the FSS and the overall STOP-BANG score. Prior studies have had conflicting results as to the influence of fatigue as a determinant of OSA risk. Wunderlin et al. and Kaynak et al. did not find high scores on fatigue measures to be associated with OSA [14, 16], whereas Veauthier et al. found in 66 MS patients that sleep-related breathing disorders (per portable PSG with EEG) were more frequent in the fatigued MS patients (27%) than in the non-fatigued MS patients (2.5%) [17]. Veauthier et al. employed both the FSS and the Modified Fatigue Impact Scale (MFIS) in their study, utilizing the MFIS to dichomotize patients into high- or low-risk groups [17]. Multiple factors aside from sleep-related breathing disorders have been reported in prior studies to contribute to MS fatigue, including central nervous system abnormalities, altered cytokine profiles, depression, heat sensitivity, physical impairment, pain, nocturia, and degree of psychosocial support [3–5, 7, 8, 12, 14, 42]. In addition, in the general population, prior studies have suggested that fatigue in OSA may not be related to apnea severity but may be due to other factors such as depression, stress, and cytokines [45, 46]. In our study, there is a significant correlation in males between the STOP-BANG score and the FSS (r=0.43, p=0.02) but not in females. Our results may suggest that the FSS score in males may bear greater relevance to OSA risk than in females.

The major limitation of the present study is that scores on the STOP and STOP-BANG questionnaires were not validated with PSG to determine the sensitivity and specificity of these screening instruments in MS patients. This was a

Table 8 Regression of ESS and FSS on STOP-BANG components

	Epworth Sleepiness Scale			Fatigue Severity Scale		
Independent variable	All (n=103)	Male (n=29)	Female (n=74)	All (n=103)	Male (n=29)	Female (n=74)
Snore	1.845 (1.435)	−0.556 (2.161)	2.862 (1.842)	0.108 (0.411)	0.567 (0.582)	−0.136 (0.492)
Tired	1.910 (0.935)*	3.513 (1.314)*	1.061 (1.154)	1.565 (0.398)**	2.295 (0.478)**	1.313 (0.526)*
Observed apnea	1.741 (1.883)	6.449 (3.159)	−0.929 (2.020)	0.777 (0.492)	1.190 (0.593)	0.475 (0.647)
High blood pressure	−0.299 (1.202)	−0.206 (2.033)	−1.273 (1.518)	−0.216 (0.383)	−0.012 (0.424)	−0.480 (0.551)
BMI (actual)	−0.198 (0.130)	−0.207 (0.268)	−0.243 (0.146)	−0.031 (0.031)	−0.022 (0.066)	−0.051 (0.034)
Age (years)	0.027 (0.040)	0.028 (0.077)	0.039 (0.049)	−0.007 (0.013)	0.002 (0.028)	−0.005 (0.014)
Neck circumference (cm)	0.370 (0.217)	0.191 (0.258)	0.481 (0.307)	0.048 (0.059)	−0.068 (0.073)	0.136 (0.087)
Gender (male=1)	−3.757 (1.454)*			−0.389 (0.379)		
Constant	−3.206 (4.816)	−0.909 (7.108)	−5.561 (7.610)	2.778 (1.659)	5.454 (1.644)**	0.464 (2.532)
Number of subjects	103	29	74	103	29	74
R^2	0.189	0.438	0.170	0.222	0.632	0.146
P-value from joint F-test non-tired STOP-BANG components	0.009	0.090	0.120	0.294	0.022	0.648

Heteroskedasticity-corrected standard errors are in parentheses. Constant also included in the regression

ESS Epworth Sleepiness Scale, *FSS* Fatigue Severity Scale

**p<0.01; *p<0.05 (see Table 2 for a complete description of the first four variables)

pilot study to first determine whether OSA was a potential problem in this population to warrant complete investigation. Without further validation, however, it cannot be concluded that a positive STOP-BANG score is equivalent to a diagnosis of OSA. This was also a small study and not population-based. Given the anonymous nature of the survey, data were not confirmed via medical record and subject to potential recall bias, including the self-reported diagnosis of MS. The current survey was also intentionally brief to expedite its administration in the clinic, and other potentially influential factors in the patients' respective medical history, including medication list and comorbid medical and psychiatric conditions, were not obtained. Ethnicity was another factor not incorporated. MS diagnosis was self-reported and therefore not based on the established criteria, which might have introduced the possibility of diagnostic misclassification. Important future steps include following up the results of this survey with PSG on a larger sample of MS patients diagnosed by McDonald's criteria, including details on disease duration, medications, disability status as well as including an analysis of comorbid conditions while incorporating the STOP-BANG and Berlin Score as well and further measures of fatigue and sleepiness.

In summary, our study reveals that over 40% of MS patients may be at higher risk for OSA based on the STOP-BANG questionnaire. Extrapolating from results using the Berlin Questionnaire in the 2005 National Sleep Foundation poll [36], MS patients appear to be at greater risk than the general population for OSA, though comparable to patients with other chronic medical conditions. Fatigue and sleepiness commonly occur in MS patients and are correlated with one another. Neither sleepiness nor fatigue alone (as defined by ESS and FSS, respectively) may significantly relate to OSA risk (as defined by the STOP-BANG questionnaire). However, our results suggest that measures of sleepiness may bear greater relevance to OSA risk in females, whereas fatigue may bear greater relevance to OSA risk in males The gender differences in which STOP- BANG is correlated with ESS in females but FSS in males may be related to sample size or the way each gender expresses symptoms. It may be helpful for clinicians evaluating MS patients to still consider OSA as a possibility in spite of the low scores on fatigue or sleepiness measures. Given the negative impact that both MS and OSA can have on quality of sleep and daytime functioning, it is important to screen for OSA in MS patients and institute early treatment to improve their overall health status and quality of life. A further prospective study incorporating detailed demographics and PSG to validate the sensitivity and specificity of the STOP-BANG questionnaire as a screening instrument in MS patients who complain of fatigue is planned.

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Conflicts of interest The authors declare that they have no conflicts of interest.

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