






# Sleep disorders in multiple sclerosis: a case-control study using the São Paulo Epidemiologic Sleep Study (Episono) database

## *Alterações de sono em esclerose múltipla: um estudo caso-controle utilizando o banco de dados do São Paulo Epidemiologic Sleep Study (Episono)*

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### Abstract

**Background** Sleep disorders such as obstructive sleep apnea and restless legs syndrome are prevalent in the general population and patients with chronic diseases such as multiple sclerosis (MS).

**Objectives** This study compared the prevalence of sleep disorders complaints, fatigue, depression, and chronotype of adult patients with multiple sclerosis (PwMS) to a representative sample of São Paulo city residents.

**Methods** A comparative study was made between PwMS and volunteers from the São Paulo Epidemiologic Sleep Study (Episono) study. We compared the scores of sleep questionnaires using the multivariate analysis of variance (MANOVA) test to evaluate the effects and analysis of variance (ANOVA) as a follow-up test. Covariates were age, sex, and physical activity. The Pearson correlation test was performed to measure the correlation between Expanded Disability Status Scale (EDSS) and the scores of the sleep questionnaires. Finally, we applied propensity score matching to reduce bias in estimating differences between the two groups. Analyses were performed using Stata 14 (StataCorp, College Station, TX, USA) and IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA).

**Results** The Episono group had worse sleep quality, and more excessive daytime sleepiness than PwMS. Obstructive sleep apnea and restless legs syndrome were more frequent in the Episono group. There was no difference in chronotype between the two groups, with morning and intermediate preference. There was no correlation between EDSS and sleep complaints. Fatigue was intensively present among PwMS.

### Keywords

- ▶ Multiple Sclerosis
- ▶ Fatigue
- ▶ Restless Legs Syndrome
- ▶ Sleep Apnea, Obstructive
- ▶ Depression
- ▶ Sleep

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**Conclusions** Disease Modifying Drug (DMD)-treated PwMS had a lower frequency of sleep complaints, no difference in chronotype, and a higher prevalence of fatigue than a sample of São Paulo city residents. The immunomodulatory drugs commonly used to treat MS may have contributed to these findings.

## Resumo

**Antecedentes** Os distúrbios do sono são prevalentes na população em geral e em pacientes com doenças crônicas, como a esclerose múltipla (EM).

**Objetivos** No presente estudo, comparamos a prevalência de queixas de distúrbios do sono, fadiga, depressão e cronotipo de pacientes adultos com EM com uma amostra representativa dos moradores da cidade de São Paulo.

**Métodos** Estudo comparativo entre pacientes com EM e voluntários saudáveis do estudo São Paulo Epidemiologic Sleep Study Episono. Comparamos as pontuações dos questionários de sono usando o teste de análise de variância multivariada (MANOVA, na sigla em inglês) para avaliar os efeitos e o teste de análise de variância (ANOVA, na sigla em inglês) como um teste de acompanhamento. As covariáveis usadas foram idade, gênero e atividade física. O teste de correlação de Pearson foi aplicado para medir a correlação entre o Expanded Disability Status Scale (EDSS) e os escores dos questionários de sono. Por fim, aplicamos o Propensity Score Matching para reduzir o viés na estimativa das diferenças entre os dois grupos.

**Resultados** O grupo Episono apresentou pior qualidade do sono e mais sonolência excessiva diurna do que os pacientes com EM. A apneia obstrutiva do sono e a síndrome das pernas inquietas foram mais frequentes no grupo Episono. Não houve diferença no cronotipo entre os dois grupos, com predomínio matutino e intermediário. Os pacientes com EM apresentaram mais fadiga do que o grupo controle.

**Conclusões** Pacientes com EM tratados apresentaram menor frequência de queixas de sono, sem diferença no cronotipo, com maior prevalência de fadiga do que uma amostra de moradores da cidade de São Paulo. Os medicamentos imunomoduladores comumente usados para tratar EM podem ter contribuído para estes achados.

## Palavras-chave

- ▶ Esclerose Múltipla
- ▶ Fadiga
- ▶ Síndrome das Pernas Inquietas
- ▶ Apneia Obstrutiva do Sono
- ▶ Depressão
- ▶ Sono

## INTRODUCTION

Multiple sclerosis (MS) is a demyelinating, progressive, degenerative autoimmune disease of the central nervous system (CNS). The symptoms depend on the disease subtype and the affected site, being notoriously heterogeneous in their clinical expressions and response to treatment.<sup>1</sup> Multiple sclerosis is one of the most common causes of neurological disability in young adults. It affects > 2 million people worldwide and is more prevalent in women.<sup>2</sup> Comorbidities are common in MS and contribute to increased disability. Depression, anxiety, pain, and fatigue are very prevalent, and sleep disorders may affect from 25 to 54% of the patients.<sup>3</sup>

Recent studies show that patients with MS (PwMS) are at a greater risk for developing sleep disorders, and their consequences may worsen or lead to fatigue and other chronic symptoms.<sup>3</sup> Sleep disorders remain underdiagnosed, unrecognized, and untreated in these patients.<sup>4</sup> Besides, chronotype can influence autoimmune diseases, and the eveningness chronotype may generate fatigue, which can be a potential confounder in diagnosing these illnesses when they are associated with MS.<sup>5</sup>

The objective of the present study was to investigate the frequency of sleep complaints in PwMS and to understand

their relationship with fatigue and disability. We compared a sample of Brazilian patients living in the city of São Paulo, state of São Paulo, with a group of people that were part of an ongoing epidemiologic sleep diseases study referred to as the Episono study.

## METHODS

### Design

This is a case-control study comparing PwMS with a control group. Patients were recruited from March to December 2016 at the Neuroimmunology Clinic from the Neurology and Neurosurgery Department of the Escola Paulista de Medicina of the Universidade Federal de São Paulo (UNIFESP, in the Portuguese acronym), a tertiary center for the treatment of patients with MS and other demyelinating diseases. The control group was composed of people who participated in the Episono study.

### Patients

Patients with MS,  $\geq 18$  years old, fulfilling the McDonald criteria revised in 2010 by Polman et al.<sup>6</sup> with a minimum 6-month follow-up, were included in the study. They were randomly selected from the scheduled appointments for the

day and were invited to participate and respond to the sleep questionnaires. The exclusion criteria were severe cognitive impairment, history of recent relapse, or corticosteroid use within the previous 4 weeks, and untreated comorbidities such as urinary tract infection, hypothyroidism, or diabetes.

A researcher trained in sleep disorders (Toscano V. G.) but not an expert conducted all the interviews and actively filled out the questionnaires during the medical appointments of the patients.

### Control group – Episono study

The São Paulo Epidemiologic Sleep Study (Episono) database is the most extensive epidemiological study of sleep disorders performed in Brazil. A team hired by the Instituto Datafolha and trained by professionals of the Instituto do Sono conducted the household interviews. Sleep questionnaires were applied during the visit of the technician to the home of the selected individual. In the second wave of the study, from July 2015 to April 2016, 715 volunteers were interviewed and responded to the sleep questionnaires.<sup>7</sup>

### Ethics approval

The research protocol was approved by the UNIFESP Research Ethics Committee (CAEE: 14058213.9.0000.5505), and all patients signed the informed consent form.

### Questionnaires

We used the same questionnaires and assessment tools employed by the Episono study to analyze the presence of complaints related to sleep disorders and depression: the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), the Morningness-Eveningness Questionnaire (MEQ-SA), the Berlin Questionnaire, and the Beck Depression Inventory (BDI). The exception was the fatigue questionnaire. The control group was investigated using the Chalder Fatigue Scale; the patients were investigated using the Fatigue Severity Scale (FSS) questionnaire. International Restless Legs Syndrome (IRLS) was not applied to all patients, but only to those who responded positively to the following question: “In the last 12 months, have you felt a strong urge to move your legs?” Only this answer was compared between groups. The complete questionnaire was applied to all volunteers in the Episono group.

### Clinical variables

We collected demographic data and information on gender, date of birth, education, profession, and physical activity during the interview, as well as neurological disability measured by Kurtzke Expanded Disability Status Scale (EDSS) scores, age at onset of symptoms, duration of disease, length of follow-up, clinical form, date of the last relapse, MS previous and current treatments, medications for other clinical conditions, comorbidities, smoking, and drinking.

### Study endpoint

The primary endpoint was to compare the frequency of sleep complaints between PwMS and the Episono database and understand their relationship with fatigue and disability.

### Statistical analysis

We described categorical data as absolute values (*n*), relative frequency (percentage), and continuous variables as mean and standard deviation (SD).

As an initial step, we conducted the multivariate analysis of variance (MANOVA) test to evaluate the effects of comparing the two groups (MS and Episono) in the five different questionnaires (PSQI, ESS, MEQ-SA, BDI, and Berlin). We added sex, age, and physical activity as covariates and univariate analysis of variance (ANOVA) for each dependent variable as sequential tests to statistically significant MANOVA. We performed the Pearson correlation test to measure the relationship between the EDSS and the scores of the sleep questionnaires. We used the Bonferroni method to control Type I error rates for multiple comparisons and tested each ANOVA at a significance level of 0.008.<sup>8,9</sup>

Different observational studies generated the MS and the Episono databases. We applied the propensity score matching (PSM) technique to adjust matching cases and controls, reducing bias in estimating “treatment effects” and controlling for imbalances between the two groups. We matched cases and controls by gender, age, and physical activity.

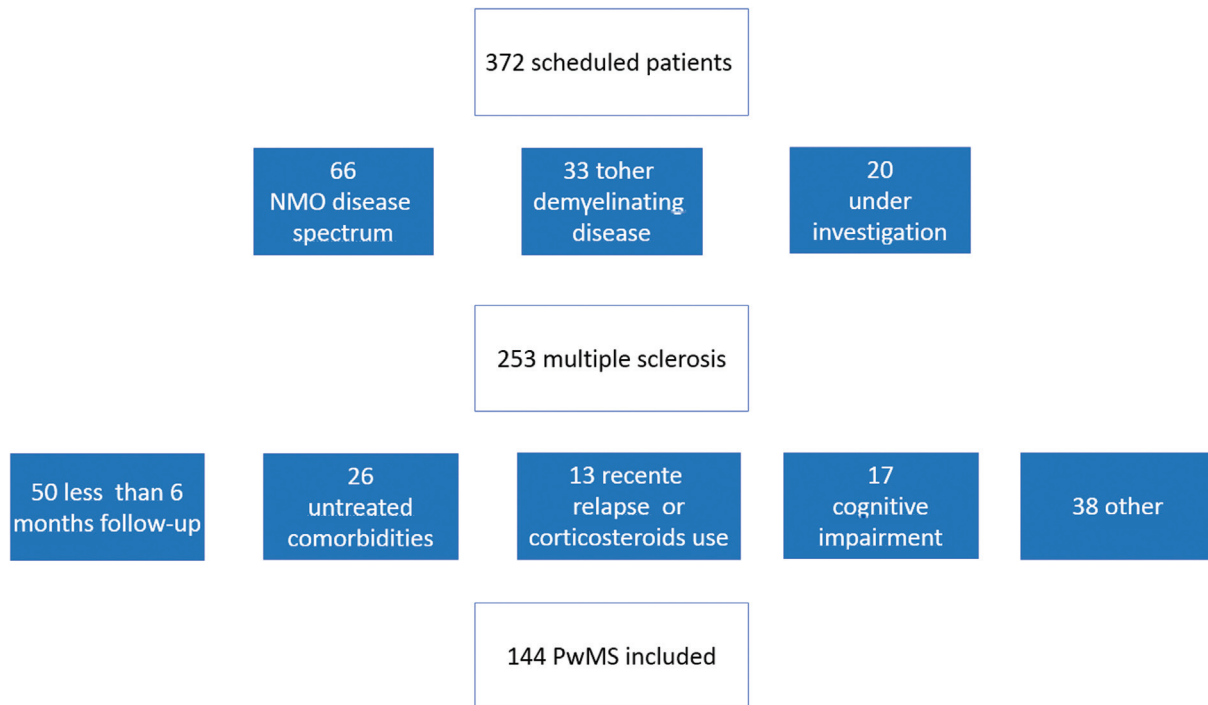
Analyses were performed using Stata Statistical Software release 14 (StataCorp, College Station, TX, USA) and IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY, USA).

## RESULTS

A total of 114 patients were interviewed, and the recruitment details are shown in ► **Figure 1**. Patient clinical data are summarized in ► **Table 1**. Relapsing-remitting MS (RRMS) was the most common clinical form of the disease (88%). The mean age at the onset of symptoms was 28.7 years old, ranging from 7 to 58 years old. The average follow-up time at the MS clinic was 6.02 years (0.5 to 25 years), and the average disease duration was 9.3 years (1 to 27 years). The EDSS ranged from zero to 8, with most patients having a mild neurological disability with an average EDSS of 2.5. Twenty-six patients (22%) had EDSS > 6.0, meaning that they needed assistance to walk. Thirty-two patients (35.6%) had a normal neurological examination. ► **Table 2** describes the most affected functional systems.

The most frequent MS disease-modifying drugs (DMDs) used were interferon- $\beta$  (25%) and fingolimod (25%), followed by glatiramer acetate (15%), natalizumab (7%), and dimethyl fumarate (6%). Only 15 (13%) patients were untreated, due to either advanced disease or a recent diagnosis.

Sixty-five patients (57%) presented any level of fatigue. Depression and anxiety were common concomitant psychiatric diseases (34.2% of the patients were on antidepressant drugs). Sixty-two patients (55%) were on medication with a known effect on sleep patterns. Within this group, patients were taking antidepressants (selective serotonin reuptake inhibitor – 28%), drugs for pain and spasticity (17.5%), anti-convulsants (14.9%), benzodiazepines, and sleep inducers (7%). ► **Table 3** summarizes the main classes of non-DMD treatment.



**Figure 1** Recruitment details. The researcher interviewed patients every Friday in 2016. During this period, 372 patients were scheduled for routine appointments, of which 253 had a confirmed diagnosis of MS, 66 of NMO disease spectrum, 33 of other demyelinating diseases and 20 was still under investigation. Among patients with MS, 50 were excluded for having less than 6 months follow-up, 26 for having untreated comorbidities, such as urinary infection, decompensated diabetes, uncontrolled hypertension, 13 for presenting recent relapse or corticosteroids use, 12 for cognitive impairment and 38 for other causes. NMO: neuromyelitis optica; PwMS: patients with multiple sclerosis. Abbreviations: NMO, neuromyelitis optica; PwMS, patients with multiple sclerosis.

► **Table 4** shows epidemiologic data and the results sleep of the questionnaires for cases and controls, showing distinct characteristics. In the MS group, patients were younger than in the Episono group (mean age of 38.1 and 50.3 years old, respectively). About two-thirds of the patients in the MS group were female, while in the Episono group, males formed a discrete majority of 55%. Almost half (46.5%) of the 114 patients in the MS group engaged in physical activity at least twice a week, while in the control group only 36.7% of the patients did it. Current smoking was reported by only 12 of the 114 patients with MS (10.5%), and alcoholism, considered here as  $\geq 1$  alcohol doses for  $> 2$  days a week, was reported by 9%. In the Episono group, 36.4% stated they were smokers, and 11% that they were alcoholics.

We found that PwMS compared with the control population were statistically different on three scales (PSQI, ESS, and Berlin). The lowest, but still statistically significant difference between the MS and control groups was in the Berlin scale ( $F=9.561$ ;  $p=0.002$ ; partial  $\eta^2=0.012$ ), in which the Episono population had, on average, a greater likelihood for obstructive sleep apnea than the MS group ( $p=0.002$ ).

The PSQI score was higher among controls than among patients (6.37 for the Episono versus 4.02 for MS). The number of subjects with  $\geq 5$  points in the PSQI was significantly higher in the Episono group (63%) than in the MS group (33%). Similarly, on the ESS (9.29 for Episono versus 6.21 for MS), the number of subjects with  $\geq 10$  points was

much higher in the Episono group (47%) than in the MS group (32%). Lack of statistical significance ( $p > 0.008$  due to the correction for multiple assessed outcomes) was obtained when comparing MS and the control group on the Morningness-Eveningness Questionnaire – Self Assessment Version (MEQ-SA) and Beck's Depression Inventory (BDI) scales..

On average, females had higher scores than males in the PSQI and BDI scales. Those who engaged in physical activity scored 2.707 points lower in the BDI scale than those who did not exercise regularly. Regarding age, the older the patients, the lower the ESS scores, and the higher the marks on MEQ-SA.

Among PwMS, the EDSS was not correlated with sleep complaints. However, fatigue and depression were strongly correlated, and we observed a moderate correlation between fatigue and the Berlin scale. The results of the Pearson correlation between the EDSS and the sleep questionnaires are presented in ► **Table 5**.

A total of 138 out of 715 volunteers (19.3%) presented restless legs syndrome, according to International Restless Legs Syndrome Rating Scale (IRLS) in the Episono study. In the MS group, only 7 out of 114 (6%) patients had a definite clinical diagnosis of RLS. Results are summarized in ► **Table 6**.

► **Table 7** demonstrates the PSM average treatment effect (ATE) between patients and controls, matched by gender, age, and physical activity. The PSQI and ESS scores were 3 and 4.5 points lower, respectively, for the MS group. Besides, patients with MS were 24.4% less likely to be at risk for

**Table 1** Clinical data – multiple sclerosis group

MS Information		Mean (n)	Min-Max (%)
Age at onset		28.7	7–58
Disease duration (years)		9.3	0.5–27
Follow-up duration (years)		6.02	0.5–25
EDSS		2.5	0.0–8.0
Clinical forms	RRMS	101	88%
	SPMS	7	7%
	PPMS	6	5%
Fatigue (FSS)	None	49	42.9
	Mild	14	12.2
	Moderate	18	15.7
	Intense	33	28.9
Concomitant diseases	Depression and anxiety	24	21.0
	Hypertension	11	9.6
	Hypothyroidism	8	7.0
MS treatment	Interferon- $\beta$	25	21.9
	Fingolimod	25	21.9
	Glatiramer acetate	15	13.1
	Natalizumab	7	6.1
	Dimethyl fumarate	6	5.2
CNS target medication use	Antidepressants	32	28.0
	Drugs for pain and spasticity	20	17.5
	Anticonvulsants	17	14.9
	Benzodiazepines and sleep inducers	8	7.0

Abbreviations: CNS, central nervous system; EDSS, Expanded Disability Status Scale; FSS, Fatigue Severity Scale; MS, multiple sclerosis; PPMS, primarily progressive multiple sclerosis; RRMS, relapse-remitting multiple sclerosis; SPMS, secondarily progressive multiple sclerosis.

obstructive sleep apnea than the control population ( $p < 0.001$ ).

## DISCUSSION

Patients with MS have a higher risk of developing sleep disorders and of even having their MS symptoms, such as fatigue, worsened by sleep disorders.<sup>10–12</sup> However, in the

**Table 2** Main Expanded Disability Score Scale functional systems affected in the multiple sclerosis group

Symptoms	Frequency (%)
Pyramidal tract	55 (48.2)
Visual symptoms	34 (29.8)
Cerebellar symptoms	29 (25.4)
Sensitivity symptoms	22 (19.2)
Brain stem	16 (14)
Bladder and anal sphincter	9 (7.8)
Mental impairment	0 (0)

present study, PwMS on regular DMD treatment had better sleep quality and less excessive daytime sleepiness (EDS) than a control group living in the same city.<sup>13</sup> It should be noted that the Episono database contains sleep information from individuals who may have sleep disorders, other neurological diseases, and clinical illnesses or not, as well as

**Table 3** The non-disease-modifying drug treatment used as a total dose by the patients with multiple sclerosis

Drug	Number of patients (%)
SSRI antidepressants	32 (28)
Anticonvulsants	17 (14.9)
Amantadine	13 (11.4)
Benzodiazepines/sleep inducers	8 (7)
Baclofen	7 (6.1)
SSNRI antidepressants	4 (3.5)
Tricyclic antidepressants	4 (3.5)

Abbreviations: SSRI, selective serotonin reuptake inhibitor; SSNRI, selective serotonin and noradrenaline reuptake inhibitor.

**Table 4** Epidemiologic and sleep questionnaires data

		MS (n = 114)	Episano (n = 715)	(Manova / Anova)
Age (years old)	Mean	38.1	50.3	p < 0.001
	Range	18 - 68	27 - 68	
Gender, n (%)	Women	82 (71.9%)	321 (45.0%)	p < 0.001
	Men	32 (28.1%)	394 (55.0%)	
Physical activity, n (%)	Yes	53 (46.5%)	263 (36.7%)	
	No	61 (53.5%)	452 (63.3%)	
Smoking, n (%)	Yes	12 (10.5%)	260 (36.4%)	
	No	94 (82.5%)	455 (63.6%)	
	Ex-smoking	8 (7.0%)	n/a	
Drinking, n (%)	Yes	10 (9.00%)	78 (11.0%)	
	No	104 (91.0%)	634 (89.0%)	
Mean questionnaire scores (±SD)	PSQI	4.02 (3.23)	6.37 (3.71)	p < 0.001
	ESS	6.21 (6.13)	9.29 (5.40)	p < 0.001
	MEQ-SA	54.60 (14.91)	59.59 (10.72)	p = 0.116
	BDI	8.32 (9.76)	9.99 (8.97)	p = 0.010
	Berlin	1.18 (0.39)	1.37 (0.48)	p = 0.002

Abbreviations: BDI, Beck Depression Inventory; Berlin, Berlin Questionnaire; ESS, Epworth Sleepiness Scale; MEQ-SA, Morningness-Eveningness Questionnaire; MS, multiple sclerosis; PSQI, Pittsburgh Sleep Quality Index.

**Table 5** Pearson correlation test

	EDSS	ESS	MEQ-SA	BDI	FSS	Berlin	PSQI
EDSS	1.000						
	114						
ESS	0.0577	1.000					
	1.000						
	114	114					
MEQ-SA	- 1.64	- 0.0948	1.000				
	1.000	1.000					
	114	114	114				
BDI	0.0351	0.2634	- 0.1007	1.000			
	1.000	0.0974	1.000				
	114	114	114	114			
Fatigue	0.1872	0.3192	- 0.1461	0.6116	1.000		
	0.9692	0.0113	1.000	0.000			
	114	114	114	114	114		
Berlin	0.0584	0.2878	- 0.2268	0.4154	0.4321	1.000	
	1.000	0.0399	0.3204	0.0001	0.000		
	114	114	114	114	114	114	
PSQI	0.2581	- 0.1069	- 0.1652	0.4255	0.3819	0.3063	1.000
	1.000	1.000	1.000	0.1625	0.3774	1.000	
	38	38	38	38	38	38	38

Abbreviations: BDI, Beck Depression Inventory; Berlin, Berlin Questionnaire; EDSS, Expanded Disability Severity Scale; ESS, Epworth Sleepiness Scale; MEQ-SA, Morningness-Eveningness Questionnaire; PSQI, Pittsburgh Sleep Quality Index.



**Table 6** Number and percentage of individuals who responded positively to the question about the urgency of moving legs

	Interviewed	Positive answer
Episono	715	138 (19.3%)
Multiple sclerosis	114	7 (6.1%)

diverse health habits. Thus, by selecting the control group from a database of people living in São Paulo, our results could have been affected by a different range of conditions and unknown health states.

The Episono group has older people and more males, explaining the higher risk for obstructive sleep apnea and lower sleep quality. However, the difference in sleep quality persisted even after matching cases and controls by gender, age, and physical activity. Patients with MS still showed better sleep quality and less EDS. It is worth considering that patients in the MS group are closely monitored at the outpatient clinic. Their MS-related symptoms, such as depression, fatigue, and pain, are treated, allowing them a better sleep quality and a lower EDS rate.

One must consider that past studies, especially those conducted > 10 years ago, may have overestimated the frequency of sleep disorders in PwMS. For instance, patients with other demyelinating diseases, such as Neuromyelitis optica spectrum disorders (NMOSD) may have been inadvertently included in these trials. In addition, this era of modern MS-modifying treatment may be contributing to alleviate the effects of the disease on the sleep patterns of patients, even though some DMDs negatively affect sleep.<sup>14</sup>

Trenkwalder et al. published a systematic review in 2016 on RLS associated with other diseases. They observed an increased RLS associated only with iron deficiency and kidney diseases.<sup>15</sup> They concluded that for all other diseases, such as MS, non-iron deficiency anemias, pulmonary and cardiovascular diseases, there is insufficient evidence in the literature to support the increased prevalence of RLS in these patients.

The presence of RLS in other autoimmune diseases makes our results even more intriguing. Inflammatory bowel diseases (IBD), such as Crohn disease and ulcerative colitis, commonly have neurological symptoms, including fatigue and RLS.<sup>16</sup> On the other hand, patients with IBD often have

anemia and micronutrient deficiency, such as iron depletion, which may not occur in PwMS.

We verified that PwMS did not have a higher prevalence of RLS compared with the control group. The frequency of RLS in PwMS was three times lower. The present study was not designed to evaluate laboratory findings and their impact on the presence of sleep disorder in the cohort described herein. Therefore, the presence or not of iron deficiency could not be accessed as a possible cause for RLS.

Indeed, our results could be a direct consequence of modern MS treatment. The anti-inflammatory effects of DMDs may account for these findings as there is a body of evidence suggesting that inflammation plays a role in the dysfunction of the dopaminergic system that leads to RLS.<sup>17,18</sup> Recently, Shaygannejad et al. described sleep disorders in PwMS, neuromyelitis optica spectrum disorder, and clinically isolated syndrome. The authors found a higher frequency of RLS in patients with secondary progressive MS when inflammation is compartmentalized inside the CNS, and the common DMDs are ineffective.<sup>19</sup> However, their study lacked a control population.

The chronotype shifts with age toward morningness. A systematic review that included studies from 27 different countries with > 36,000 participants confirmed it.<sup>20</sup> There is evidence in the literature that links chronotype and autoimmune diseases. Chrobak et al.<sup>5</sup> found more evening chronotype individuals in a group of patients with IBD compared with a control group. Crohn disease and ulcerative colitis share common characteristics with MS: they are T cell-mediated autoimmune diseases and respond to the same treatment with monoclonal antibodies acting through blockade of  $\alpha$  4-integrin molecules present in the membrane of lymphocytes. Therefore, it seemed plausible to investigate the chronotype among our patients.

According to the MEQ-SA scores, there is no difference in chronotype between the groups in the present study. Most individuals in both groups have a morning or intermediate preference. Interestingly, the MS group is 12 years younger than the Episono group. The loss of neuronal synapses, chronic inflammation, and oxidative stress, present in the brain of PwMS, contribute to an early aging brain<sup>21</sup> and possibly disrupt the circadian rhythm. Further investigation is needed, especially evaluating brain MRI enhancing lesions, brain atrophy, and chronotype.

**Table 7** Comparable results between the multiple sclerosis and Episono groups using propensity score matching (PSM-ATE)

Outcomes	Coefficient ATE (MS versus Episono)	Robust std. error	Z	p-value	CI	
PSQI	- 3.000	0.395	-7.600	< 0.001	-3.785	-2.234
ESS	- 4.591	0.753	-6.100	< 0.001	-6.067	-3.116
MEQ-SA	- 4.137	2.099	-1.970	0.049	-8.252	-0.022
BDI	- 3.163	1.520	-2.080	0.038	-6.143	-0.183
Berlin	- 0.244	0.030	-0.759	< 0.001	-0.308	-0.181

Abbreviations: BDI, Beck Depression Inventory; Berlin, Berlin Questionnaire; CI, confidence interval; ESS, Epworth Sleepiness Scale; MEQ-SA, Morningness-Eveningness Questionnaire; PSQI, Pittsburgh Sleep Quality Index.

Fatigue is a common symptom in PwMS, and it exists regardless of sleep disorders, although their presence could aggravate it.<sup>22,23</sup> Braga et al.<sup>24</sup> showed that fatigue was present in 64% of patients with RRMS and was strongly associated with depression in a recent study. In addition, the authors found a relationship between EDS and fatigue. Our study corroborates these findings and shows that 55% of PwMS presented with fatigue with variable degrees of severity, and one-third of them also presented with depression. However, the use of antidepressants was not restricted to those with psychiatric diseases. In some cases, fatigue was the reason for it, adding an extra layer of complexity. The correlation between fatigue and depression was the strongest and it was independent of neurological disability.

Depression is the most common psychiatric disorder associated with MS.<sup>25</sup> Nonetheless, no significant differences between the groups were noted even after applying the propensity scores matching analysis. This result is biased since 34.3% of the patients were on at least one full-dose antidepressant drug. It is essential to acknowledge that such treatment could be a confounding factor as some antidepressants improve sleep quality,<sup>26</sup> especially in patients with chronic insomnia, which is often associated with depression. Besides, we observed that practice of physical activity was negatively related to the BDI scores, both in the MS and Episono groups, which confirms some of the results described by Mayo et al., in which frequent or vigorous physical exercises are associated with lower rates of depression.<sup>27</sup>

It is worth noting the limitations of our study. Cases and controls came from different observational datasets obtained by distinct researchers, albeit using the same questionnaires. However, in terms of post-hoc sample size evaluation, the MANOVA design with 1 factor (that is, MS versus Episono with unbalanced sample size) and 5 response variables with 829 subjects achieved 100% power to test the *group* factor if a Wilks Lambda approximate F- test is used, with a 0.008 significance level. Besides, matching cases and controls by age, gender, and physical activity allowed for a better comparison between the groups. The Episono dataset provided information on a sample of residents of the city of São Paulo, enabling us to have a control group more similar to the general population.

Although we performed a comparative analysis between PwMS and data from the Episono study, we did not include a questionnaire to diagnose insomnia and evaluate the quality of life. Therefore, we may have failed to detect insomnia as a cause of reduced sleep quality in some patients. On the other hand, the PSQI showed that PwMS with poor sleep quality have difficulty initiating (22%) or maintaining sleep (21%), suggesting chronic insomnia disorder, even when excluding patients with sphincter involvement. We could not assess more broadly the sleep of patients, as we did not have a sleep diary or polysomnography information that could have been compared with the control group.

In addition, there were few patients with chronic progressive MS. We cannot say whether these patients are at greater risk of developing sleep disorders since the small

number of patients with progressive disease prevents us from performing further analysis on this subgroup. Furthermore, we evaluated a treated sample of patients in many aspects, such as depression, spasticity, and pain, in addition to MS. This evaluation could be a potential source of bias in the present study. Conceivably, treatment naïve, recently diagnosed patients, or those with chronic progressive disease could show different results.

Our data suggest that a properly treated population of patients with MS does not necessarily present with sleep complaints compared with a control population.

In conclusion, the prevalence of complaints related to sleep disorders in treated PwMS was lower than among residents of the city of São Paulo. The chronotype profile was not different, with both groups presenting predominantly morning or intermediate profiles. Fatigue was strongly present in PwMS, regardless of sleep complaints. Although the present study has limitations, we believe our results in PwMS sleep complaints could result from modern MS treatment.

#### Authors' Contributions

VGT: Study design, data collection, interpretation of data, manuscript draft; FMC, GFP: Study design regarding data collection on sleep disorders, interpretation of data, manuscript review; ST: Provided the Episono study database as the comparative population to the study, manuscript review; EMLO: study design, interpretation of data, review of the final manuscript.

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#### Conflict of Interest

The authors have no conflict of interests to declare.

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