

Younger age, female sex, and high number of awakenings and arousals predict fatigue in patients with sleep disorders: a retrospective polysomnographic observational study

Christian Veauthier^{1,2}

¹Department of Neurology, Hanse-Klinikum, Stralsund, Germany;

²Department of Neurology, Centre Hospitalier de Belfort-Montbéliard (CHBM), Montbéliard, France

Background: The Fatigue Severity Scale (FSS) is widely used to assess fatigue, not only in the context of multiple sclerosis-related fatigue, but also in many other medical conditions. Some polysomnographic studies have shown high FSS values in sleep-disordered patients without multiple sclerosis. The Modified Fatigue Impact Scale (MFIS) has increasingly been used in order to assess fatigue, but polysomnographic data investigating sleep-disordered patients are thus far unavailable. Moreover, the pathophysiological link between sleep architecture and fatigue measured with the MFIS and the FSS has not been previously investigated.

Methods: This was a retrospective observational study (n = 410) with subgroups classified according to sleep diagnosis. The statistical analysis included nonparametric correlation between questionnaire results and polysomnographic data, age and sex, and univariate and multiple logistic regression.

Results: The multiple logistic regression showed a significant relationship between FSS/MFIS values and younger age and female sex. Moreover, there was a significant relationship between FSS values and number of arousals and between MFIS values and number of awakenings.

Conclusion: Younger age, female sex, and high number of awakenings and arousals are predictive of fatigue in sleep-disordered patients. Further investigations are needed to find the pathophysiological explanation for these relationships.

Keywords: fatigue, sleep disorders, multiple sclerosis, polysomnography, Modified Fatigue Impact Scale, Fatigue Severity Scale, nocturnal awakening, age

Introduction

Fatigue is the most frequent symptom in multiple sclerosis (MS).¹ The Multiple Sclerosis Council defines MS related fatigue as a “subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities,”² and has recommended evaluation with the 21-item Modified Fatigue Impact Scale (MFIS) to measure fatigue,² which is a smaller version of the 40-item Fatigue Impact Scale (FIS).³

Krupp et al,⁴ in 1989, published the unidimensional Fatigue Severity Scale (FSS), which is widely used not only in MS, but also in stroke,⁵ Parkinson's disease,⁵ lung diseases,⁶ myotonic dystrophy,⁷ neuroborreliosis,⁸ HIV infection,⁹ and cancer,¹⁰ and in sleep disorders such as insomnia,¹¹ shift working,¹² restless legs syndrome (RLS),^{13,14} and obstructive sleep apnea.¹⁵

Correspondence: Christian Veauthier
Centre Hospitalier de Belfort-Montbéliard (CHBM), 2 Rue du Dr Flamand, 25211 Montbéliard, France
Tel +33 6 80 75 60 30
Fax +49 3212 28 28 668
Email cveauthier@web.de

Table I Age and polysomnographic data

	All patients			Untreated SBRD			Treated SBRD			PLMD/RLS		
	All	M	F	All	M	F	All	M	F	All	M	F
Number	410	290	120	231	176	55	102	80	22	19	6	13
%	100	70.7	29.3	56.3	42.9	13.4	24.9	19.5	5.4	4.7	1.5	3.2
Age (years)												
Mean	58.1	58.3	57.6	59.0	58.4	60.9	61.0	61.1	60.7	52.1	47.5	54.2
SEM	0.7	0.6	0.6	0.6	0.7	1.2	0.6	0.7	1.2	0.6	0.1	1.2
25%–75%	51.0–68.0	51.0–68.0	51.0–69.0	52.0–68.0	52.0–66.0	53.0–72.0	54.0–69.0	53.8–69.0	54.0–69.5	42.0–56.0	38.5–58.0	51.0–57.0
AHI/hour												
Mean	20.0	21.7	15.7	32.3	33.3	29.2	3.4	2.7	5.7	3.5	5.0	1.3
SEM	1.1	1.3	2.0	1.1	1.3	2.0	1.1	1.3	2.0	1.1	1.6	2.0
25%–75%	1.5–31.1	1.6–34.6	1.1–21.8	18.6–42.9	19.6–42.8	10.4–43.8	0.2–1.6	0.2–1.6	0.2–2.1	1.0–4.7	1.0–4.7	1.0–4.5
SpO₂% min												
Mean	82.9	82.9	84.5	78.0	78.8	78.6	89.6	89.7	89.5	87.5	85.9	88.2
SEM	0.5	0.6	0.8	0.5	0.6	1.0	0.5	0.6	1.0	0.5	0.7	1.0
25%–75%	80.0–90.0	79.0–90.0	84.0–91.0	74.8–86.0	75.0–86.0	74.8–87.0	88.0–92.0	88.0–92.0	87.8–92.0	85.0–92.0	78.2–92.3	86.0–93.0
Sleep efficacy (%TST/TiB)												
Mean	72.3	72.2	72.5	72.2	72.9	69.7	71.1	70.8	72.8	73.8	66.0	77.5
SEM	0.6	0.8	1.0	0.6	0.8	1.1	0.6	0.8	1.1	0.7	1.0	1.1
25%–75%	66.5–80.8	66.5–80.9	66.4–80.5	66.8–80.9	68.0–81.3	60.5–77.9	64.2–78.2	63.3–78.3	64.9–78.7	70.7–85.7	55.3–81.7	71.6–86.0
NREM-3/4 (%TiB)												
Mean	12.4	9.9	17.9	7.5	6.1	12.0	18.5	16.4	26.0	25.0	28.4	23.5
SEM	0.6	0.6	1.2	0.6	0.6	1.2	0.6	0.6	1.2	0.6	0.8	1.2
25%–75%	1.2–20.2	0.8–16.8	7.0–25.4	0.5–11.9	0.3–8.8	1.2–19.0	9.2–25.2	8.2–24.6	18.3–34.2	15.6–29.7	5.1–44.1	16.6–30.3
Number of awakenings (per night)												
Mean	11.8	10.8	14.4	1.0	10.6	12.8	8.7	8.6	9.2	24.4	25.5	23.9
SEM	0.5	0.5	1.2	0.5	0.5	1.2	0.5	0.5	1.2	0.5	0.7	1.2
25%–75%	6.3–13.0	6.0–11.0	7.0–18.0	6.0–12.0	6.0–11.0	6.8–14.3	6.0–9.0	6.0–9.0	6.0–9.3	15.0–31.0	18.5–31.8	13.5–33.5
Arousal index (per hour)												
Mean	25.1	26.5	20.6	47.0	30.4	25.2	19.8	20.9	15.7	19.2	22.1	17.8
SEM	0.7	0.8	1.1	0.7	0.8	1.2	0.7	0.9	1.2	0.7	1.0	1.2
25%–75%	15.0–30.6	16.1–32.3	12.5–25.6	28.0–59.5	19.3–38.9	14.3–30.0	13.3–23.9	14.3–24.5	10.9–21.1	13.5–22.1	18.8–26.4	12.6–21.8
Sleep latency (minutes)												
Mean	45.5	44.2	48.7	29.0	46.1	50.2	43.4	40.4	54.7	32.5	27.4	34.9
SEM	1.4	1.6	3.0	1.4	1.6	0.3	1.4	1.6	3.0	0.1	2.0	3.0
25%–75%	27.0–58.0	27.0–56.0	26.3–62.8	18.6–36.3	28.0–58.0	29.8–62.3	28.9–52.8	27.0–50.8	35.0–80.3	16.0–47.0	13.4–36.3	16.0–52.0

Abbreviations: AHI, apnea/hypopnea index; NREM-3/4, non-rapid eye movement stage 3/4; PLMD, periodic limb movement disorder; RLS, restless legs syndrome; SEM, standard error of the mean; SpO₂% min, minimal desaturation; SBRD, sleep-related breathing disorder; TiB, time in bed; TST, total sleep time; F, female; M, male.

The *International Classification of Sleep Disorders* second edition (ICSD-2) mentions “exhaustion” as a minimal criterion of sleep apnea,¹⁶ but in general there are no objective measurements to differentiate fatigue from exhaustion. Complaints of fatigue may be as important as those of sleepiness are to obstructive sleep apnea syndrome (OSAS) patients,¹⁷ and consequently, continuous positive airway pressure (CPAP) improves fatigue substantially in OSAS patients.¹⁸ (Interestingly, women suffering from OSAS appear to have complaints of fatigue more frequently than men with OSAS).¹⁷

Hossain et al¹⁹ investigated 283 patients by polysomnography in a sleep laboratory. Sixty-four percent of referred patients reported pathological fatigue without overlap of sleepiness (mean FSS 5.1; mean Epworth Sleepiness Scale

[ESS]²⁰ 6.9), 19% were highly fatigued and sleepy (mean FSS 5.4; mean ESS 17.2), 13% did not feel either fatigue or sleepiness (mean FSS 2.1; mean ESS 5.4), and only 4% reported pathological sleepiness without overlap of fatigue (mean FSS 1.9; mean ESS 14.5).

In summary, fatigue and sleepiness can occur together, but fatigue and sleepiness can be independent manifestations of a sleep disorder;²¹ there are many patients suffering from sleep disorders with fatigue but without sleepiness. In all likelihood, fatigue is under-recognized in sleep medicine. This underemphasis may contribute to the overlooking of treatable sleep disorders, with enormous consequences for misdiagnosed patients.

Veauthier et al²² performed the first cross-sectional polysomnographic trial in the context of MS-related fatigue.

Table I (Continued)

	Insomnia			Parasomnia			Hypersomnia, narcolepsy, myasthenia			No sleep disorder		
	All	M	F	All	M	F	All	M	F	All	M	F
Number	22	6	16	3	2	1	13	8	5	20	21	8
%	5.4	1.5	3.9	0.7	0.5	0.2	3.1	2.0	1.2	4.9	2.9	2.0
Age (years)												
Mean	54.3	55.7	53.8	69	68.0	71.0	44.1	45.7	41.6	49.6	50.7	48.0
SEM	0.6	0.8	1.2	0.9	1.1	0.0	0.6	0.7	1.7	0.6	0.9	1.3
25%–75%	49.0–63.3	41.3–70.0	50.0–57.5	59.0–77.0	59.0–77.0	71.0–71.0	33.0–56.0	32.0–56.0	28.5–55.0	43.5–57.0	45.8–65.0	42.3–57.0
AHI/hour												
Mean	6.2	13.7	3.0	15.7	9.5	28.1	3.4	5.2	0.9	2.2	2.6	1.6
SEM	1.1	1.4	2.1	1.7	2.1	0.0	1.1	1.3	2.6	1.1	1.5	2.0
25%–75%	0.9–5.9	2.8–21.2	0.6–4.8	7.5–28.1	7.5–11.5	28.1–28.1	0.4–4.3	0.6–11.9	0.3–2.0	0.8–2.6	0.9–2.6	0.8–2.5
SpO2% min												
Mean	89.4	87.7	90.0	87.3	89.0	84.0	90.3	89.0	92.2	89.1	88.4	90.1
SEM	0.5	0.6	1.1	0.8	1.1	0.0	0.5	0.6	1.4	0.5	0.7	1.1
25%–75%	88.0–91.0	83.3–91.5	88.0–91.3	84.0–89.0	89.0–89.0	84.0–84.0	89.3–94.0	83.0–94.0	89.5–94.5	88.3–91.0	88.5–91.0	87.5–91.8
Sleep efficacy (%TST/TiB)												
Mean	70.9	67.0	72.6	72.6	69.8	78.2	75.9	72.2	81.2	76.8	76.9	76.7
SEM	0.7	0.8	1.1	1.0	1.3	0.0	0.7	0.8	1.4	0.7	1.0	1.1
25%–75%	59.6–82.7	55.2–85.5	63.7–81.5	60.7–78.9	60.7–78.9	78.2–78.2	69.2–87.4	63.9–83.0	72.1–91.3	70.6–84.5	68.5–85.1	71.7–83.1
NREM-3/4 (%TiB)												
Mean	13.5	7.8	16.0	20.3	25.4	10.3	14.1	11.3	18.9	22.5	17.6	29.8
SEM	0.6	0.7	1.2	0.9	1.1	0.0	0.6	0.6	1.6	0.6	0.7	1.3
25%–75%	5.7–21.2	4.8–10.1	5.7–24.4	10.3–29.7	21.0–29.7	10.3–10.3	5.6–19.3	0.3–19.3	15.8–23.5	15.4–23.7	13.5–21.2	19.0–45.8
Number of awakenings (per night)												
Mean	20.6	21.7	20.1	23.3	24.5	21.0	17.8	18.1	17.3	10.7	10.1	11.5
SEM	0.5	0.6	1.2	0.9	1.1	0.0	0.5	0.5	0.2	0.5	0.7	1.3
25%–75%	8.3–31.0	7.5–35.5	8.8–31.0	21.0–28.0	21.0–28.0	21.0–21.0	7.0–26.0	7.0–26.0	8.8–27.5	6.0–14.0	5.3–10.8	6.5–19.5
Arousal index (per hour)												
Mean	17.4	20.3	16.2	30.5	28.5	34.7	19.7	19.1	21.0	15.0	15.8	13.7
SEM	0.7	0.9	1.2	1.0	1.3	0.0	0.7	0.8	1.6	0.7	1.0	1.3
25%–75%	10.8–22.6	11.6–29.5	9.8–21.2	24.6–34.7	24.6–32.3	34.7–34.7	15.1–25.6	15.3–25.6	12.9–33.6	10.3–17.8	12.2–17.4	7.5–19.3
Sleep latency (minutes)												
Mean	44.8	43.8	45.2	41.5	42.8	39.0	32.6	32.3	33.3	58.7	58.3	59.3
SEM	1.5	1.8	3.2	2.4	2.6	0.0	0.5	1.7	4.2	1.5	2.1	3.2
25%–75%	21.0–58.9	16.8–74.5	21.0–49.3	26.0–59.5	26.0–59.5	39.0–39.0	10.0–44.0	10.0–44.0	7.8–61.0	41.8–69.8	37.0–59.5	47.8–75.8

They found a significant relationship between relevant sleep disorders (including sleep-related breathing disorders [SRBDs], RLS, periodic limb movement disorder [PLMD], insomnia, and others) on the one hand and fatigue measured with the MFIS and the FSS on the other hand (mean MFIS in fatigued MS patients 42.8 [standard deviation {SD} 18.3] and 20.5 [SD 17] in non-fatigued patients [$P < 0.001$]). After performing a receiver operating characteristic analysis,²³ they recommended polysomnographic investigations in all fatigued MS patients, when MFIS > 34 or Pittsburgh Sleep Quality Index (PSQI)²⁴ > 5 , so as not to overlook treatable sleep disorders.²³

Two different sleep studies have shown a significant relationship between MS-related fatigue and sleep disorders,^{22,25} and, in the corresponding follow-up trials,

medical sleep treatment led to an improvement of MS-related fatigue.^{26,27}

Aside from the abovementioned studies,^{10,11,19,21} there are only a few polysomnographic studies investigating fatigue measured with the FSS,^{28,29} and there are no other polysomnographic studies investigating fatigue measured with the MFIS in the general population.

Hossain et al described FSS mean values from 4.4 (SD 1.6) to 5.1 (SD 1.0) in OSAS, RLS, PLMD, depression, narcolepsy, parasomnia, delayed sleep phase syndrome, and insomnia,¹⁹ but as there have been, to date, no pathophysiological explanations for fatigue caused by sleep disorders, the question remains: is it caused by reduced sleep efficacy, disrupted sleep, suppressed deep sleep, intensified desaturation, or an increased number of hypopnea/apnea episodes?

Table 2 Questionnaire results

	All patients			Untreated SRBD			Treated SRBD			PLMD/RLS		
	All	M	F	All	M	F	All	M	F	All	M	F
Number	410	290	120	231	176	55	102	80	22	19	6	13
%	100	70.7	29.3	56.3	42.9	13.4	24.9	19.5	5.4	4.7	1.5	3.2
MFIS²												
Mean	32.4	30.1	38.0	32.5	31.9	35.8	28.8	24.2	45.5	44.1	32.2	48.6
SEM	1.0	1.2	1.7	1.0	1.3	1.8	1.0	1.3	1.8	1.0	1.6	1.8
25%–75%	15–49	12.0–45.0	23.8–52.0	16–47.5	15.0–45.3	22.0–49.0	10–45.5	5.5–40.5	31.5–56.3	31.8–55.8	23.0–57.0	40.5–60.5
FSS⁴												
Mean	4.0	3.7	4.6	4.1	4.1	4.2	3.5	3.1	5.0	4.5	4.0	4.5
SEM	0.1	0.1	0.2	1.1	0.1	0.2	1.1	0.1	0.2	0.1	0.1	1.2
25%–75%	2.2–5.7	2.0–5.2	3.1–6.2	2.2–5.7	2.2–5.7	2.4–5.9	2.0–5.0	1.6–4.4	3.8–6.7	3.9–5.8	2.8–5.2	3.1–5.8
ESS²⁰												
Mean	8.4	8.3	8.7	8.7	8.5	9.1	7.3	7.4	7.0	9.9	7.8	7.6
SEM	0.3	0.4	0.5	0.4	0.5	0.5	0.7	0.6	3.4	1.4	0.4	0.5
25%–75%	5–11	4.3–11.0	5.0–11.0	5–12	5.0–11.0	5.0–12.8	4–10	3.8–10.3	3.5–9.0	7–13.5	1.8–11.8	5.0–10.0
PSQI²⁴												
Mean	8.2	7.6	10.0	8.2	7.9	9.8	6.7	6.3	8.4	11.4	10.2	12.3
SEM	1.0	0.3	0.5	0.3	0.3	0.5	0.3	0.3	0.5	0.3	0.4	0.1
25%–75%	5–12	4.0–11.0	6.0–13.0	5–11	4.0–11.0	7.0–13.0	4–10	3.0–8.0	5.0–12.0	8–15	6.5–15.0	9.0–15.0

Abbreviations: ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; PLMD, periodic limb movement disorder; PSQI, Pittsburgh Sleep Quality Index; RLS, restless legs syndrome; SEM, standard error of the mean; SpO₂% min, minimal desaturation; SRBD, sleep-related breathing disorder; F, female; M, male.

The aims of this study were: to describe the MFIS values in patients admitted to a sleep laboratory and to investigate which polysomnographic parameters can predict fatigue measured with the MFIS and the FSS.

Methods

Patients

In this retrospective observational study, all consecutive patients who were admitted to the sleep laboratory of the Hanse-Klinikum, Stralsund, Germany between February 1, 2011 and January 31, 2012 were included.

Questionnaires

All patients admitted to the sleep laboratory completed the MFIS, FSS, ESS, and PSQI.

Polysomnography

Polysomnographic data were retrospectively analyzed. These whole-night measurements were made after an impedance test and a biosignal test over a period of 8 hours, comprising: C3/C4 electroencephalograph (EEG) electrodes to the contralateral mastoid electrode; ground electrode; electrooculogram on the ipsilateral mastoid electrode; bipolar chin electromyogram (EMG) of the muscle mentalis or muscle submental (according to biosignal testing and anatomical

conditions); nasal airflow (pressure sensor); thoracic and abdominal breathing (piezoelectric measurement); position sensor; snoring signal; pulse oximetry; pulse, electrocardiogram; and bipolar two-point EMG electrodes on both anterior tibial muscles.

The polysomnograph readings were scored according to the criteria of Rechtschaffen and Kales,³⁰ using 30-second epochs. The following polysomnographic parameters were included in the analysis: apnea/hypopnea index (AHI) per hour of sleep, according to the American Academy of Sleep Medicine;³¹ minimal desaturation (SpO₂% min); sleep efficacy (ratio total sleep time/time spent in bed); deep sleep (ratio non-rapid eye movement sleep stage 3 and 4 [NREM-3/4]/time spent in bed); number of awakenings; arousal index per hour of sleep; and sleep latency (time to first sleep epoch in minutes).

Subgroups

Sleep diagnoses were made according to the ICSD-2.¹⁶ Patients were divided for statistical reasons into different subgroups: (1) untreated SRBDs; (2) treated SRBDs (patients were treated with CPAP or bilevel therapy); (3) PLMD and RLS; (4) insomnia; (5) parasomnia; (6) other neurological diseases such as narcolepsy, hypersomnia, and MS (due to a low number of patients and small sample sizes, these patients

Table 2 (Continued)

	Insomnia			Parasomnia			Hypersomnia narcolepsy, myasthenia			No sleep disorder		
	All	M	F	All	M	F	All	M	F	All	M	F
Number	22	6	16	3	2	1	13	8	5	20	12	8
%	5.4	1.5	3.9	0.7	0.5	0.2	3.1	2.0	1.2	4.9	2.9	2.0
MFIS²												
Mean	33.5	38.7	31.5	7.7	2.0	19.0	40.6	42.5	37.6	26.1	19.8	34.8
SEM	1.1	1.4	1.8	1.6	2.2	0.0	1.1	1.2	2.2	1.1	1.6	1.9
25%–75%	15–47.5	13.8–56.3	15.0–44.0	0.0–19.0	0.0–4.0	19.0–19.0	22.3–57.5	29.3–54.5	12.0–62.0	5–47	0.0–34.0	16.3–51.8
FSS⁴												
Mean	4.3	4.0	4.5	2.2	1.4	4.0	5.2	5.2	5.2	3.6	2.9	5.2
SEM	1.1	0.1	0.2	0.2	0.2	0.0	0.1	0.1	0.2	1.1	0.2	0.2
25%–75%	2.9–5.8	2.8–5.2	3.1–5.8	1.1–4.0	1.1–1.6	4.0–4.0	3.7–6.6	3.7–6.4	2.8–6.7	1.0–5.0	1.0–4.1	3.8–6.6
ESS²⁰												
Mean	7.7	7.8	7.6	3.0	3.0	3.0	12.7	11.6	15.3	8.9	8.4	9.5
SEM	0.8	0.4	0.1	0.7	0.6	0.0	1.3	0.4	0.3	1.1	0.5	0.1
25%–75%	4–10	1.8–11.8	5.0–10.0	2.0–4.0	2.0–4.0	3.0–3.0	7.8–16.0	7.0–16.0	14.0–16.0	7.0–10.5	7.0–9.5	4.0–14.0
PSQI²⁴												
Mean	13.2	13.3	13.1	4.5	3.0	6.0	10.6	12.0	5.0	7.9	7.1	8.8
SEM	0.3	0.3	0.5	0.4	0.1	0.0	0.3	0.3	0.0	0.3	0.4	0.5
25%–75%	11–15	13.0–14.0	11.0–15.0	3.0–6.0	3.0–3.0	6.0–6.0	7.0–14.5	9.3–15.3	5.0–5.0	5.0–11.3	4.3–11.5	5.0–12.5

were classified into one subgroup even though these diseases are quite different); and (7) patients admitted to the sleep laboratory for tiredness or sleepiness but without pathological findings in the medical sleep investigations (exclusion of a sleep disorder).

Statistical analysis

The results were expressed as mean, SD, and range. Following an exploratory analysis of the data and after a (negative) check for normality of the underlying distributions, differences between subgroups with respect to MFIS, ESS, PSQI, and FSS were (univariately) analyzed using the Mann–Whitney *U* test. Spearman correlation coefficients were calculated to assess the relationship between questionnaire results, and polysomnographic parameters and age, and scatter plots were performed to demonstrate these relationships. We defined Spearman's rank correlations (Spearman's rho) as follows: for values between 0.9 and 1, the correlation is very strong; for values between 0.7 and 0.89, the correlation is strong; values between 0.5 and 0.69 show a moderate correlation; for values between 0.3 and 0.49, the correlation is moderate to low; and for values <0.3, the correlation is weak and not important.

Patients were classified into subgroups by MFIS (MFIS greater versus less than or equal to MFIS mean) and FSS

(FSS greater versus less than or equal to FSS mean) values. Afterwards, a logistic regression was performed in order to predict the outcome of these two dependent variables (greater versus less than or equal to FSS mean/MFIS mean) with age, sex, and polysomnographic parameters, including AHI, SpO₂% min, sleep efficacy, NREM-3/4, number of awakenings, arousal index, and sleep latency, as predictor variables. This analysis was performed in two steps: first, a univariate analysis with all predictor variables; subsequently, all significant variables remained in the final model of multiple logistic. Odds ratios were calculated. Statistical significance was established at $P < 0.05$.

All tests should be understood as constituting exploratory data analysis, such that neither previous power calculations nor subsequent adjustments for multiple testing have been made. Analysis was performed with SPSS software (v19; IBM Corporation, Armonk, NY, USA).

Results

Demographics, polysomnographic data, and questionnaire results

In sum, 410 patients 20 to 86 years (290 men and 120 women) were investigated. Table 1 displays the demographic and polysomnographic data and Table 2 shows the questionnaire results.

Table 3 Univariate nonparametric correlations between questionnaires, and age and PSG parameters

	FSS⁴		MFIS²		ESS²⁰		PSQI²⁴	
	Spearman's rho	Significance (P)	Spearman's rho	Significance (P)	Spearman's rho	Significance (P)	Spearman's rho	Significance (P)
All patients								
Scale								
FSS			0.742	<0.0001	0.289	<0.0001	0.488	<0.0001
MFIS	0.742	<0.0001			0.382	<0.0001	0.520	<0.0001
ESS	0.289	<0.0001	0.382	<0.0001			0.202	0.006
PSQI	0.488	<0.0001	0.520	<0.0001	0.202	0.006		
PSG								
AHI	0.098	0.065	0.077	0.136	0.047	0.457	0.132	0.031
SpO2% min	-0.047	0.374	-0.025	0.634	0.018	0.783	-0.078	0.207
Sleep efficacy	-0.005	0.921	0.010	0.839	0.078	0.219	-0.065	0.290
NREM-3/4	-0.036	0.503	-0.002	0.970	-0.096	0.131	-0.120	0.051
Awakening	0.098	0.068	0.158	0.002	0.176	0.005	0.278	<0.0001
Arousal index	0.038	0.481	-0.059	0.257	-0.056	0.382	-0.052	0.400
Sleep latency	0.053	0.321	0.006	0.909	-0.065	0.306	0.063	0.304
Age	-0.220	<0.0001	-0.152	0.003	-0.116	0.067	-0.120	0.050
Untreated SRBD patients								
Scale								
FSS			0.686	<0.0001	0.213	0.015	0.480	<0.0001
MFIS	0.686	<0.0001			0.387	<0.0001	0.469	<0.0001
ESS	0.213	0.015	0.387	<0.0001			0.225	0.021
PSQI	0.480	<0.0001	0.469	<0.0001	0.225	0.021		
PSG								
AHI	0.092	0.198	0.065	0.343	0.113	0.185	0.076	0.352
SpO2% min	-0.035	0.622	0.005	0.940	-0.034	0.689	-0.006	0.943
Sleep efficacy	-0.006	0.929	0.076	0.268	0.076	0.374	-0.046	0.576
NREM-3/4	-0.020	0.776	0.049	0.478	-0.127	0.137	-0.142	0.083
Awakening	0.061	0.392	0.120	0.080	0.152	0.075	0.253	0.002
Arousal index	0.083	0.244	-0.047	0.492	-0.052	0.542	0.073	0.377
Sleep latency	0.037	0.608	-0.019	0.781	-0.005	0.953	0.021	0.802
Age	-0.199	0.005	-0.142	0.037	-0.157	0.064	-0.026	0.754
Treated SRBD patients								
Scale								
FSS			0.830	<0.0001	0.192	0.176	0.447	<0.0001
MFIS	0.830	<0.0001			0.356	0.012	0.546	<0.0001
ESS	0.192	0.176	0.356	0.012			0.131	0.403
PSQI	0.447	<0.0001	0.546	<0.0001	0.131	0.403		
PSG								
AHI	0.044	0.677	0.080	0.449	-0.084	0.541	0.328	0.005
SpO2% min	-0.065	0.534	-0.160	0.125	0.107	0.437	-0.244	0.037
Sleep efficacy	-0.072	0.495	-0.161	0.124	-0.203	0.137	-0.117	0.323
NREM-3/4	0.150	0.150	0.108	0.303	-0.262	0.053	-0.036	0.763
Awakening	0.026	0.803	0.077	0.464	0.117	0.396	0.138	0.246
Arousal index	-0.182	0.080	-0.260	0.012	0.058	0.672	-0.282	0.016
Sleep latency	0.102	0.332	0.151	0.148	-0.085	0.539	0.151	0.201
Age	-0.171	0.102	-0.032	0.759	0.145	0.291	-0.157	0.184
PLMD and RLS patients								
Scale								
FSS			0.325	0.219	0.303	0.271	0.089	0.783
MFIS	0.325	0.219			0.272	0.291	0.452	0.163
ESS	0.303	0.271	0.272	0.291			-0.275	0.442
PSQI	0.089	0.783	0.452	0.163	-0.275	0.442		
PSG								
AHI	0.055	0.835	-0.040	0.875	0.240	0.353	0.444	0.148
SpO2% min	0.025	0.925	0.463	0.053	0.346	0.173	-0.407	0.189

(Continued)

Table 3 (Continued)

	FSS ⁴		MFIS ²		ESS ²⁰		PSQI ²⁴	
	Spearman's rho	Significance (P)	Spearman's rho	Significance (P)	Spearman's rho	Significance (P)	Spearman's rho	Significance (P)
Sleep efficacy	0.134	0.607	0.116	0.847	0.145	0.580	-0.221	0.491
NREM-3/4	0.060	0.819	0.558	0.016	0.359	0.157	0.355	0.257
Awakening	-0.477	0.053	0.013	0.959	0.349	0.170	-0.203	0.527
Arousal index	0.138	0.599	-0.159	0.528	-0.302	0.239	-0.323	0.305
Sleep latency	-0.020	0.938	0.046	0.856	-0.623	0.008	0.327	0.299
Age	-0.167	0.522	-0.092	0.717	0.036	0.890	0.677	0.016
Insomnia patients								
Scale								
FSS			0.551	0.022	0.474	0.063	0.267	0.523
MFIS	0.551	0.022			0.232	0.340	-0.115	0.753
ESS	0.474	0.063	0.232	0.340			0.453	0.221
PSQI	0.267	0.523	-0.115	0.753	0.453	0.221		
PSG								
AHI	-0.422	0.104	-0.019	0.937	-0.094	0.711	0.296	0.406
SpO2% min	0.406	0.119	0.303	0.194	0.210	0.403	-0.113	0.756
Sleep efficacy	-0.091	0.736	-0.074	0.755	0.054	0.831	0.006	0.986
NREM-3/4	0.367	0.162	-0.177	0.455	0.084	0.740	0.167	0.645
Awakening	0.138	0.610	0.054	0.823	0.265	0.289	0.099	0.786
Arousal index	0.055	0.841	0.135	0.569	0.061	0.811	0.661	0.038
Sleep latency	0.610	0.012	0.145	0.543	0.286	0.250	0.605	0.064
Age	-0.100	0.702	-0.091	0.694	-0.150	0.539	-0.258	0.445
Patients with MS, narcolepsy, hypersomnia								
Scale								
FSS			0.914	<0.0001	0.185	0.633	0.821	0.089
MFIS	0.914	<0.0001			-0.056	0.877	0.900	0.037
ESS	0.185	0.633	-0.056	0.877			-0.400	0.600
PSQI	0.821	0.089	0.900	0.037	-0.400	0.600		
PSG								
AHI	-0.471	0.143	-0.102	0.753	0.366	0.333	-0.600	0.400
SpO2% min	0.490	0.126	0.467	0.125	-0.527	0.145	0.800	0.200
Sleep efficacy	0.132	0.698	-0.133	0.681	0.557	0.119	0.000	1.000
NREM-3/4	-0.378	0.281	-0.482	0.133	-0.035	0.929	-0.800	0.200
Awakening	0.165	0.648	-0.264	0.432	0.235	0.543	0.600	0.400
Arousal index	0.049	0.894	0.209	0.537	-0.261	0.497	0.800	0.200
Sleep latency	-0.049	0.894	0.055	0.873	-0.322	0.398	-0.400	0.600
Age	-0.058	0.857	-0.019	0.950	0.809	0.005	-0.300	0.624
Patients without sleep disorder								
Scale								
FSS			0.890	<0.0001	0.754	0.019	0.467	0.126
MFIS	0.890	<0.0001			0.538	0.135	0.583	0.029
ESS	0.754	0.019	0.538	0.135			0.185	0.661
PSQI	0.467	0.128	0.583	0.029	0.185	0.661		
PSG								
AHI	0.188	0.503	0.168	0.493	0.350	0.356	-0.137	0.640
SpO2% min	0.075	0.790	0.329	0.169	0.249	0.518	0.064	0.828
Sleep efficacy	-0.043	0.878	-0.044	0.858	-0.067	0.864	-0.368	0.196
NREM-3/4	0.595	0.019	0.480	0.037	0.506	0.164	0.146	0.618
Awakening	0.267	0.336	0.307	0.202	0.140	0.720	0.196	0.501
Arousal index	0.477	0.072	0.111	0.652	-0.034	0.932	0.192	0.512
Sleep latency	0.225	0.420	-0.175	0.473	0.059	0.881	0.363	0.202
Age	-0.229	0.412	-0.186	0.447	0.204	0.598	0.003	0.991

Parasomnia patients: due to small sample size, correlations could not be calculated.

Notes: Definition of the correlations of Spearman's rho: very strong (0.9–1); strong (0.7–0.89); moderate (0.5–0.69); moderate to low (0.3–0.49); weak (<0.3). All significant values ($P < 0.05$) with a Spearman's rho greater or equal to 0.30 (low/moderate/strong/very strong correlation) are highlighted with bold and italic.

Abbreviations: AHI, apnea/hypopnea-index; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; NREM-3/4, non-rapid eye movement stage 3/4; PLMD, periodic limb movement disorder; PSG, polysomnographic; PSQI, Pittsburgh Sleep Quality Index; RLS, restless legs syndrome; Spearman's rho, Spearman's rank correlations; SpO2% min, minimal desaturation; SRBD, sleep-related breathing disorder.

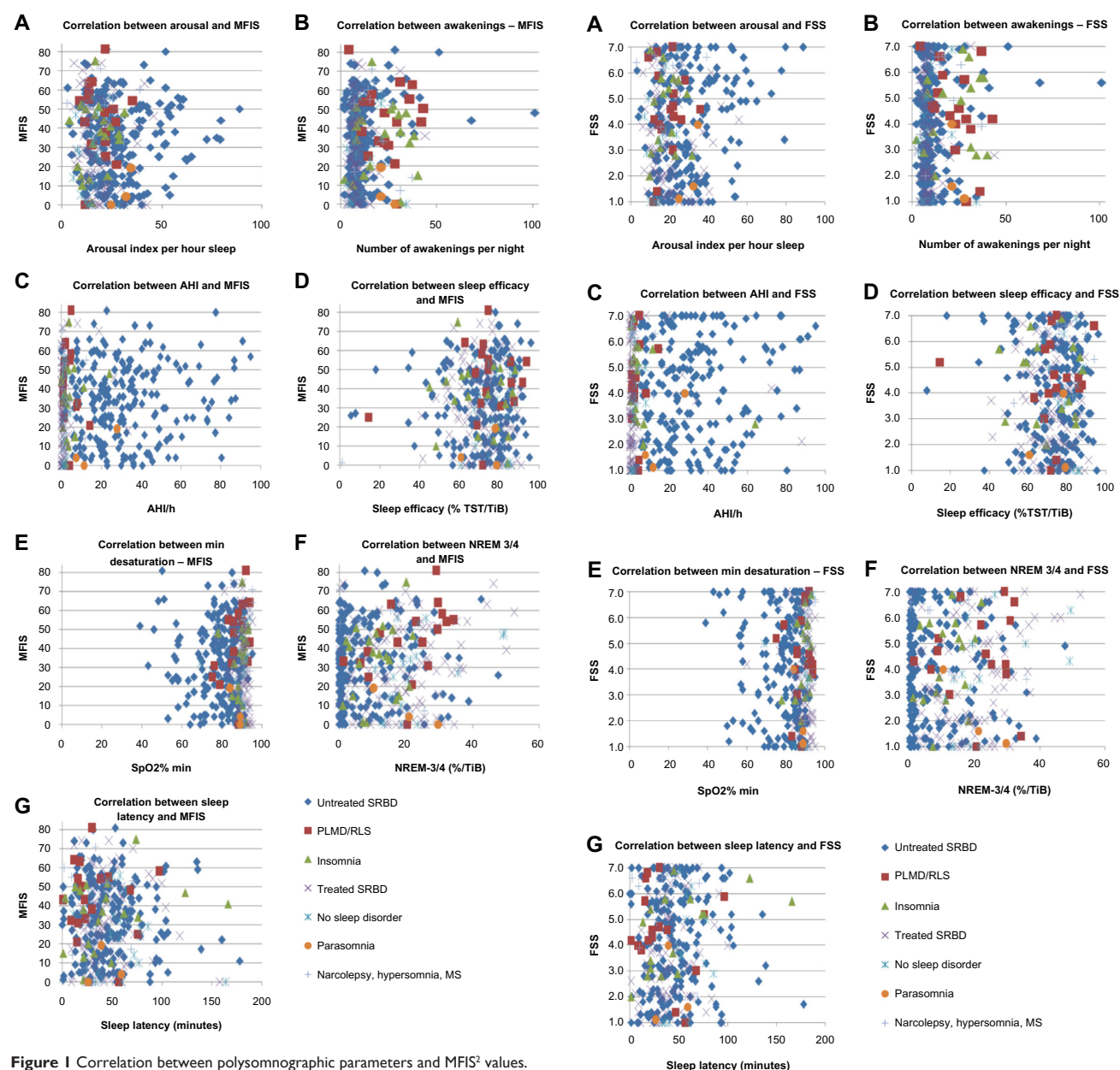


Figure 1 Correlation between polysomnographic parameters and MFIS² values.
Notes: Correlations between MFIS and (A) arousal; (B) awakenings; (C) AHI; (D) sleep efficacy; (E) SpO₂% min; (F) NREM-3/4; and (G) sleep latency. The scatter plots show a correlation between a high number of awakenings and high MFIS values. Note the higher amount of deep sleep in treated SRBD patients, which seems not to have an impact on MFIS or FSS values. It must also be pointed out that PLMD/RLS patients showed a high number of awakenings.
Abbreviations: AHI, apnea/hypopnea index; MFIS, Modified Fatigue Impact Scale; MS, multiple sclerosis; NREM-3/4, non-rapid eye movement sleep stage 3/4; PLMD, periodic limb movement disorder; RLS, restless legs syndrome; SpO₂% min, minimal desaturation; SRBD, sleep-related breathing disorder; TiB, time in bed; TST, total sleep time; FSS, Fatigue Severity Scale.

Nonparametric correlation

Table 3 shows the nonparametric correlations.

Correlations between different questionnaires

There was a moderate to strong correlation between MFIS and FSS values in the whole cohort and in all subgroups except for the PLMD/RLS subgroup.

Figure 2 Correlation between polysomnographic parameters and FSS⁴ values.
Notes: Correlations between FSS and (A) arousal; (B) awakenings; (C) AHI; (D) sleep efficacy; (E) SpO₂% min; (F) NREM-3/4; and (G) sleep latency. The scatter plots show a correlation between a high arousal-index and high FSS values.
Abbreviations: AHI, apnea/hypopnea index; MS, multiple sclerosis; NREM-3/4, non-rapid eye movement sleep stage 3/4; PLMD, periodic limb movement disorder; RLS, restless legs syndrome; SpO₂% min, minimal desaturation; SRBD, sleep-related breathing disorder; TiB, time in bed; TST, total sleep time; FSS, Fatigue Severity Scale.

There was a moderate correlation between MFIS and PSQI in the whole cohort and in SRBD patients (treated and untreated) and in patients without sleep disorders or with narcolepsy/hypersomnia/MS (but not in PLMD/RLS patients nor insomnia patients).

There was a moderate correlation between FSS and PSQI in SRBD patients (treated and untreated).

There was a low correlation between ESS values and MFIS in untreated SRBD patients and a moderate correlation between ESS values and FSS in patients without sleep disorders.

Correlations between patient age and questionnaires

Higher age was related to increased PSQI values in PLMD/RLS patients and with increased ESS values in patients with narcolepsy/hypersomnia/MS (Table 3).

Correlation between polysomnographic data and questionnaires

With respect to polysomnographic data, a low correlation could be found between increased AHI and lower minimal desaturation on the one hand and increased PSQI values on the other in treated SRBD patients.

Furthermore, there was a low correlation between the number of awakenings and PSQI in all patients and untreated SRBD patients. Similarly, there was a low correlation between an increased arousal index and higher PSQI values in treated SRBD and insomnia patients.

Figures 1 and 2 show the relationships between MFIS/FSS values and polysomnographic parameters by scatter plots. Whereas the graphical visualization did not show any correlation between MFIS/FSS values and AHI, SpO₂% min, sleep efficacy, sleep latency, or deep sleep, the scatter plots did visualize a correlation between MFIS values and the number of awakenings and between FSS values and a high arousal index.

In the subgroup without sleep disorders, we did find a moderate nonparametric correlation between increased deep sleep (NREM-3/4) and higher MFIS and FSS values and, similarly, between deep sleep and MFIS in PLMD/RLS patients.

In PLMD/RLS patients, lower sleep latency was correlated with increased ESS values. In insomnia patients, higher FSS values were correlated with increased sleep latency.

Univariate and multiple logistic regressions

We introduced the dichotomous variable “MFIS higher than MFIS mean (34.2)” (yes or no) and the dichotomous variable “FSS higher than FSS mean (4.0)” (yes or no) in order to calculate a multiple logistic regression.

The univariate logistic regression showed no significant relationship with SpO₂% min, sleep efficacy, sleep latency, or deep sleep. A significant relationship could be found with age, sex, and number of awakenings for MFIS as well as FSS (Table 4). Furthermore, there was a significant relationship with arousal index and AHI only for FSS.

The multiple logistic regression (Table 4) investigating the FSS, including age, sex, arousal index, number of awakenings, and AHI, demonstrated a significant relationship with age, sex, and arousal index, whereas AHI and number of awakenings were not significant. Younger age, female sex, and high arousal index were highly predictive of increased FSS scores.

In regards to MFIS, the multiple logistic regression (Table 4) investigating the MFIS, including age, sex, and number of awakenings, confirmed the significant relationship with age, sex, and number of awakenings. Younger age, female sex, and high numbers of awakenings predicted high MFIS values.

Discussion

This is the first study, to our knowledge, to investigate the relationship between sleep disorders and MFIS values, and we observed a number of important findings.

Firstly, this study clearly shows that sleep disorders can lead to high MFIS values in sleep-disordered patients who are not suffering from MS.

Secondly, our results show both high MFIS and FSS values in sleep-disordered patients without MS and, above all, a strong correlation between MFIS and FSS for all patients and all subgroups except for PLMD/RLS patients. (The fact that this correlation could not be demonstrated in PLMD/RLS patients could be due to small sample size).

Thirdly, the correlation between PSQI and MFIS values in all patients (except for PLMD/RLS and insomnia patients) and between PSQI and FSS in SRBD patients, suggests causation of fatigue by sleep disorders (the lack of correlation in some subgroups may be caused by small sample size). This could be confirmed by multiple logistic regressions, showing that a high number of awakenings were in line with a higher risk of developing fatigue measured with the MFIS and that a high arousal index increased the risk of developing fatigue measured with the FSS. This possible causative role of awakenings and arousals in the pathophysiology of fatigue is of particular interest, and further studies should be performed to elucidate its etiology.

Guilleminault et al used cyclic alternating pattern (CAP) to investigate the relationship between sleep instability and fatigue in patients with upper airway resistance syndrome (UARS) compared with healthy controls.³² They found higher arousal indexes and sleep disturbances measured with CAP analysis in patients with UARS that correlated with sleepiness and fatigue.

Feige et al summarized the hyperarousal concept in their review about sleep microstructural differences in chronic insomnia.³³ They recommended spectral analysis of the

Table 4 Univariate and multiple logistic regressions

	Univariate logistic regressions			Multiple logistic regressions		
	OR	95% CI	P-value	OR	95% CI	P-value
FSS¹						
AHI/hour	1.011	1.001–1.020	0.033	1.005	0.992–1.017	0.484
SpO2% min	0.978	0.957–1.000	0.051			
Sleep efficacy (% TST/TiB)	0.994	0.977–1.011	0.459			
NREM-3/4 (% of TiB)	1.007	0.988–1.025	0.479			
Number of awakenings	1.024	1.000–1.049	0.047	1.018	0.993–1.043	0.155
Arousal index/hour	1.020	1.004–1.036	0.017	1.022	1.001–1.044	0.043
Sleep latency (minutes)	1.003	0.995–1.012	0.416			
Age (years)	0.977	0.960–0.995	0.010	0.974	0.956–0.992	0.006
Sex (F/M)	2.047	1.259–3.327	0.004	2.387	1.418–4.020	0.001
MFIS²						
AHI/hour	1.008	0.998–1.017	0.106			
SpO2% min	1.002	0.982–1.023	0.817			
Sleep efficacy (% TST/TiB)	1.004	0.989–1.020	0.598			
NREM-3/4 (% of TiB)	1.006	0.988–1.023	0.517			
Number of awakenings	1.052	1.023–1.081	<0.0001	1.043	1.015–1.073	0.002
Arousal index/hour	1.009	0.994–1.024	0.255			
Sleep latency (minutes)	0.998	0.991–1.005	0.606			
Age (years)	0.981	0.964–0.964	0.026	0.981	0.964–0.999	0.042
Sex (F/M)	2.377	1.483–3.811	<0.0001	2.108	1.292–3.441	0.003

Notes: The independent variables in the first regression include all polysomnographic parameters and age and sex. All variables that were significant in the first univariate analysis (age, sex, the number of awakenings, and for FSS values, additionally, arousal index and AHI) remained in the final model of multiple logistic regressions. The independent variables age and sex predict high FSS and MFIS values after multiple logistic regressions. In addition, a high number of awakenings predict high MFIS values, and a high arousal index predicts high FSS values. ORs were calculated, which reflect the probability to develop fatigue measured with MFIS and FSS. Bold italic font indicates significant odds ratios.

Abbreviations: AHI, apnea/hypopnea index; CI, confidence interval; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; NREM-3/4, non-rapid eye movement sleep stage 3/4; OR, odds ratio; SpO2% min, minimal desaturation; TiB, time in bed; TST, total sleep time; F, female; M, male.

sleep EEG, microarousal, and CAP analysis as a research instrument of sleep in insomnia. It would be promising to investigate fatigue as well with these methods in patients without known sleep disorders, in order to find out what drives fatigue.

On the other hand, little is known about the impact of arousal on fatigue in sleep disorders. Yue et al³⁴ found a significant relationship between emotional fatigue measured with the Multidimensional Fatigue Symptom Inventory short form³⁵ and spontaneous movement arousals in untreated OSAS patients. It is worth noting that previous studies have not shown a significant association between the severity of OSAS (AHI, SpO2% min) and fatigue scores.^{36,37} In our study, there was also no significant relationship between fatigue and AHI or SpO2% min after multiple logistic regressions.

Previous polysomnographic investigations of consecutive MS patients showed a significant association of sleep disorders with fatigue (FSS/MFIS),²² but not with sleepiness (ESS). Supporting this finding, the works by Hossain et al¹⁹ and Aguillard et al²¹ showed that, in sleep-disordered patients without MS, fatigue and sleepiness can occur independently as well as together.

In the present study, there was not a significant relationship between MFIS values and ESS values (only untreated SRBD patients showed a low correlation between ESS values and MFIS). The fact that we found a strong correlation between ESS values and FSS values in patients without sleep disorders remains without explanation. We have to note that these patients were not healthy controls, but rather fatigued and sleepy patients without pathological findings either in the primary health care setting or in the sleep laboratory.

Overall, as we performed multiple logistic regressions only for MFIS and FSS values, we cannot interpret the correlations between ESS and PSQI values and age or sex or polysomnographic parameters. Our study was focused on the relationship between sleep disorders and FSS and MFIS.

In our study, women had a higher risk of suffering from fatigue than men. Our results are in line with a previous study,¹⁷ suggesting that, in SRBD patients, fatigue may be particularly correlated with female sex: in our study, female sex was predictive of high FSS and MFIS values. Currently, we have no explanation for this relationship and further studies are needed to investigate the pathophysiological mechanisms. Similarly, we have no explanation for the fact

that younger age is predictive of fatigue and further studies are needed to understand this relationship as well.

The present study has some methodological limitations: due to the retrospective design and owing to the lack of exclusion criteria, we cannot exclude that some patients have other reasons for fatigue as a possible confounder. On the other hand, this study reflects the daily clinical praxis with consecutive patients over 1 year.

Conclusion

Younger age, female sex, and high number of awakenings and arousals are predictive of fatigue in sleep-disordered patients. Further investigations are needed to find the pathophysiological link for this relationship. This study proves that high MFIS and FSS values can occur in sleep-disordered patients.

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Disclosure

The author reports no conflicts of interest in this work.

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