Autonomic symptom burden is an independent contributor to multiple sclerosis related fatigue

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Abstract

Objectives: To investigate a possible association between autonomic dysfunction and fatigue in people with multiple sclerosis.

Methods: In 70 people with multiple sclerosis early in the disease course (51 females, mean age 33.8±9.1) quantitative sudomotor axon reflex test, cardiovascular reflex tests (heart rate and blood pressure responses to Valsalva maneuver and heart rate response to deep breathing) and the tilt table test were performed. Participants completed the Composite Autonomic System Score-31, Modified Fatigue Impact, Beck Depression and Epworth Sleepiness scales. Cut-off scores of ≥38 or ≥45 on the Modified Fatigue Impact Scale were used to stratify patients into a fatigued subgroup (N=17 and N=9, respectively).

Results: We found clear association between fatigue and subjective tests of the autonomic nervous system: fatigued patients scored significantly worse on Composite Autonomic System Score-31 and there was strong correlation between Modified Fatigue Impact Scale and Composite Autonomic System Score-31 (r_s =0.607, p<0.001). On the other hand, we found only modest association between fatigue and objective tests of the autonomic nervous system: there was a clear trend of lower sweating outputs on all measure sites, reaching statistical significance for distal leg and foot. We found weak correlations between Modified Fatigue Impact Scale and Valsalva ratio (r_s =-0.306, p=0.011), Modified Fatigue Impact Scale and quantitative sudomotor axon reflex test of the forearm, proximal and distal lower leg (r_s =-0.379, p=0.003, r_s =-0.356, p=0.005 and r_s =-0.345, p=0.006, respectively). A multiple regression model showed that Composite Autonomic System Score-31, Beck depression scale and Epworth Sleepiness Scale were independent predictors of fatigue (p=0.005, p=0.019 and p=0.010, respectively).

Conclusion: These results suggest that people with multiple sclerosis, already early in their disease course, suffer from objective and subjective impairments of the autonomic nervous system and suggest an association between autonomic nervous system impairment and multiple sclerosis related fatigue.

Key words: Fatigue, depression, sleep, multiple sclerosis

Introduction

Fatigue is one of the most common symptoms of many neurological conditions and it is defined as extreme and persistent mental and/or physical tiredness, weakness or exhaustion (1). It can be primary, when it is considered to be part of the underlying neurological condition, or secondary, when it results from the presence of other concomitant circumstances or diseases (2).
Fatigue is one of the most frequent and the most burdensome symptoms of multiple sclerosis (MS) (3). Multiple sclerosis related fatigue (MSRF) is reported in up to 80% of the people with MS (pwMS), and over 55% of patients report fatigue as the worst symptom experienced from MS (4). Several MS specific processes may be responsible for primary MSFR, like impaired interactions between functionally related cortical and subcortical areas, activation of proinflammatory cytokines and dysregulation of the neuroendocrine system (5, 6, 7). However, a substantial proportion of pwMS also have concomitant depression and sleep disorders, which are strongly related to secondary MSRF (8, 9).
It has recently been suggested that the dysregulation of the autonomic nervous system (ANS) can lead to many MS-related clinical symptoms/comorbidities, including fatigue, depression and sleep disorders (10). Also, it has been demonstrated that ANS dysfunction is frequent in MS and it is present even in the earliest stages of the disease, with parasympathetic dysfunction present in 5 %, sympathetic in 42.6 % and sudomotor in 32.7 % of patients (11).
With the hypothesis that ANS dysfunction is an important contributor to MSRF, we aimed to investigate the role of ANS dysfunction in MSRF, taking into consideration the presence of depression and sleep disorders.

Methods

Patients who participated in the BACIS project (12), in which consecutive patients with CIS were recruited into a two-year prospective clinical and neurophysiological follow-up from October 2014 until April 2016, were asked to participate in an MS comorbidities substudy at month 24 visit. All patients signed informed consent and the study was approved by Ethical Committees of the University Hospital Center Zagreb and the University of Zagreb, School of Medicine.
During the month 24 visit, testing of the ANS was performed. It consisted of Quantitative Sudomotor Axon Reflex Test (QSART) performed with Q-Sweat (WR Medical Electronics Co Maplewood, MN, USA) (13), testing of cardiovascular reflexes (heart rate and blood pressure responses to Valsalva maneuver and heart rate response to deep breathing) and the tilt table test (Task Force Monitor (TFM), CNSystems Medizintechnik AG, Austria) (13,14). Composite Autonomic Scoring Scale (CASS) was utilized to quantify autonomic dysfunction (15).
Following ANS testing, 70 participants filled in validated Croatian versions of the Composite Autonomic System Score-31 (COMPASS-31) (16), the Modified Fatigue Impact Scale (MFIS), the Beck depression scale (BDI-2) and Epworth Sleepiness Scale (ESS) (17). Clinically relevant BDI-2 result was considered if the score was >18 (18).
Previous studies have used cut-off scores of ≥38 or ≥45 on the MFIS to define fatigue, so in our analysis, we used both cut-off points in order to stratify patients into a fatigued

subgroup (N=17 and N=9, respectively) and a non-fatigued subgroup (N=53 and N=61, respectively) (19,20). For each participant, Expanded Disability Status Scale (EDSS) and current use of disease modifying therapy (DMT) was noted.
The primary objective was to evaluate differences in ANS tests and COMPASS-31, BDI-2 and ESS between fatigued and non-fatigued subgroups.
Secondary outcomes were to correlate MFIS with objective tests of ANS function and subjective measures of dysautonomia (COMPASS-31), depression (BDI-2) and daytime sleepiness (ESS).
Finally, in order to examine the influence of age, sex, depression, daytime sleepiness, autonomic symptom burden and current use of DMT on the fatigue measured with MFIS, a multiple linear regression model was used.

Statistical analysis
Statistical analysis was performed using the IBM SPSS software, version 20. The Kolmogorov–Smirnov test was applied to test whether the data has a normal distribution. Differences in the distribution of qualitative variables were determined with the $\chi 2$ test (sex), while the differences in quantitative variables were determined with the use of parametric t test (age, respiratory sinus arrhythmia (RSA), Valsalva ratio (VR), QSART results) or nonparametric Mann–Whitney (EDSS, CASS, ESS, BDI-2, COMPASS-31). To determine the correlation between the MFIS variable and other variables (age, RSA, VR, QSART, COMPASS-31, CASS, ESS, BDI-2, EDSS) the Spearman correlation method was used. Multiple linear regression model based on six predictors (age, sex, depression defined as BDI-2 score >18, ESS, total sum of COMPASS-31 and current use of DMT) was used in order to determine significant predictors for the presence of fatigue measured with MFIS and its subtypes (physical fatigue, cognitive fatigue and psychosocial fatigue). Also, additional regression analysis for every domain of COMPASS-31 was performed with previously mentioned predictors in the model. For the predictors in multiple regression models, p values less than 0.05 were considered as significant. For analysis that included more comparisons on the same set of data, p values corrected with Bonferroni correction were considered as significant.

Results

Baseline patients' characteristics are presented in table 1. Thirty-five (50%) patients were on DMTs (7 on teriflunomide, 8 on dimethyl fumarate, 6 on interferon beta, 13 on glatiramer acetate and 1 on alemtuzumab).

Descriptive measures for patients with and without fatigue

Differences in all studied parameters between fatigued and non-fatigued MS patients defined either as MFIS ≥45 or ≥38 are presented in table 2. Fatigued patients according to the both cut-off values were older and scored significantly worse on BDI-2 and COMPASS-31. There was a clear trend of lower sweating outputs an all measure sites, reaching statistical significance for distal leg (MFIS ≥45) and foot (MFIS≥38).

Correlations of subjective and objective ANS tests

Results of the correlation between parameters of objective autonomic nervous system testing and different domains of COMPASS-31 are presented in Supplementary table 1. There was statistically significant correlation between the RSA and bladder domain of the COMPASS-31 (r_s =-0.358, p=0.002) and between QSART of the proximal leg and gastrointestinal domain (r_s =-0.383, p=0.002), QSART of the distal leg and secretomotor domain (r_s =-0.394, p=0.002) and QSART of the distal leg and the gastrointestinal domain (r_s =-0.381, p=0.002).

Correlations of fatigue with objective and subjective ANS tests, depression and daytime sleepiness

We found significant correlations between MFIS and age (r_s=0.329, p=0.005), MFIS and VR (r_s =-0.306, p=0.011), MFIS and QSART of the forearm, proximal and distal lower leg (r_s =-0.379, p=0.003, r_s =-0.356, p=0.005 and r_s =-0.345, p=0.006, respectively) (Figure 1), MFIS and BDI-2 (r_s =0.756, p<0.001), and MFIS and COMPASS-31 (r_s =0.607, p<0.001) (Figure 2). Also, there was statistically significant correlation between the MFIS and every domain of COMPASS-31 (orthostatic intolerance, r_s =0.426, p<0.001; vasomotor, r_s =0.387, p=0.001; secretomotor, r_s =0.409, p<0.001; gastrointestinal, r_s =0.503, p<0.001; bladder, r_s =0.433, p<0.001; pupilomotor, r_s =0.720, p<0.001).

Regression analysis

A multiple regression model was used to predict the presence of fatigue measured with the MFIS based on age, sex, depression defined as BDI-2 score >18, daytime sleepiness measured with ESS, autonomic dysfunction measured with COMPASS-31 and current use of DMT. Multiple regression model statistically significantly predicts the MFIS variable (F=11.366, p<0.001), with a R^2=0.536. Total sum of COMPASS-31, BDI-2 and ESS were independent predictors for the presence of fatigue measured with the MFIS (B=0.464, p=0.005, B=17.344, p=0.019 and B=1.111, p=0.01, respectively). As MFIS can distinguish different types of fatigue (physical, cognitive and psychosocial) we further analysed influence of the studied parameters on these three types of MSRF. There was statistically significant correlation between the age and cognitive fatigue (r_s =0.295, p=0.013). Results of the regression analysis with different types of fatigue (physical, cognitive and psychosocial) as outcome variables are presented in Table 3. The only statistically significant predictor for cognitive fatigue was COMPASS-31, while statistically significant predictors for physical fatigue were ESS, BDI-2 and COMPASS-31.
Finally, in order to examine the possible influence of age, sex, depression defined as BDI-2 score >18, ESS, different domains of the COMPASS-31 and current use of DMT on the fatigue measured with MFIS the regression analysis was performed (Supplementary table 2). The regression analysis showed that that orthostatic intolerance and bladder domains of the COMPASS-31 were not statistically significant independent predictors of MFIS, while other domains (vasomotor, secretomotor, gastrointestinal and pupilomotor) were.

Discussion

We have found that pwMS who suffer from fatigue score significantly worse on COMPASS-31, a patient-related outcome evaluating autonomic symptoms. Furthermore, COMPASS-31 independently predicted fatigue, regardless of depression and/or daytime sleepiness.
Several studies used different objective tests of ANS in order to investigate possible role of ANS dysfunction in development of MSRF. Initial studies focused on correlation of different tests of cardiovascular autonomic function (heart rate and blood pressure variability, responses to postural changes, pressure tests, the Valsalva maneuver, deep breathing, and hyperventilation), and were largely negative, or if positive, confounded by age effects on autonomic tests (21,22). In one study, the consistent decrease of blood pressure response to sustained grip in combination with increased fatigue was observed (23). Our study confirmed these observations, as we were unable to show differences in any of the studied cardiovascular reflexes between fatigued and non-fatigued patients.
On the other hand, we found clear association between MSRF and subjective measures of ANS dysfunction. Since the introduction of COMPASS-31, it has become possible to systematically assess quantitative autonomic symptoms. One of the initial studies investigating the relationship of autonomic symptom burden to quality of life, fatigue and other established disease parameters was performed by Cortez and colleagues (24). This study has shown that autonomic symptom burden is correlated with decreased quality of life and increased fatigue, despite the fact that out of 100 enrolled patients, only 41 completed COMPASS-31 questionnaire in full. Furthermore, this study did not address possible covariates of fatigue like depression or daytime sleepiness, nor did authors test whether obtained results are still significant after using multivariate regression analysis. Another study showed that COMPASS-31 predicts the level of cognitive fatigue independent of age, disease duration, EDSS, and mental impairment (25). We have confirmed this finding in our study, showing that the COMPASS-31 is the only independent predictor of cognitive fatigue. Furthermore, we have replicated the finding that the pupillomotor domain of the COMPASS-31 is an important contributor to the MSRF. A recent study investigating cognition and fatigue using pupillary responses to light, found a tendency toward a smaller pupillary response in pwMS with fatigue, possibly explaining observation of this association (26).
One thing that can explain the association between MSRF and subjective dysautonomia and lack of association between MSRF and objective dysautonomia is discrepancy between patient reported symptoms and laboratory findings in structural disorders of the ANS. In line with this, one study has shown that even patients with severe orthostatic hypotension can be completely asymptomatic (27). Similarly, when we correlated domains of the COMPASS-31 and results of the cardiovascular reflexes and QSART, we only observed significant correlations between QSART results and gastrointestinal and secretomotor domains of the COMPASS-31, suggesting that this dissociation in subjective and objective dysautonomia may be pertinent to MS, as well.
Pathophysiology of MSRF is very complex, and the role of structural or functional brain abnormalities, the contribution of neurochemical imbalance, neuroendocrine dysfunction, neuroimmune dysregulation and peripheral nervous system contribution, have all been explored in in the generation of this symptom (28).
Several of these hypotheses are interesting regarding the possible role of autonomic nervous system dysfunction in MSRF. The presence of immunological dysregulation is the basis of MS, and inflammatory and neuroendocrine factors may differentially mediate fatigue (29). Recently it has been suggested that pathologic interactions between the immune and the autonomic systems may fail to trigger anti-inflammatory mechanisms,

which are essential to prevent repeated inflammatory attacks, a key pathogenic feature of MS (30). The parasympathetic part of the ANS has a major role in alerting the central nervous system about the presence of inflammation via inflammatory cytokines (31). These afferent signals are transmitted by the vagal nerve and trigger an anti-inflammatory response, termed “cholinergic anti-inflammatory pathway” (30).

Peripheral nervous system contribution to MSRF is a controversial topic, however it has been suggested that sensory perception resulting from a complex integration of physiological, biochemical, and other sensory feedback from the periphery may contribute to MSRF (32). Interestingly, we found a significant negative correlation between MFIS result and sweat volume on different sites measured with QSART. QSART has been traditionally used as a marker of peripheral cholinergic postganglionic nerve affection, and thus its value was mainly in the diagnosis of small fiber neuropathy. As MS is a central nervous system disorder, results of our study can be interpreted in two ways: either QSART can detect central disorders of thermoregulation or peripheral nervous system is also affected in MS. An argument for the former is a study that showed that QSART values can be abnormal even with preganglionic lesions (33). An argument for the latter came from several studies questioning whether MS is a pure central nervous system disorder. Jende and colleagues have demonstrated peripheral nerve lesions in pwMS in vivo by high resolution MRI (34). These lesions are defined by an increase of proton-spin-density and a decrease of T2-relaxation time, indicating changes in the microstructural organization of the extracellular matrix in peripheral nerve tissue in MS. Furthermore, it has also been suggested that pwMS may exhibit significant small fiber damage, which is associated with neurological disability from MS (35, 36). One of the main consequences of sudomotor dysfunction in MS is heat sensitivity, and it has been suggested that heat sensitivity in MS might contribute to premature fatigue either through passively induced rises in body temperature or through exercise (37). The results of our study give a possible pathophysiological explanation of this association, although we did not asses changes in body temperature in the presented patient group. Despite this theoretical background, the relationship between fatigue symptoms and dysautonomia in MS received minor interest.

The limitations of this study are possible selection bias as not all participants of the BACIS project participated in the substudy. It has to be emphasized that we enrolled a specific group of pwMS very early in the disease course and that the percentage of patients with fatigue was comparatively low. Furthermore, not all participants had QSART performed due to financial limitations. Finally, ESS measures daytime sleepiness, a similar feeling as fatigue, however a recent study has shown that ESS was significantly associated with sleepiness, tiredness, and lack of energy, but not fatigue (38).

Despite of this, the results of this study suggest an association between autonomic dysfunction, especially sudomotor dysfunction and fatigue in MS patients. Further studies with long term follow-up are warranted.

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Tables

Table 1. Baseline patients' characteristics.

	Mean/median	Standard deviation	Range
Age (years)	33.8	9.1	
Sex (females)	51		
EDSS	1.0		0-4.0
Scales			
MFIS	22		0-70
ESS	5		0-18
BDI-2	4		0-50
COMPASS-31	8.5		0-57.7
OI	0		0-32
Vasomotor	0		0-4.2
Secretomotor	0		0-6.4
GI	2.7		0-13.4
Bladder	0		0-7.8
Pupillomotor	1		0-4.0
ANS tests			
VR	2.2	0.5	
RSA	21.9	8.2	
QSART forearm (µl)*	0.885	0.727	
QSART proximal lower leg (µl)*	1.099	0.805	
QSART distal lower leg (µl)*	1.425	0.942	
QSART foot (µl)*	0.597	0420	
CASS total*	1		0-5
CASS adrenergic	0		0-3
CASS cardiovagal	0		0-1
CASS sudomotor*	0		0-3

*QSART results were available for 62 patients.

EDSS – expanded disability status scale, COMPASS-31 - Composite Autonomic System Score-31, OI – orthostatic intolerance; GI – gastrointestinal; MFIS - Modified Fatigue Impact Scale, BDI-2 - Beck depression scale, ESS - Epworth Sleepiness Scale (ESS), VR – Valslava ratio, RSA – respiratory sinus arrhythmia, QSART - Quantitative Sudomotor Axon Reflex Test; CASS - Composite autonomic scoring scale

Table 2. Differences in all studied parameters between fatigued and non-fatigued MS patients defined either as MFIS ≥45 or ≥38.

	MFIS<45	MFIS≥45	p	MFIS<38	MFIS≥38	p
Age (years)#	32.3±7.8	44.4±11.2	**<0.001**	31.6±7.5	40.8±10.6	**<0.001**
Sex (females)	43	8	0.43	36	15	0.13
EDSS#	1	2	0.06	1	1.5	0.10
Scales						
ESS#	5	6	0.51	5	11	**0.009**
BDI-2#	2.5	20.5	**<0.001**	2	16	**<0.001**
COMPASS-31*	6.5913	38.2579	**0.001**	6.1786	24.8016	**<0.001**
OI*	0	16	0.01	0	16	0.007
Vasomotor*	0	0	0.009	0	0	0.008
Secretomotor*	0	4.2857	**0.001**	0	4.2857	**0.002**
GI*	2.6786	6.2500	**<0.001**	1.7857	5.3571	**0.001**
Bladder*	0	2.2222	**0.001**	0	1.1111	**0.002**
Pupillomotor*	1	2.3333	**<0.001**	1	2.0000	**<0.001**
ANS tests						
VR#	2.3±0.5	1.8±0.3	0.03	2.3±0.5	2.0±0.3	0.04
RSA#	22.5±8.3	17.9±6.5	0.14	23.0±8.6	18.3±5.4	0.02
QSART forearm (µl)**	0.94±0.75	0.52±0.44	0.131	1.02±0.77	0.50±0.38	0.013
QSART proximal lower leg (µl)**	1.15±0.83	0.78±0.53	0.202	1.23±0.87	0.74±0.44	0.030
QSART distal leg (µl)**	1.25	0.64	**0.009**	1.56±0.96	1.06±0.82	0.060
QSART foot (µl)**	0.64±0.43	0.37±0.23	0.075	0.68±0.44	0.37±0.25	**0.001**
CASS total**	1	2	0.07	1	2	0.045
CASS adrenergic**	0	0.5	0.53	0	1	0.10
CASS cardiovagal**	0	0	0.46	0	0	0.26
CASS sudomotor**	0	1	0.07	0	1	0.20

* Bonferroni corrected p-value = 0.007; # Bonferroni corrected p-value = 0.017; ** Bonferroni corrected p-value = 0.013; Bold indicates statistically significant difference.
EDSS – expanded disability status scale, COMPASS-31 - Composite Autonomic System Score-31, OI – orthostatic intolerance; GI – gastrointestinal; MFIS - Modified Fatigue Impact Scale, BDI-2 - Beck depression scale, ESS - Epworth Sleepiness Scale (ESS), VR – Valslava ratio, RSA – respiratory sinus arrhythmia, QSART - Quantitative Sudomotor Axon Reflex Test; CASS - Composite autonomic scoring scale

Table 3. Regression analysis with different types of fatigue (physical, cognitive and psychosocial) as outcome variables.

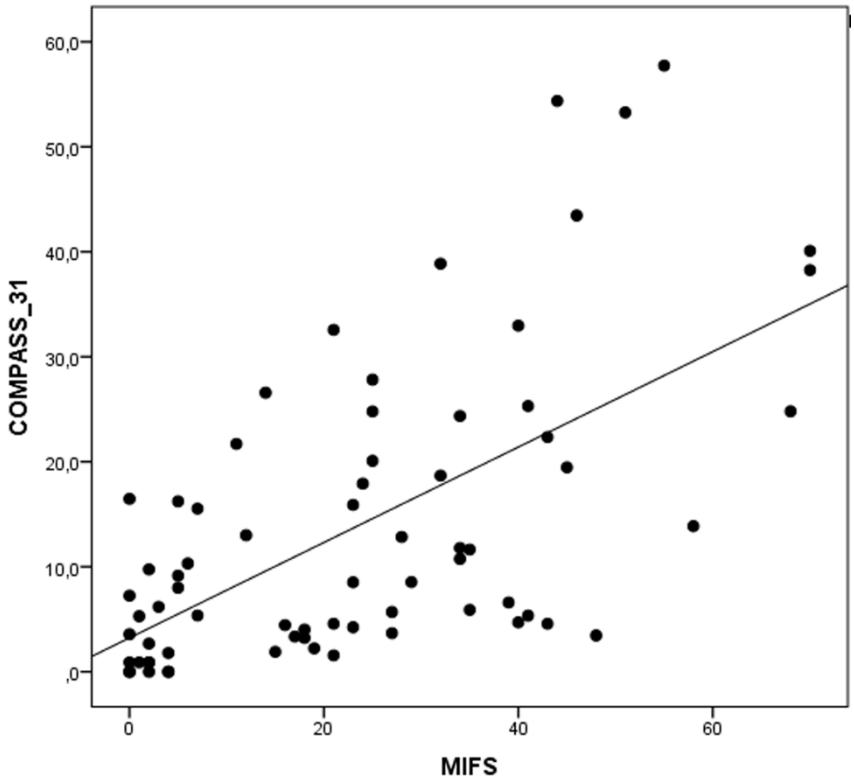
Predictor	B	P value
Model with cognitive fatigue, (F=6.874, p<0.001), with a R^2=0.411		
Sex	-1.011	0.620
Age	0.069	0.530
Use of DMT	-0.995	0.585
ESS	0.353	0.113
BDI-2	6.034	0.114
COMPASS-31*	0.216	**0.012**
Model with physical fatigue, (F=13.516, p<0.001), with a R^2=0.579		
Sex	0.137	0.936
Age	0.044	0.630
Use of DMT	-1.275	0.402
ESS*	0.645	**0.001**
BDI-2*	7.500	**0.020**
COMPASS-31*	0.219	**0.003**
Model with psychosocial fatigue, (F=13.938, p<0.001), with a R^2=0.586		
Sex	0.216	0.608
Age	0.010	0.675
Use of DMT	-0.320	0.396
ESS*	0.142	**0.003**
BDI-2*	2.647	**0.001**
COMPASS-31*	0.045	**0.011**

COMPASS-31 - Composite Autonomic System Score-31, BDI-2 - Beck depression scale, ESS - Epworth Sleepiness Scale (ESS), DMT – disease modifying therapy; *statistically significant predictor

Figures

Figure 1. Correlations between Modified Fatigue Impact Scale (MFIS) and Quantitative Sudomotor Axon Reflex Test (QSART) of the forearm, proximal lower leg, distal lower leg and foot (r_s= -0.379, p=0.003, r_s= -0.356, p=0.005, r_s= -0.345, p=0.006 and r_s= -0.249, p=0.051, respectively; Bonferroni corrected p-value = 0.0125)

Figure 2. Correlation between Modified Fatigue Impact Scale (MFIS) and Composite Autonomic System Score-31 (COMPASS-31) (r_s=0.607, p<0.001; Bonferroni corrected p-value = 0.007)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30,0
20,0
10,0
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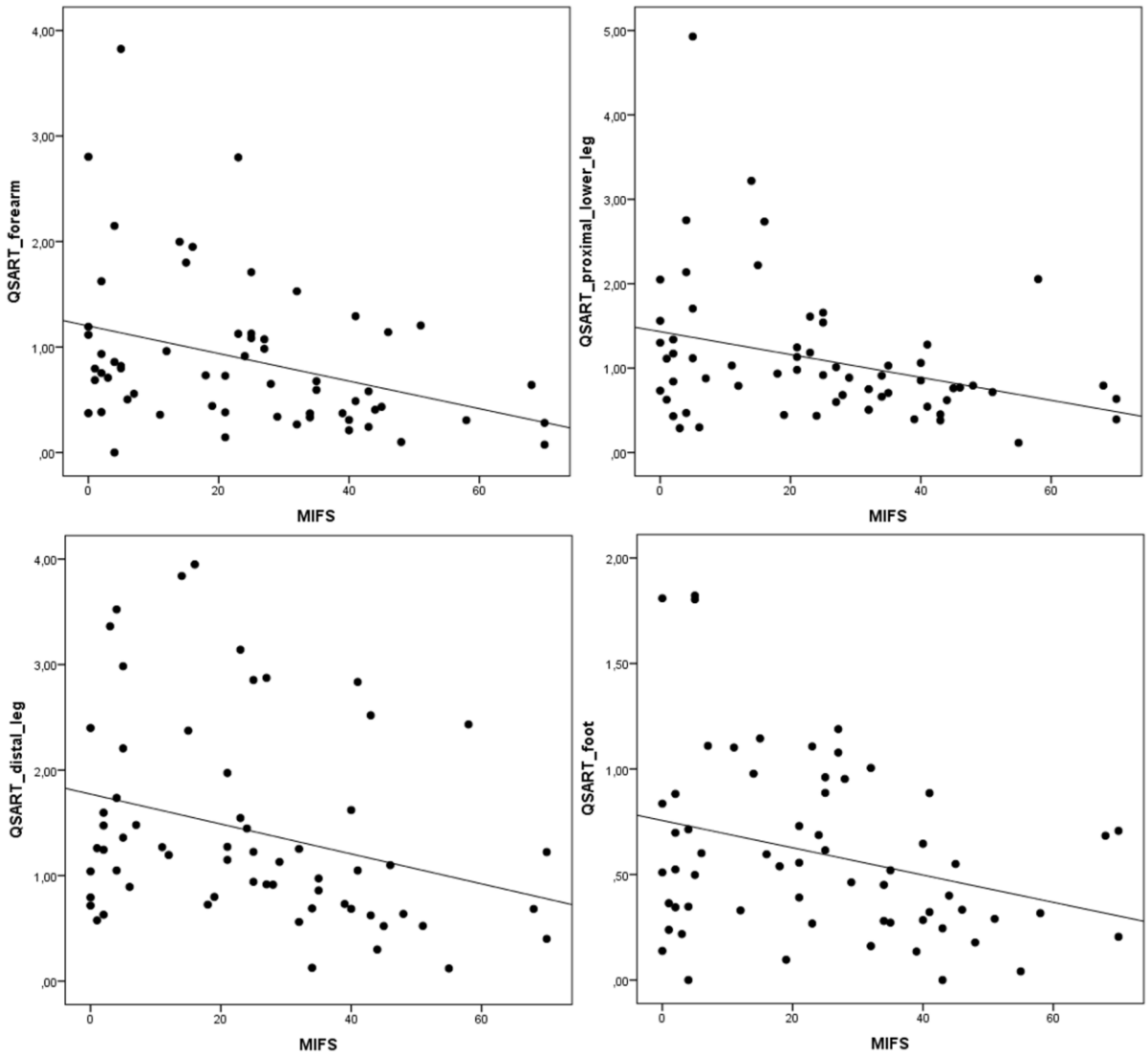
COMPASS_31
0
20
40
60
MIFS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40
60
MIFS
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3,00
2,00
1,00
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0
20
40
60
MIFS
QSART_distal_leg
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MIFS
QSART_foot
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