

ARTIGO ORIGINAL/ORIGINAL ARTICLE

Physical Activity in Young Relapsing Remitting Multiple Sclerosis Patients: A Case-Control Study**Atividade Física em Pacientes Jovens com Esclerose Múltipla Surto Remissão: Um Estudo Caso-Controlo**

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Abstract

Introduction: Physical activity (PA) is known to be beneficial in patients with multiple sclerosis (MS); nevertheless, previous studies reported lower PA rates among these patients. Our study aims to assess PA in relapsing-remitting MS (RR-MS) patients and compare it with PA from healthy controls (HC). We also aim to assess the correlation between PA, fatigue, and sleep health.

Methods: A convenience sample including patients diagnosed with RR-MS (EDSS < 4.0), followed in the Neurology-Demyelinating Diseases consultation of a tertiary hospital, who agreed to participate in the study, compared to age- and sex-matched controls, was evaluated for objective PA for 7 days, using a Xiaomi Mi Band 5[®] arm-band (MiBand). This instrument reported daily step count, kilometer (km) count, active time, hours of sleep, and sleep score. The subjective assessment was derived from the self-reporting International Physical Activity Questionnaire (IPAQ) long version. Quality of sleep and fatigue in RR-MS patients were assessed using the SATED score and the Modified Fatigue Impact Scale (MFIS), respectively.

Results: Twenty-three RR-MS patients and 21 matched HC were included. No differences were found in either IPAQ or MiBand regarding PA comparison between RR-MS patients and HC: RR-MS patients revealed a mean active time of 84.81 minutes/day, 6712 steps/day, and 4.28 km/day, while HC had 74.95 min/day, 5421 steps/day and 3.59 km/day. People who self-reported higher PA levels had higher measured active time ($r = 0.524$; $p = 0.001$). RR-MS patients with higher scores in MFIS (higher fatigue levels) showed lower PA levels ($p = 0.021$) and lower SATED scores, meaning poor sleep health ($p < 0.001$).

Conclusion: Self-reported physical activity correlates with objective measurements, while higher levels of fatigue and poor sleep health correlate with lower PA levels in RR-MS patients. Adequate evaluation is important to promote healthy physical activity habits. A bigger sample is needed to explore differences between groups regarding PA levels.

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Palavras-chave:

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Resumo

Introdução: A atividade física (AF) é benéfica nos pacientes com esclerose múltipla (EM); no entanto, estudos anteriores reportam menores níveis de AF nestes doentes. O nosso estudo pretende avaliar a AF de doentes com EM surto-remissão (EM-SR) e compará-la com a AF de controlos saudáveis (CS). Pretendemos também avaliar a correlação entre AF, fadiga e qualidade do sono.

Métodos: Foi utilizada uma amostra incluindo pacientes diagnosticados com EM-SR (EDSS<4.0), seguidos na consulta de Doenças Desmielinizantes de um hospital terciário, que aceitaram participar no estudo, comparados com controlos emparelhados por idade e sexo. A AF foi avaliada de forma objetiva durante 7 dias, utilizando uma pulseira Xiaomi Mi Band 5® (MiBand), que registou número de passos diários, distância em quilómetros (km), tempo ativo, horas de sono e pontuação de sono. A avaliação subjetiva foi obtida através do autorrelato do Questionário Internacional de Atividade Física (IPAQ). A qualidade do sono e a fadiga nos pacientes com EM-SR foram avaliadas utilizando a pontuação SATED e a Escala Modificada de Impacto da Fadiga (MFIS), respetivamente.

Resultados: Foram incluídos 23 doentes com EM-SR e 21 CS. Não se observaram diferenças significativas entre grupos no IPAQ ou na MiBand. Os doentes com EM-SR tiveram, em média, 84,81 min/dia de tempo ativo, 6712 passos/dia e 4,28 km/dia, enquanto os CS registaram 74,95 min/dia, 5421 passos/dia e 3,59 km/dia. Maior AF auto-reportada correlacionou-se com maior tempo ativo ($r=0,524$; $p=0,001$). Nos doentes com EM-SR, níveis elevados de fadiga (MFIS) associaram-se a menor AF ($p=0,021$) e pior qualidade do sono (SATED, $p<0,001$).

Conclusão: A atividade física auto-reportada correlaciona-se com medições objetivas. Níveis mais elevados de fadiga e pior qualidade do sono associam-se a menor AF nos doentes com EM-SR. A avaliação adequada da AF é essencial para a promoção de hábitos saudáveis. Estudos com amostras maiores são necessários para explorar diferenças entre grupos.

Introduction

Multiple sclerosis (MS) is a neurodegenerative disease that frequently has negative effects on the physical and psychological well-being of patients, compromising their quality of life.¹⁻³

Frequently, MS patients decrease their physical activity (PA), as they are afraid of an exacerbation of the symptoms²; however, few studies have objectively studied the PA levels of these patients, evaluating only the self-perception of PA with questionnaires.⁴ Other studies suggested that aerobic PA promotes aerobic capacity, mobility, visuospatial perception, memory, and improves fatigue and quality of life of Relapsing-Remitting MS (RR-MS) patients.^{2,5-7} Information in the literature is even more scarce in the Portuguese population.

Fatigue is one of the most disabling side effects in MS patients,^{8,9} appearing to result in severe limitation of dai-

ly activity.¹⁰ Likewise, poor sleep health can result in the worsening of MS symptoms and compromise their daily PA.¹¹ Moreover, previous studies have shown that lower levels of daily PA are associated with higher scores in MFIS and poor sleep health.^{12,13}

In this study, we aim to compare the PA levels of RR-MS patients with those of healthy controls (HC). We also aim to correlate the level of PA with the quality of sleep and fatigue in these patients. We believe that a patient-oriented exercise approach complements pharmacological therapy of RR-MS and possibly helps to demystify the belief that PA exacerbates the symptoms of these patients. The results of this study may be useful to learn more about the habits of our patients, further contributing to the development of PA programs adapted to each patient's limitations.

Methods

Study participants

Participants were enrolled at the Demyelinating Diseases consultation of Centro Hospitalar Universitário de São João (CHUSJ), a tertiary hospital in Portugal, from January 2021 to February 2022. For RR-MS patients, inclusion criteria included: age between 18 and 35 years old at the moment of enrollment, diagnosis of RR-MS according to McDonald Criteria 2017,¹⁴ a score of Expanded Disability Status Scale (EDSS) < 4.0 in the last appointment, absence of relapses or infections in the past 30 days, follow-up in the Neurology-Demyelinating Diseases consultation of CHUSJ, and absence of orthopedic or any other condition that could affect daily physical activity.

For the matched control group, the inclusion criteria were age between 18 and 35 years old at the time of enrollment and absence of any neurological diagnosis or orthopedic impairing conditions.

The present study was approved by the local Ethics Committee of CHUSJ and conducted in conformity with the Declaration of Helsinki in its currently applicable form. All participants gave written informed consent to participate in the study and publish their results.

Subjective assessment of daily PA

To subjectively assess PA among patients and controls, we used the Portuguese translation of the long version of the International Physical Activity Questionnaire (IPAQ),¹⁵ which reports the amount and intensity of people's PA by a recall of the previous 7 days. The questionnaire was applied in paper-and-pen form.

After applying data cleaning rules according to the Guidelines for Data Processing and Analysis of the IPAQ,¹⁶ the results were coded as time per day spent in PA of different intensity: time spent walking; time spent in moderate PA (MPA); and time spent in vigorous PA (VPA). These times were summed to calculate the total duration of daily PA (TPA). We chose to present results in minutes/day for easier comparison with data from MiBand.

Both intensity and duration of PA were coded separately in four activity of daily life (ADL) domains, such as work, active transportation, domestic/yard, and leisure. We applied data scoring rules to classify the participants into the IPAQ categories of low, moderate, and high PA levels.¹⁶

We also collected information about participants' occupational status.

Objective assessment of daily PA

We used the PA monitor Xiaomi Mi Band 5® (MiBand) and gathered its information on the mobile phone application Mi Fit®. Participants started wearing MiBand after completing IPAQ and were instructed to wear it over 7 days throughout day and night if it did not bother their sleep, and to remove it only for any water activities. The band was placed around the wrist according to the user's manual.

MiBand reported PA as accelerometrically derived step count, walked distance in kilometers (km), and active time per day. It also recorded hours of sleep and a sleep score out of 100 points, based on sleeping hours, time spent in each sleep stage, and night awakenings.

For comparison with IPAQ data, we used the mean active time per day. As MiBand does not distinguish walking time, MPA and VPA, we compared only the active time given by the wrist band (in minutes/day) with TPA derived from IPAQ (also in minutes/day).

Fatigue and sleep assessment

In RR-MS patients, the EDSS score was calculated during the appointment preceding IPAQ completion and MiBand utilization.

MFIS was applied to all RR-MS patients and we calculated the total MFIS score and also the cognitive and physical subscales of the MFIS, according to the Portuguese MFIS validated version.¹⁷ This score ranges from 0 to 84 points, with scores lower than 38 reflecting an absence of fatigue and, above that, higher scores reflecting higher fatigue levels.

We assessed sleep using the SATED score, also validated for the adult Portuguese population.¹⁸ This score evaluates five domains of sleep, which have been associated with different health outcomes. Those are sleeping satisfaction, alertness state during waking hours, sleep timing, sleep efficiency, and sleep duration. It has specific quantitative criteria for four out of the five domains, which can be summed up to give us one single score, ranging from 0 (poor sleep health) to 10 (good sleep health).

Statistical analysis

Statistical analysis was performed with SPSS version 28. All tests were two-tailed and significant results were assumed when $p < 0.05$. No alpha-error correction was applied for multiple testing in this study.

Differences between the two groups (HC and RR-MS

patients) regarding age and body mass index (BMI) were calculated using independent t-tests. Sex and employment status were compared using the χ^2 -test.

MiBand parameters were compared using independent t-tests. Differences between both groups concerning IPAQ parameters were analyzed using Mann-Whitney U-tests.

The Spearman rank correlation was used for IPAQ data, EDSS, total and subscores of MFIS and SATED score. To correlate EDSS scores with IPAQ categories, we used the Jonckheere-Terpstra-Test, while to relate MiBand step count and active time with IPAQ categories, ANOVA with Bonferroni post hoc testing was performed.

All analyses relating IPAQ to MiBand were performed for the whole group, while correlations with EDSS and MFIS were only performed for the MS patients' group.

Results

Study cohort and data cleaning

23 RR-MS patients and 21 age- and sex-matched HC were included in our study. We could not obtain data from the MiBand of 7 RR-MS patients and 1 HC, either because they did not use the wrist band properly or because there were technical issues with the data extraction. Thus, our analysis refers to 23 RR-MS and 21 HC for the IPAQ response, and to 16 RR-MS patients and 20 HC for MiBand utilization (**Table 1**).

Truncation of IPAQ active time according to the guidelines of data processing of IPAQ had to be applied in 5 participants (3 RR-MS patients and 2 HC).

No significant differences were noted between the two groups regarding age (27.87 ± 4.70 in RR-MS

Table 1. Sociodemographic characteristics of RR-MS patients and age- and sex-matched HC.

		RR-MS patients	HC	p-value
Participants	N	23	21	
Sex	Female/Male	18/5	16/5	0.870
Age (years)	Mean (\pm SD)	27.87 (\pm 4.7)	27.33 (\pm 3.9)	0.310
Occupational status	Employed/unemployed/student	18/2/3	14/2/5	0.634
BMI (kg/m²)	Mean (\pm SD)	24.17 (\pm 3.6)	24.49 (\pm 3.2)	0.102
EDSS	Median (Min-Max)	1.0 (0.0-3.0)		

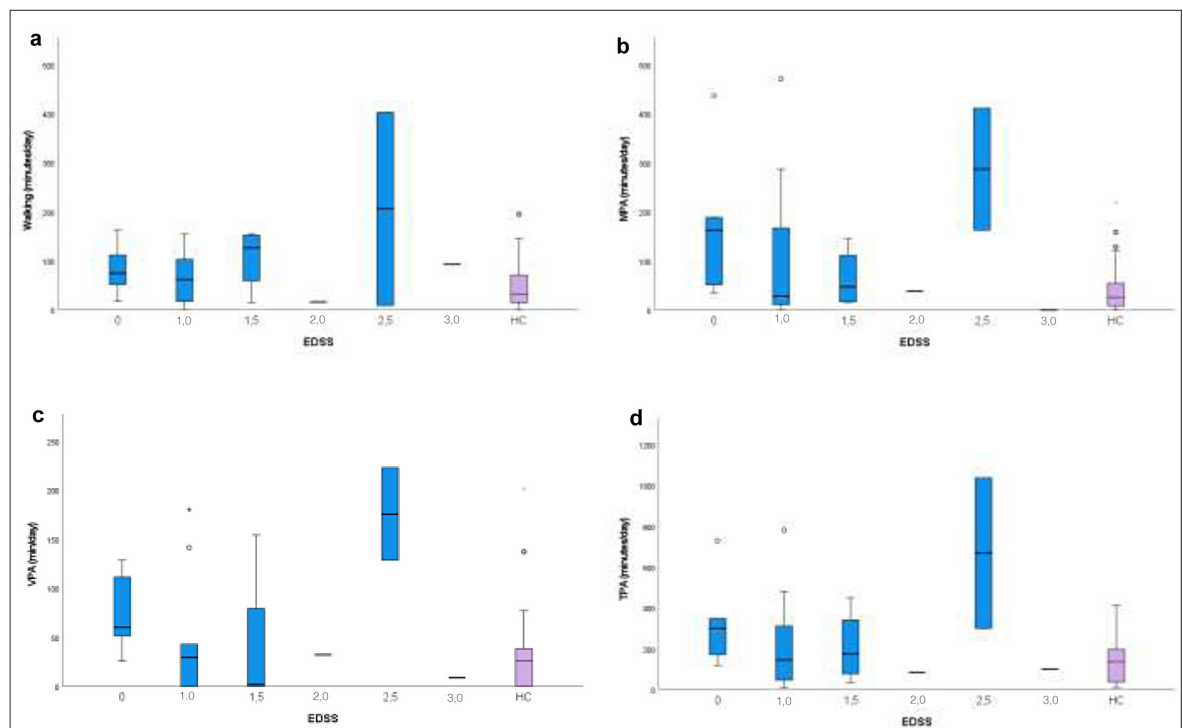


Figure 1. Relation between EDSS score and selected activity parameters of IPAQ. **a** Walking duration ($\rho = -0.002$; p -value 0.992) **b** MPA duration ($\rho = -0.217$; p -value 0.320) **c** VPA duration ($\rho = -0.082$; p -value .710) and **d** TPA duration ($r = -0.108$; p -value 0.623). Results of HC are in pink for reference. All RR-MS patients are depicted in blue.

group vs 27.33 ± 3.90 in controls), BMI (24.17 ± 3.60 vs 24.49 ± 3.20), employment status (18 vs 14 employed), and male/female proportion (18/5 vs 16/5) (**Table 1**).

Subjective daily PA assessment with IPAQ long form

We explored group differences in total duration of PA (171.43 ± 1026.43 min/day in case group vs 137.14 ± 400.00 min/day in HC group, $p=0.100$). Different domains of PA were also explored, such as Walking (74.29 ± 402.86 vs 32.14 ± 195.00 ; $p=.0217$), MPA (51.43 ± 471.43 vs 25.71 ± 218.57 ; $p=0.063$) and VPA (32.86 ± 222.86 vs 25.71 ± 201.43 ; $p=0.201$) (**Table 2**).

Higher EDSS scores were not significantly associated with reduced levels of PA in any domain (**Fig. 1**).

We also compared the distribution of study participants into the three IPAQ categories – low, moderate, and high PA level (**Table 2**). In both cases and controls, most participants (69.6% of RR-MS patients and 52.4% of HC) were considered to have high activity levels (**Fig. 2a**). EDSS scores did not differ across IPAQ PA levels in RR-MS patients (**Fig. 2b**).

Objective daily PA assessment with MiBand

RR-MS patients revealed a mean active time of 84.81 minutes/day, 6712 steps/day, and 4.28 km/day, while HC

had 74.95 min/day, 5421 steps/day and 3.59 km/day. Differences between groups were not significant for any of the mentioned parameters ($p=0.313$ for active time; $p=0.198$ for step count; $p=0.214$ for km count) (**Table 2**).

The correlation between EDSS and MiBand parameters was not significant either for step count, km count nor active time (**Fig. 3**).

We noted that all three MiBand parameters increased with the increase of IPAQ category ($r=0.402$; $p=0.015$ for step count; $r=0.469$; $p=0.034$ for km count and $r=0.531$; $p=0.023$ for active time).

Associations between subjective and objective PA assessment

For comparison between both PA assessment methods, we used IPAQ TPA time (minutes/day) and MiBand active time (minutes/day).

We found that the ones who reported more PA time per day in IPAQ had higher objectively assessed active time (Spearman correlation: $r=0.524$; $p=0.001$), irrespective of being RR-MS patients or HC.

Fatigue and sleep assessment and their impact on PA

Regarding fatigue assessment, higher scores of total

Table 2. Amount of daily physical activity in RR-MS patients and HC subjectively assessed with IPAQ and objectively assessed with armband MiBand.

		RR-MS patients N=23	HC N=21	p-value
Subjective (IPAQ)				
	PA at work (min/day)	85.71 (± 480.00)	10.71 (± 385.71)	0.280
	PA as transportation (min/day)	12.86 (± 180.00)	6.43 (± 120.00)	0.088
	PA as leisure (min/day)	25.71 (± 154.29)	17.14 (± 158.57)	0.509
	PA domestic (min/day)	25.71 (± 291.43)	17.14 (± 90.00)	0.137
	TPA (min/day)	171.43 (± 1026.43)	137.14 (± 400.00)	0.100
	Total Walking (min/day)	74.29 (± 402.86)	32.14 (± 195.00)	0.217
	Total MPA (min/day)	51.43 (± 471.43)	25.71 (± 218.57)	0.063
	Total VPA (min/day)	32.86 (± 222.86)	25.71 (± 201.43)	0.201
	IPAQ category (n and % of group)			0.504
	Low	2 (8.7%)	3 (14.3%)	
	Moderate	5 (21.7%)	7 (33.3%)	
	High	16 (69.6%)	11 (52.4%)	
Objective (MiBand)		N=16	N=20	
	Step count (steps/day)	6712.50 (± 3366.76)	5421.98 (± 2536.9)	0.198
	Km count (km/day)	4.28 (± 1.96)	3.59 (± 1.32)	0.214
	Active time (min/day)	84.81 (± 31.96)	74.95 (± 25.91)	0.313
	Sleeping hours (h/night)	7.32 (± 0.94)	7.75 (± 1.08)	0.216
	Sleeping score (out of 100)	77.70 (± 11.24)	79.32 (± 6.08)	0.583

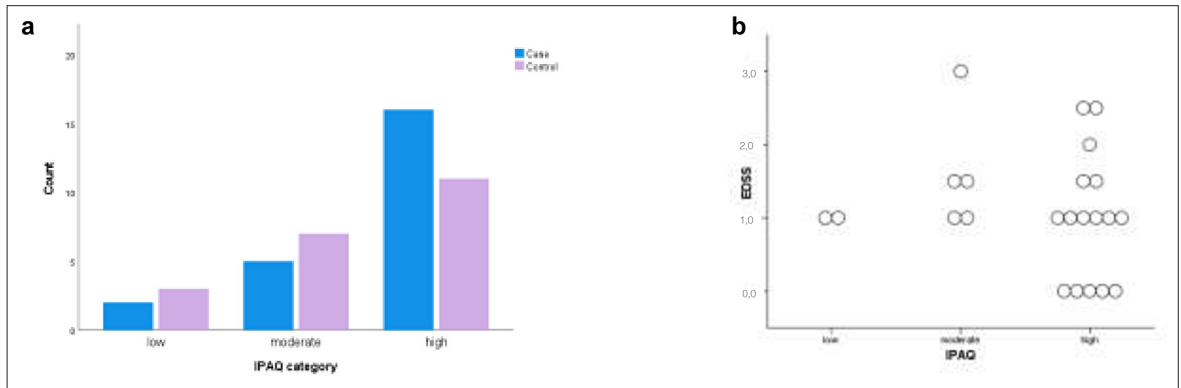


Figure 2. IPAQ categories of PA level. **a** Frequency per category in RR-MS patients and HC, **b** Relation of IPAQ category with EDSS.

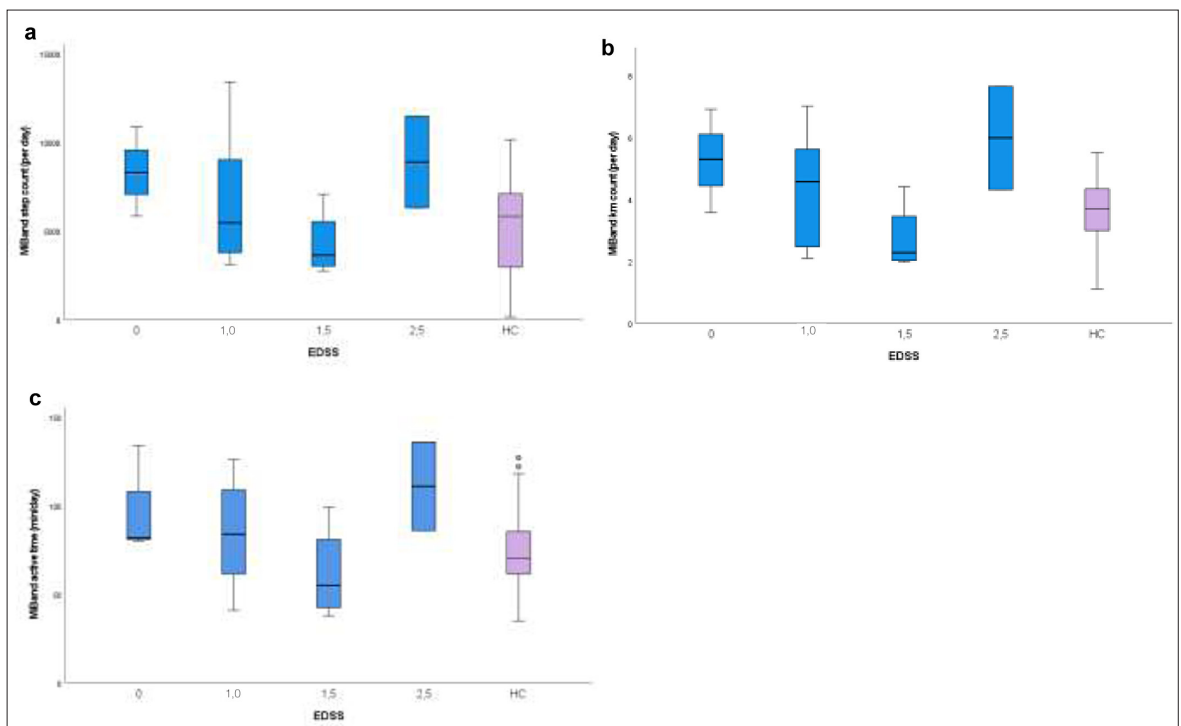


Figure 3. Relation between EDSS score and activity parameters of MiBand. **a** steps per day ($\rho = -0.204$; p -value 0.450), **b** km per day ($\rho = -0.222$; p -value 0.408) **c** active time per day ($\rho = -0.054$; p -value 0.841). Results of HC are in pink, while RR-MS are depicted in blue. Note that the subjects with EDSS scores of 2.0 and 3.0 were excluded from this analysis due to missing MiBand data.

MFIS score and its cognitive subscale were significantly associated with lower MPA, VPA, and TPA levels (**Table 3**).

Regarding the physical subscale of MFIS, higher scores were only significantly associated with VPA levels of IPAQ (**Table 3**).

Regarding the correlation between MFIS score and IPAQ category, we found that the increase of MFIS score was significantly related to lower IPAQ categories ($p = 0.007$).

Walking time was not significantly correlated with MFIS or any of its subscales (**Table 3**).

The objectively measured MiBand parameters were not significantly correlated with the total MFIS score or with its subscales (**Table 3**).

We evaluated the correlation between EDSS score and MFIS, but, although a tendency to report higher MFIS scores was noted among patients with higher EDSS scores, this correlation was not statistically significant ($p = 0.164$). The same was observed for the relation between EDSS and SATED score ($p = 0.088$).

We also found that RR-MS patients with higher

Table 3. Association of MFIS, its subscores and SATED score with daily PA parameters from IPAQ and MiBand.

			rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value	rho	p-value
MFIS cognitive subscale	11.00 (84.84)	0-39	0.0053	0.809	-0.531	0.009	-0.643	<0.001	-0.507	0.014	-0.244	0.363	-0.173	0.522	-0.152	0.574
MFIS physical subscale	12.00 (70.17)	0-34	-0.077	0.728	-0.329	0.125	-0.478	0.021	-0.394	0.063	-0.150	0.578	-0.100	0	-0.125	0.644
MFIS total	25.00 (286.68)	0-73	-0.049	0.824	-0.445	0.033	-0.626	0.001	-0.477	0.021	-0.160	0.553	-0.119	0.660	-0.127	0.640
SATED score	8.00 (4.31)	2-10	0.049	0.755	-0.067	0.664	0.138	0.373	0.011	0.941	-0.135	0.434	-0.139	0.418	-0.104	0.546

MFIS, its subscores and SATED score were reported as median (variance) and range and their association with daily PA parameters from IPAQ and MiBand were evaluated using Spearman correlations.

SATED scores had lower total ($r = -0.700$; $p < 0.001$), physical ($r = -0.676$; $p < 0.001$) and cognitive ($r = -0.711$; $p < 0.001$) MFIS scores.

The correlation between SATED score and PA levels was assessed for all participants and SATED score did not have a statistically significant correlation with any of the subjective and objective PA parameters (**Table 3**). We also did not find a significant correlation between the IPAQ category and SATED score, irrespective of being RR-MS patients or HC ($p = 0.603$).

For the objectively measured parameters of sleeping hours per night and sleeping score, there was no statistically significant between-groups difference (**Table 2**).

We assessed the correlation between self-reported SATED score and objectively measured sleeping hours and sleeping score and although a statistically significant correlation was not found between SATED score and sleeping hours ($r = 0.091$; $p = 0.597$), we found that people with higher SATED scores have higher sleeping scores measured by MiBand ($r = 0.386$; $p = 0.035$).

Discussion

In this study, we compared PA levels between MS patients and HC from a Portuguese tertiary hospital. We found that people who self-report higher levels of PA during the day had, in fact, higher objectively measured PA levels. This may indicate that IPAQ correlates well with objective PA in RR-MS patients and thus, it might be an applicable and useful tool to evaluate patients' PA during Demyelinating Diseases consultation. As expected from previous studies,^{4,19} objectively measured PA increased with higher IPAQ categories.

We also found higher levels of fatigue in RR-MS patients when PA levels are lower, as reported in previous works.^{5,6,9,12} For the total and cognitive subscales of MFIS, higher MPA, VPA, and TPA levels were significantly correlated with less fatigue, but only higher

VPA was significantly associated with lower scores in the physical subscale of MFIS. Also, as expected, fatigue was negatively correlated with the IPAQ category, since people with higher PA levels tend to report less fatigue. Although we cannot assume whether fatigue levels are a cause or consequence of physical activity levels, our results support that PA can help to improve fatigue, as previously reported.²⁰

Regarding the SATED score, we found that people who sleep better (higher SATED score) have lower levels of fatigue, as described in a previous study.²¹ In our work, participants who had higher SATED scores also had higher MiBand sleeping scores, as expected, although an association with sleeping hours was not assessed. This could imply that better sleeping scores are more associated with sleep quality than with sleeping hours per se; given its importance, this aspect should be assessed in future studies.

When comparing subjective and objective assessments of PA, we found that people tend to overestimate their PA in IPAQ. This could be a result of an overestimated engagement in MPA, previously described by Shook JT *et al.*²²

We were expecting a reduction of PA among RR-MS when compared with HC, according to what was described by Krüger T *et al.*⁴ and Kinnet-Hopkins D *et al.*²³ However, we did not find differences between RR-MS and HC regarding the duration of daily PA.

When PA was subjectively measured with IPAQ, we expected to find lower PA levels among RR-MS patients, according to what was described by Krüger T *et al.*⁴ However, we did not find differences between RR-MS patients and HC regarding any of the PA parameters. For objectively measured PA, no differences were reported between groups as well, but a tendency for RR-MS patients to exercise more than HC was observed, contrary to what was described in previous works.^{24,25}

This may result from the fact that our sample size is not big enough to find differences between groups. However, it may also reflect a difference in our population, with RR-MS patients being more aware of the benefits of PA and, therefore, more motivated than healthy individuals to engage in different types of exercise.

Although we were expecting PA levels of RR-MS patients to correlate with their disability status, according to previous studies,^{26,27} in our work, higher EDSS scores were not significantly associated with reduced PA.

An important aspect of IPAQ, which could be a target for an intervention approach, is that it collects the context of PA. In our study, most RR-MS patients reported using private or public transportation when traveling between places. We believe that it could be appropriate to promote active transportation, rather than solely promote an increase in PA in a leisure/sports context.²⁸ Knowing the context of our patients' PA, is an opportunity to, during a consultation, find the areas with a major lack of PA and build a more individualized PA plan, promoting the improvement of daily performance.

The objectively assessed PA did not significantly correlate with MFIS, meaning that probably most of the activity MiBand recorded in RR-MS patients was walking time, since this was the only parameter of IPAQ that did not significantly correlate with the total MFIS score in our study. This could be another proof of people's tendency to overestimate their performance in MPA and VPA.²²

EDSS did not significantly correlate with MFIS, although we were expecting a positive correlation between disability and fatigue.⁹ This might also be a consequence of our small cohort.

SATED score did not have a significant correlation with any type of PA derived from IPAQ or objectively assessed PA, even though we were expecting higher PA levels to be associated with better sleep health and consequently, higher SATED scores.^{13,21,29}

Our study is the first to assess PA levels of patients with RR-MS in the Portuguese population, both with subjective and objective methods, and to compare those with PA levels of HC. It is also the first study in Portugal to correlate PA levels with sleep health and fatigue. Limitations of the present study include the small size of our cohort, the non-discriminatory function of MiBand, which did not allow us to assess the type of PA that constituted the active time of each participant, and the exclusion of RR-MS patients with EDSS 2.0 and

3.0 from the objective PA analysis because of missing MiBand data. There may also be a possible selection bias, in which patients with higher EDSS may have been less willing to participate in this study. Another potential selection bias related to participant motivation might be that MS patients who agreed to take part in this research were more health-conscious, motivated, or already engaged in regular PA compared to the broader MS population. This heightened awareness and willingness to participate could have influenced their PA levels during the study period, potentially leading to an overestimation of habitual PA among these patients.

Our data support current evidence that fatigue and sleep health correlate with PA levels in RR-MS patients and further exploration of this matter seems relevant to improve PA prescription by doctors and other health care providers for RR-MS patients.

Conclusion

In this study, self-reported PA among MS patients and controls correlated well with objective measurements. Also, higher levels of fatigue and poor sleep health correlated with lower PA levels in RR-MS patients. A bigger sample is needed to explore group differences regarding PA levels, namely between RR-MS patients and HC. An adequate evaluation of these parameters will probably help health care providers to promote and advise patients regarding healthy PA habits. ■

Awards and Previous Presentations

This abstract was previously presented at the 8th Congress of the European Academy of Neurology in Vienna, Austria, June 25-28, 2022

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Contributorship Statement / Declaração de Contribuição

IM: Conceived and designed the study, handled material preparation, data collection and analysis; wrote the first draft; contributed to early and later drafts

BM: Handled material preparation and data collection; contributed to early and later drafts; performed critical reviews

CC: Handled material preparation and data collection; contributed to early and later drafts; performed critical reviews

DF: Handled material preparation and data collection; con-

tributed to early and later drafts; performed critical reviews

JG: Validated the study; provided study resources; performed critical reviews

MJS: Validated the study, provided study resources; performed critical reviews

AC: Conceived and designed the study; handled material preparation and data collection; performed critical reviews; supervised the study

All authors approved the final manuscript to be published.

IM: Concebeu e desenhou o estudo, foi responsável pela preparação do material, recolha e análise de dados; redigiu a primeira versão do manuscrito; contribuiu significativamente para as versões iniciais e finais

BM: Foi responsável pela preparação do material e recolha de dados; contribuiu para as versões iniciais e finais; realizou revisão crítica

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