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Exploring fatigue in Marfan and hypermobile Ehlers-Danlos syndromes: an analytical cross-sectional study in two Italian healthcare centres

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ABSTRACT

Objective This study investigates the prevalence and underlying factors of fatigue in individuals with Marfan syndrome (MFS) and hypermobile Ehlers-Danlos syndromes (hEDS), highlighting the necessity for focused research on this symptom within these patient populations.

Design Cross-sectional, multicentre study.

Setting Data were collected from participants diagnosed with MFS or hEDS across multiple healthcare centres.

Participants The study enrolled 282 participants (127 with MFS and 155 with hEDS).

Primary and secondary outcome measures Fatigue was measured using the Fatigue Severity Scale (FSS). Additional assessments included the Patient Health Questionnaire-9 (PHQ-9) for depression and the Insomnia Severity Index (ISI) for sleep disturbances.

Results Participants with hEDS exhibited significantly higher median fatigue scores (FSS median=5.9, IQR=5.00–6.44) compared with the MFS group (FSS median=4.0, IQR=2.88–5.00). Significant predictors of fatigue included being female, having hEDS, participating in psychotherapy, and elevated scores on depression and insomnia scales. In the overall sample, hEDS significantly predicted fatigue (B=0.430, p=0.022), with depression and insomnia as strong influencers (PHQ-9: B=0.12, p<0.001; ISI: B=0.092, p<0.001). Notably, 80% of the hEDS group reported clinically relevant fatigue levels, compared with 31.5% in the MFS group. Daily persistence of fatigue was especially pronounced in hEDS, with 72.2% reporting everyday fatigue versus 25.2% in MFS. Temporal fatigue patterns also differed, with a more evenly distributed pattern throughout the day in hEDS, correlating with higher insomnia scores.

Conclusions The results underscore the severe impact of fatigue on individuals with hEDS compared with those with MFS, suggesting the need for targeted, multidisciplinary management strategies to enhance quality of life.

Trial registration number NCT05712564.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study design was a multicentre, cross-sectional analysis, allowing for a broad and diverse participant base across multiple centres specialising in Marfan syndrome and hypermobile Ehlers-Danlos syndrome.
⇒ Rigorous use of validated scales (Fatigue Severity Scale, Patient Health Questionnaire-9, Insomnia Severity Index) ensured reliable measurement of fatigue, depression and insomnia.
⇒ Adherence to Strengthening the Reporting of Observational Studies in Epidemiology guidelines strengthened the study's methodological rigour and reproducibility.
⇒ The cross-sectional design prevents causal inferences between observed associations and fatigue outcomes.
⇒ Reliance on self-reported data introduces the potential for response biases, affecting the accuracy of symptom reporting.

INTRODUCTION

Chronic syndromes profoundly impact the quality of life, often through symptoms that persistently challenge daily functioning and health-related quality of life.[1 2] Among these symptoms, fatigue stands out as a particularly debilitating yet frequently overlooked aspect.[1] In particular, self-perceived fatigue, commonly described as 'an overwhelming sense of tiredness, lack of energy and feeling of exhaustion, mental, physical or both',[3] which differs from fatigability (ie, the decline in performance of given tasks) has increasingly been studied in genetic conditions and is currently recognised as an important clinical factor affecting patients' daily life.[4] It is a common denominator in various heritable connective tissue disorders, including Marfan syndrome (MFS, OMIM # 154700) and hypermobile Ehlers-Danlos syndrome (hEDS), which are connective tissue disorders with systemic manifestations.[5 6] While considerable attention has been devoted to these

syndromes' more overt physical complications, fatigue has received relatively scant consideration. This oversight is significant, considering fatigue's pervasive impact on individuals' capacity to engage in everyday activities and maintain a satisfactory quality of life.[5 7]

MFS and hEDS, although distinct in their genetic aetiologies and clinical manifestations, share common challenges due to their nature as systemic connective tissue disorders.[6] MFS, primarily affecting the body's cardiovascular, skeletal and ocular systems, arises from mutations in the *FBN1* gene, influencing the structure and function of connective tissues.[8] Diagnostic criteria for MFS rely on the revised Ghent nosology of 2010, employing the combination of major criteria, including cardiovascular comorbidities (aortic aneurysms and dissections) and ocular phenotypes (lens dislocation), as well as minor criteria, such as skeletal alterations.[9] On the other hand, hEDS is characterised by joint hypermobility, skin hyperextensibility and tissue fragility, with no identified underlying genetic aetiology, setting it apart from other types of Ehlers-Danlos syndromes (EDS).[10] Diagnostic criteria for evaluation refer to the 2017 international classification, which includes 13 types of EDS with hEDS having no underlying genetic aetiology identified.[11] Despite these differences, individuals with either MFS or hEDS often report fatigue as a significant symptom, impacting their physical, emotional and social well-being.[12 13]

Understanding the differences in fatigue between MFS and hEDS is critical because fatigue is a multidimensional phenomenon with physical, psychological and social components, necessitating personalised approaches to management.[12 13] For example, fatigue in MFS may arise from cardiovascular complications or musculoskeletal stress, while in hEDS, it is more commonly linked to insomnia, pain and psychological distress.[12 14–16] Despite systematic reviews highlighting fatigue as a significant issue in heritable connective tissue diseases, research into its multifaceted nature and syndrome-specific mechanisms, particularly in hEDS, remains limited.[12 13 17–21] This gap is concerning, given the variability in how individuals experience fatigue and the complex interplay of physical, cognitive and emotional factors that contribute to it. A deeper understanding of these differences is essential to enhance clinical management and improve patient's quality of life.

The current scenario highlights a significant gap in understanding the nuanced experiences of fatigue in these populations, given the complex and multifaceted nature of MFS and hEDS. Fatigue in these syndromes may be influenced by a wide range of factors, including physiological aspects such as cardiovascular and respiratory conditions and psychological dimensions like depression and anxiety.[12 13 17–21] Inadequate management strategies risk overlooking these differences, particularly in settings like Italy and similar countries, where fatigue is often managed similarly across syndromes despite distinct underlying causes.[22] Addressing this gap is crucial to improving diagnosis, tailoring treatment and enhancing clinical practice. Moreover, the role of sleep quality, frequently disrupted in these populations and with insomnia being a prevalent symptom,[5 23] warrants further investigation. Understanding these determinants is vital, as they may differentially affect the severity and experience of fatigue in individuals with MFS and hEDS.

The complexity of fatigue as a symptom in MFS and hEDS necessitates a more in-depth understanding, particularly in terms of its distribution across these populations. Prior research is still limited in terms of epidemiological descriptions, highlighting the need for comprehensive data to inform effective management strategies.[12 13 17–21] This study was therefore designed to describe the manifestation of fatigue among individuals with MFS and hEDS and gather detailed data on its prevalence and variability. Focusing on hEDS ensures that the findings apply to the largest subset of patients, providing meaningful insights into fatigue within this population, especially considering that hEDS is the most common type of EDS.[11] The descriptive aim served as a foundational step in identifying and understanding the various determinants influencing fatigue. A range of factors, including cardiovascular health, respiratory function, psychological well-being and the impact of insomnia, were explored to ascertain their collective and individual contributions in determining fatigue in these populations. This analytical step paves the way for future syndrome-specific, in-depth analyses to further refine management strategies and tailor interventions to the unique needs of each population.

METHODS

Study design

This analytical cross-sectional study focused on adults diagnosed with MFS and hEDS. The approach was carefully designed to capture a comprehensive picture of fatigue in these populations, encompassing various potential determinants such as physiological, psychological and lifestyle factors, as indicated in previous studies.[1 13] The reporting of this research was guided by the 'Strengthening the Reporting of Observational Studies in Epidemiology' statement and checklist to ensure transparency and completeness. The original protocol is detailed in online supplemental file 1.

Sample size

In establishing the sample sizes for MFS and hEDS groups in this study, an a priori power analysis was conducted using G*Power, V.3.1.9.6.[24] This analysis aimed to determine the necessary sample sizes to detect effect sizes ranging from 0.08 to 0.50, reflecting the anticipated variability of effects in these conditions. The choice of this range was based on the anticipated variability and subtlety of the effects in these conditions.[12 13 17–21] The lower bound of 0.08 was included to ensure sensitivity to subtle yet clinically significant associations, acknowledging the nuanced impact of various predictors on fatigue in rare

diseases. Conversely, the upper limit of 0.50 was selected to cover more pronounced effects, providing a comprehensive understanding across a spectrum of potential influences. This range reflects a realistic expectation for the variation in the impact of different factors on fatigue in MFS and hEDS, considering the study's design with 11 predictors, a two-tailed test, an alpha error probability of 0.05 and a power of 0.90. For the smallest effect size of 0.08, the analysis indicated that a minimum sample size of 134 participants per group was required to achieve the desired power. However, considering a typical 25% non-response rate observed in similar observational studies,[5] we invited 168 patients per group to ensure adequate enrolment. Sensitivity analyses tested deviations in effect sizes and response rates. For smaller effect sizes (eg, 0.05), the required sample increased significantly, while higher effect sizes (eg, 0.60) required fewer participants, aligning with the anticipated variability. The invitation buffer mitigated lower response rates (<75%), confirming that the recruitment strategy met the study's analytical needs.

Setting and eligibility criteria

The study was conducted at two specialised heritable connective tissue disorders centres in Italy, which employ a multidisciplinary approach to treating these patients, encompassing expertise from cardiologists, clinical geneticists, nurse practitioners and psychologists.[25] These centres are dedicated to providing comprehensive clinical care for patients with MFS and hEDS, facilitating regular follow-ups in an outpatient clinic.

Eligible participants were identified from clinic records and invited to participate during their routine follow-up visits or through phone or email contact. Approximately 170 patients per group (MFS and hEDS) met the inclusion criteria. Of these, 127 patients with MFS (response rate=76%) and 155 patients with hEDS (response rate=92%) agreed to participate, resulting in an overall response rate of 84% (see online supplemental file 2). The most common reason for non-participation was lack of interest.

Eligibility criteria included being at least 18 years old, having a confirmed diagnosis of either MFS or hEDS, and possessing proficient Italian language skills (speaking, reading and writing). For MFS, confirmed diagnoses adhered to the 2010 revised Ghent nosology, which incorporates major criteria such as aortic root dilation, ectopia lentis and specific systemic features, as well as genetic testing confirming *FBN1* mutations when available.[9] For hEDS, diagnoses were based on the 2017 international classification criteria, which require generalised joint hypermobility, two or more additional features (such as systemic manifestations of a connective tissue disorder or a family history of hEDS), and exclusion of alternative diagnoses and other EDS subtypes.[11] Individuals with cognitive impairments were excluded; these impairments were identified through routine cognitive assessments documented in patients' medical records. Only patients with cognitive assessments conducted within the last 2 years were considered for inclusion. Excluding individuals with cognitive impairments was necessary to enhance the internal validity of the study, as cognitive impairments could confound self-reported measures of fatigue and associated factors, such as depression and insomnia.

Procedure

The detailed participant flow diagram is available in online supplemental file 2. A total of 335 eligible patients were invited to participate in the data collection process, resulting in a response rate of 84%, with 282 individuals completing a series of self-report questionnaires collected using a web-based platform. This platform was specifically designed to ensure compliance with the General Data Protection Regulation, guaranteeing the confidentiality and privacy of patient data.[26] Participants were asked to complete a series of self-report questionnaires to assess various measurements, including fatigue, depression, insomnia and health-related variables, and collect sociodemographic, clinical and anamnestic data. The average estimated time for completing these questionnaires was approximately 16 min, a duration determined to be sufficiently comprehensive yet considerate of patient time and effort. Furthermore, a validation process was implemented to ensure the accuracy and reliability of the self-reported clinical and anamnestic data. This validation step involved a cross-check conducted by a clinician who had access to the electronic medical records of the enrolled patients. This aspect was crucial for verifying the self-reported information against the medical records, thereby enhancing the validity of the data collected through the application.

Measurements

The study involved a comprehensive assessment of various parameters to understand the impact of fatigue and associated factors on patients with MFS and hEDS. The data collected included sociodemographic information such as sex (male, female, other), age (years), education level (primary school, lower secondary school, higher secondary school, university), years since diagnosis and profession (active worker—work from office, active worker—work from home, occasional worker, retired, unemployed).

Medical status and history were thoroughly documented, covering aspects like the presence of cardiovascular diseases, hypertension, use of cardiovascular medications, respiratory diseases and other diseases, including visual impairments. A detailed focus was given to cardiovascular diseases, where specific conditions such as heart valve dysfunction, arrhythmias, cardiac valve pathologies, aortic dissections and aortic aneurysms were assessed. Another focus was on other diseases, including thyroid dysfunction, neuropathies, joint diseases, scoliosis, multiple conditions among the listed diseases and other comorbidities. Body mass index (BMI) was calculated for each participant. Mental health status and treatment were

also recorded, noting ongoing psychotherapy and the use of antidepressants and insomnia medications.

Depression was assessed using the Italian version of the Patient Health Questionnaire-9 (PHQ-9), a widely recognised self-administered instrument.[27] The PHQ-9 consists of nine items, each corresponding to the diagnostic criteria for major depressive disorder in the DSM-IV. Participants rated the frequency of symptoms experienced over the past 2 weeks on a scale ranging from 0 (not at all) to 3 (nearly every day). The total score, ranging from 0 to 27, categorises depression severity as follows: 0–4=no depressive symptoms, 5–9=subthreshold depression (minimal depressive symptoms), 10–14=mild major depression (minor depression), 15–19=moderate major depression and ≥20=severe major depression. Higher scores indicate more severe depressive symptoms.

Insomnia was evaluated using the Italian version of the Insomnia Severity Index (ISI), a brief self-report questionnaire designed to assess the nature, severity and impact of insomnia.[28] The ISI contains seven items, each rated on a 5-point Likert scale (0–4), assessing the severity of sleep onset, sleep maintenance, early morning awakening problems, satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem and the level of distress caused by the sleep disturbance. The total score, ranging from 0 to 28, is interpreted as follows: 0–7 indicating no clinically significant insomnia, 8–14 representing subthreshold insomnia, 15–21 indicating clinical insomnia (of moderate severity) and 22–28 representing clinical insomnia (of severe severity). Higher scores indicate more severe insomnia symptoms.

Fatigue was measured using the Fatigue Severity Scale (FSS), a tool specifically designed to evaluate the impact of fatigue on daily functioning.[29] The FSS comprises nine statements requiring participants to rate their agreement on a scale of 1 (strongly disagree) to 7 (strongly agree). The scale measures the severity of fatigue symptoms and their effects on physical, emotional and cognitive functioning. The overall score is obtained by calculating the average of the item scores, with a higher average score reflecting greater fatigue severity. This scale is particularly useful in distinguishing fatigue from clinical depression, as it focuses more on the physical aspects of fatigue rather than mood-related symptoms. The FSS demonstrates a sensitivity of 82.0% and a specificity of 87.0% in detecting fatigue when scores are ≥4.67.

Data analysis

The analytical approach of this study was structured in a multi-step process to address its two primary aims. Initially, categorical variables were summarised using frequencies to provide a basic understanding of the distribution within the study population. For quantitative variables, their distribution was first examined to determine normality. Depending on this assessment, appropriate summary statistics were employed, such as mean and SD for normally distributed data or median and IQR for non-normally distributed data. Comparisons between MFS and hEDS of the collected variables were performed by employing non-parametric tests for categorical variables and non-normally distributed quantitative variables, while parametric tests were employed to compare normally distributed quantitative variables. As multiple comparisons may inflate type I errors, Bonferroni's correction of the significance level was applied in this stage, where the the adjusted significance level is 0.0025.

The first aim of the study (ie, to describe fatigue), which involved synthesising the distribution of variables related to fatigue, was addressed through this descriptive analysis. This step provided a foundational understanding of how fatigue was manifested across the study population. To fulfil the second aim (ie, to ascertain determinants of fatigue), linear regression models were employed. The initial model was applied to the overall sample and included 'disease' (coded as 1 for MFS and 2 for hEDS) as a covariate. Other predictors in this model included sex, age, education, years from diagnosis, count of comorbidities, BMI, participation in psychotherapy, use of antidepressant medications, use of insomnia medications, and scores from the PHQ-9 and ISI questionnaires. Subsequently, two additional models were performed separately within the MFS and hEDS subgroups. This stratified approach was crucial to understanding the unique relationships between predictors and fatigue in each condition. It allowed for a more nuanced analysis that could capture differences in how fatigue is influenced by various factors in MFS and hEDS patients, acknowledging the distinct characteristics of these two syndromes. Several strategies were employed in assessing the fit of each model. The overall fit was evaluated using R^2, providing insight into the proportion of variance in fatigue that the predictors could explain. Additionally, residual analysis was conducted to check the assumptions underlying linear regression. This included examining residuals for normality, homoscedasticity and independence. The analytics were performed in R environment, V.4.3.2 for Windows (R Core Team, 2021).

Patient and public involvement

Patient organisations were actively involved in the development and execution of this study. We collaborated with two patient organisations: the Italian Ehlers-Danlos Syndrome Association and the J. Peter Onlus Association. These groups provided insights that supported the study design, particularly in ensuring that the research questions and outcome measures were relevant and meaningful to patients with MFS and hEDS.

RESULTS

Sample characteristics

The study comprised 282 participants; 127 were diagnosed with MFS, and 155 were diagnosed with hEDS. The detailed characteristics of the sample are elaborated on in

table 1 (the adjusted significance level for these multiple comparisons is 0.0025).

Regarding gender distribution, the sample was predominantly female, comprising 71.3% (n=201) of the total. A significant difference was observed between groups, with females representing 87.1% of the hEDS group and 52% of the MFS group ($\chi^2_{(1)}$=42.07; p<0.001). The average age of participants was 39.97 years (SD=13.03), with no statistically significant difference between the groups ($t_{(249)}$=−1.454; p=0.147). Educational achievements varied, with 40.4% (n=114) having completed higher secondary school and 41.8% (n=118) holding a university degree.

The median duration since diagnosis was 9 years (IQR=5–17 years), with MFS patients showing a longer duration compared with hEDS patients (U=6069.5; p<0.001). Professional status varied, with over half (52.8%; n=149) being active workers, either working from the office or home. The hEDS group had a significantly higher proportion of home-based workers (Fisher=22.059; p<0.001). Unemployment was noted in 24.5% (n=69) of the sample, more pronounced in the MFS group (33.1%; n=42).

In terms of medical status, cardiovascular diseases were prevalent in 70.21% (n=198) of the sample, particularly among MFS patients (80.31%; n=102) ($\chi^2_{(5)}$=926.649; p<0.001). Hypertension and cardiovascular medication use were reported in 11.35% (n=32) of participants, with higher occurrences in the hEDS group (13.5%; n=21). Other diseases like respiratory conditions and visual impairments were common in both groups.

A focused analysis on cardiovascular diseases among 198 participants showed heart valve dysfunction (39.9%; n=79) and aortic aneurysms (17.68%; n=35) as prevalent conditions, especially in the MFS group (Fisher=67.750; p<0.001). Of the 244 participants with other diseases, joint diseases (24.18%; n=59) and scoliosis (39.34%; n=96) were notably frequent in the hEDS group ($\chi^2_{(6)}$=81.200; p<0.001).

BMI values were comparable across groups (median=21.61 kg/m^2; IQR=19.35–24.22; p=0.076). The use of ongoing psychotherapy, antidepressants and insomnia medications was more prevalent in the hEDS group ($\chi^2_{(1)}$=18.84; p<0.001 for psychotherapy, $\chi^2_{(1)}$=9.432; p=0.002 for antidepressants, and $\chi^2_{(1)}$=24.779; p<0.001 for insomnia medications). Depression and insomnia, as assessed by the PHQ-9 and ISI, showed higher average scores in the hEDS group ($t_{(279)}$=−9.322; p<0.001 for PHQ-9 and $t_{(279)}$=−8.540; p<0.001 for ISI).

Fatigue, measured using the FSS, indicated more pronounced symptoms in the hEDS group ($t_{(252)}$=−8.425; p<0.001).

Fatigue

As depicted in figure 1, the distribution of fatigue scores, as measured by the FSS, demonstrates a broader range and higher median values (p<0.001) in the hEDS group (median=5.9; IQR=5.00–6.44; mean=5.48±1.46) compared with MFS (median=4.0; IQR=2.88–5.00; mean=3.88±1.68). The FSS scores in the EDS group predominantly ranged above the clinical threshold (scores ≥4.67=124; 80%), suggesting a higher prevalence of clinically relevant fatigue within this cohort, which significantly contrasted with 31.5% (n=40) in the MFS group ($\chi^2_{(1)}$=67.486; p<0.001). Additionally, the daily persistence of fatigue was particularly pronounced in the hEDS group, where 72.2% (n=109) reported experiencing fatigue every day compared with 25.2% (n=30) in the MFS group (Fisher=65.317; p<0.001).

When examining the temporal pattern of fatigue, it was found that a significant portion of the participants experienced fatigue in the afternoon (49.3%; n=133). However, the hEDS group reported a more evenly distributed pattern of fatigue throughout the day ($\chi^2_{(2)}$=25.849; p<0.001), which aligns with the higher scores observed for insomnia as measured by the ISI ($t_{(279)}$=−8.540; p<0.001).

Determinants of fatigue

To ascertain the determinants of fatigue among individuals with MFS and hEDS, linear regression analyses were conducted and presented in table 2 and figure 2; the latter illustrates the standardised beta coefficients across the three models.

In the overall sample, the regression analysis (model 1) yielded a significant F-test of overall significance ($F_{(12)}$=27.036, p<0.001), indicating that the model adequately explained sample statistics. This model accounted for 54.9% of the variance in fatigue scores. Within this model, disease type (Std. B=0.430, p=0.022), sex (males vs females; Std. B=0.370, p=0.040), participation in psychotherapy (yes vs no, Std. B=−0.457, p=0.019), PHQ-9 score (Std. B=0.12, p<0.001) and ISI score (Std. B=0.092, p<0.001) emerged as significant predictors of fatigue. The analysis of residuals indicated that they were normally distributed and had a mean close to zero, suggesting that the model's assumptions were adequately met.

For the MFS subgroup (model 2), the F-test was also significant ($F_{(11)}$=7.891, p<0.001), with the model explaining 43.0% of the variance in fatigue scores. The PHQ-9 score was a significant predictor (Std. B=0.478, p<0.001). The model's residuals followed a normal distribution, supporting the suitability of the regression model for this subgroup.

Similarly, the regression analysis for the hEDS subgroup (model 3) was significant (F=11.544, p<0.001), with an R^2 of 47.4%, indicating that the model explained nearly half of the variability in fatigue scores. Significant predictors included PHQ-9 score (Std. B=0.351, p<0.001) and ISI score (Std. B=0.382, p<0.001). The distribution of residuals was normal, which suggests a good fit of the model to the data.

Figure 3 provides a nuanced comparative analysis of the determinants of fatigue by juxtaposing the regression coefficients from the three models. Part A, showcasing the regression coefficients across models, illustrates how various predictors align or diverge in their influence on

Table 1 Sample characteristics

	Overall (N=282)		Marfan syndrome (N=127)		Hypermobile Ehlers-Danlos syndrome (N=155)		
	N	%	N	%	N	%	Comparisons
Sex							
Male	81	28.70	61	48	20	12.9	$\chi^2_{(1)}$=42.07; p<0.001
Female	201	71.30	66	52	135	87.1	
Age							
Years (mean; SD)	39.97	13.03	38.75	14.06	41.05	12.06	$t_{(249)}$=−1.454; p=0.147
Education							
Primary school	2	0.70	2	1.6	0	0	Fisher=9.571; p=0.014
Lower secondary school	48	17.00	30	23.6	18	11.6	
Higher secondary school	114	40.40	48	37.8	66	42.6	
University	118	41.80	47	37	71	45.8	
Years from diagnosis							
Years (median; IQR)	9	5–17	13	7–23	8	4–12	U=6069.5; p<0.001
Profession							
Active worker—work from office	149	52.80	71	55.9	78	50.3	Fisher=22.059; p<0.001
Active worker—work from home	32	11.30	8	6.3	24	15.5	
Occasional worker	20	7.10	3	2.4	17	11	
Retired	12	4.30	3	2.4	9	5.8	
Unemployed	69	24.50	42	33.1	27	17.4	
Medical status							
Cardiovascular diseases	198	70.21	102	80.31	96	61.90	$\chi^2_{(5)}$=926.649; p<0.001
Hypertension	32	11.35	11	8.66	21	13.50	
Cardiovascular medications	133	47.16	97	76.38	36	23.20	
Respiratory diseases	52	18.44	18	14.17	34	21.90	
Other diseases	244	86.52	104	81.89	140	90.30	
Visual impairments	98	34.75	56	44.09	42	27.10	
Focus on cardiovascular diseases (N=198)							
Heart valve dysfunction	79	39.90	31	30.39	48	50.00	Fisher=67.750; p<0.001
Arrhythmias	36	18.18	6	5.88	30	31.25	
Cardiac valve pathologies	24	12.12	14	13.73	10	10.42	
Aortic dissections	24	12.12	19	18.63	5	5.21	
Aortic aneurysms	35	17.68	32	31.37	3	3.13	
Focus on other diseases (N=244)							

Continued

Table 1 Continued

	Overall (N=282)		Marfan syndrome (N=127)		Hypermobile Ehlers-Danlos syndrome (N=155)		
	N	%	N	%	N	%	Comparisons
Thyroid dysfunction	30	12.30	12	11.54	18	12.86	$\chi^2_{(6)}$=81.200; p<0.001
Neuropathies	21	8.61	3	2.88	18	12.86	
Joint diseases	59	24.18	8	7.69	51	36.43	
Scoliosis	96	39.34	71	68.27	25	17.86	
Multiple conditions among the above	20	8.20	1	0.96	19	13.57	
Other comorbidities	18	7.38	9	8.65	9	6.43	
BMI							
kg/m^2 (median; IQR)	21.61	19.35–24.22	21.33	19.11–23.41	21.83	19.71–24.54	U=8632.5; p=0.076
Ongoing psychotherapy							
Yes	65	23	14	11	51	32.9	$\chi^2_{(1)}$=18.84; p<0.001
Antidepressant medications							
Yes	37	13.1	8	6.3	29	18.7	$\chi^2_{(1)}$=9.432; p=0.002
Insomnia medications							
Yes	60	21.3	10	7.9	50	32.3	$\chi^2_{(1)}$=24.779; p<0.001
Depression							
Score PHQ-9 (mean; SD)	9.19	6.05	6.01	4.51	11.8	4.74	$t_{(279)}$=−9.322; p<0.001
No depressive symptoms	70	24.8	52	40.9	18	11.6	$\chi^2_{(4)}$=67.771; p<0.001
Minimal depressive symptoms	94	33.3	54	42.5	40	25.8	
Minor depression	61	21.6	15	11.8	46	29.7	
Moderate major depression	37	13.1	4	3.1	33	21.3	
Severe major depression	20	7.1	2	1.6	18	11.6	
Insomnia							
Score ISI (mean; SD)	9.5	5	7.02	4.13	11.53	4.74	$t_{(279)}$=−8.540; p<0.001
No clinically significant insomnia	110	39	78	61.4	32	20.6	$\chi^2_{(3)}$=57.895; p<0.001
Subthreshold insomnia	119	42.2	43	33.9	76	49	
Clinical insomnia (moderate severity)	53	18.8	6	4.7	47	30.3	
Fatigue							

Continued

Table 1 Continued

	Overall (N=282)		Marfan syndrome (N=127)		Hypermobile Ehlers-Danlos syndrome (N=155)		
	N	%	N	%	N	%	Comparisons
FSS score (mean; SD)	4.76	1.75	3.88	1.68	5.48	1.46	$t_{(252)}$=−8.425; p<0.001
Clinically relevant fatigue	164	58.2	40	31.5	124	80	$\chi^2_{(1)}$=67.486; p<0.001
Fatigue in the last two weeks							
Never	9	3.3	9	7.6	0	0	Fisher=65.317; p<0.001
Sometimes	122	45.2	80	67.2	42	27.8	
Every day	139	51.5	30	25.2	109	72.2	
Fatigue (when)							
In the morning	66	24.4	25	21	41	27.2	$\chi^2_{(2)}$=25.849; p<0.001
In the afternoon	133	49.3	78	65.5	55	36.4	
All day	71	26.3	16	13.4	55	36.4	

Adjusted alpha is 0.05/20=0.0025 (Bonferroni correction).
BMI, body mass index; Fisher, Fisher's exact test; FSS, Fatigue Severity Scale; ISI, Insomnia Severity Index; N, sample size; p, p value (statistical significance level); PHQ-9, Patient Health Questionnaire-9 (depression assessment).

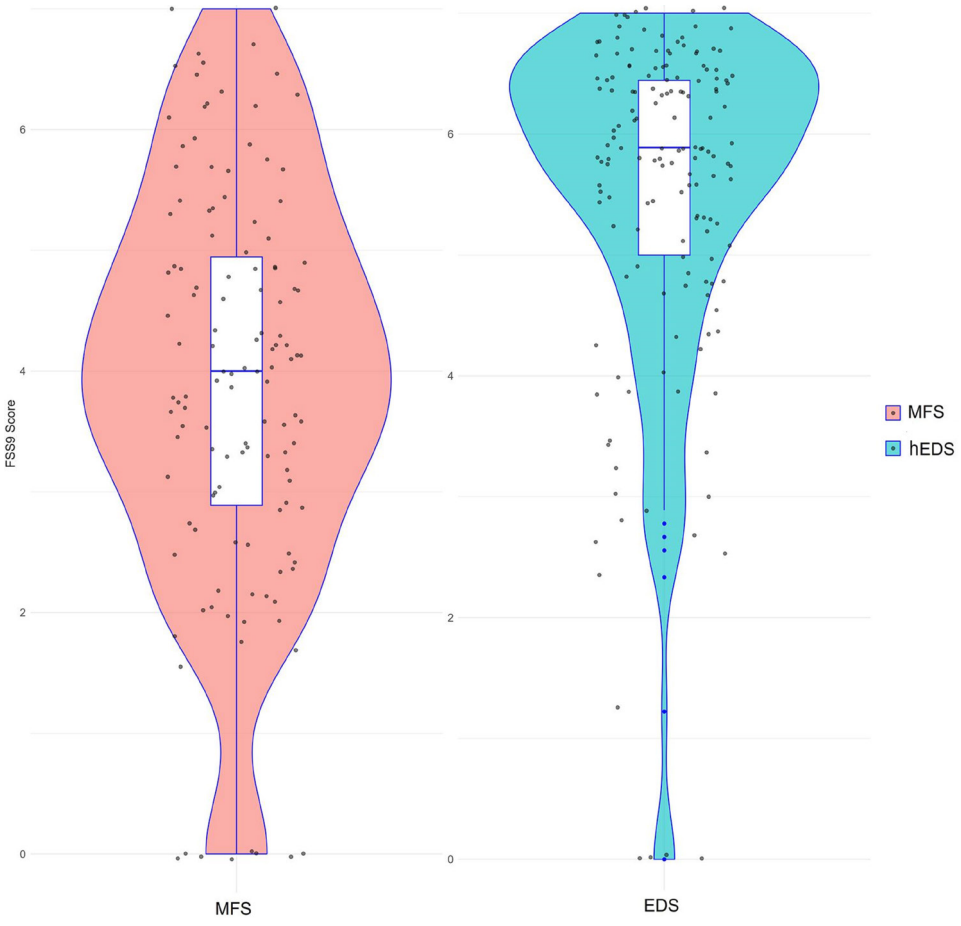

Figure 1 Distribution of the fatigue scores in patients with MFS (n=127) and hEDS (n=155). FSS, Fatigue Severity Scale; hEDS, hypermobile Ehlers-Danlos syndromes; MFS, Marfan syndrome.

Table 2 Models to ascertain determinants of fatigue (FSS score is the outcome)

	Std. B	SE	Beta	95% CI		P value
Model 1: determinants in the overall sample (N=282)						
Intercept	0.732	0.575		−0.401	1.865	0.205
Disease (1=MFS; 2 EDS)	0.430	0.187	0.122	0.061	0.798	0.022
Sex (1=male; 2=female)	0.370	0.18	0.096	0.016	0.724	0.040
Age (years)	0.006	0.006	0.044	−0.006	0.018	0.344
Education (ordered categories from 1 to 4)	0.100	0.098	0.043	−0.094	0.293	0.311
Years from diagnosis	0.009	0.007	0.056	−0.005	0.023	0.215
Comorbidities (counts)	0.282	0.172	0.073	−0.056	0.62	0.101
BMI	−0.003	0.017	−0.009	−0.036	0.029	0.840
Participation in psychotherapy (yes vs no)	−0.457	0.193	−0.11	−0.837	−0.077	0.019
Antidepressant medications (yes vs no)	0.143	0.243	0.028	−0.334	0.62	0.556
Insomnia medications (yes vs no)	−0.056	0.205	−0.013	−0.46	0.347	0.783
Score PHQ-9	0.12	0.019	0.413	0.083	0.157	<0.001
Score ISI	0.092	0.022	0.262	0.048	0.135	<0.001
Model 2: determinants in the subgroup of MFS (N=127)						
Intercept		0.862	1.383	−0.324	3.091	0.111
Sex (1=male; 2=female)	0.045	0.256	0.152	−0.355	0.659	0.554
Age (years)	0.119	0.010	0.014	−0.006	0.035	0.173
Education (ordered categories from 1 to 4)	0.104	0.150	0.215	−0.082	0.512	0.155
Years from diagnosis	0.001	0.012	0	−0.023	0.024	0.987
Comorbidities (counts)	0.111	0.321	0.466	−0.17	1.102	0.150
BMI	−0.091	0.034	−0.037	−0.104	0.03	0.273
Participation in psychotherapy (yes vs no)	−0.051	0.409	−0.271	−1.082	0.539	0.508
Antidepressant medications (yes vs no)	0.032	0.526	0.219	−0.823	1.261	0.678
Insomnia medications (yes vs no)	0.008	0.505	0.05	−0.951	1.05	0.922
Score PHQ-9	0.478	0.035	0.178	0.108	0.248	<0.001
Score ISI	0.142	0.039	0.058	−0.019	0.134	0.139
Model 3: determinants in the subgroup of hEDS (N=155)						
Intercept		1.011	1.731	−0.268	3.73	0.089
Sex (1=male; 2=female)	0.106	0.288	0.467	−0.102	1.036	0.107
Age (years)	0.006	0.008	0.001	−0.015	0.017	0.923
Education (ordered categories from 1 to 4)	−0.003	0.137	−0.007	−0.279	0.264	0.958
Years from diagnosis	0.098	0.009	0.014	−0.004	0.032	0.131
Comorbidities (counts)	0.063	0.197	0.195	−0.194	0.584	0.323
BMI	0.041	0.019	0.012	−0.026	0.049	0.537
Participation in psychotherapy (yes vs no)	−0.125	0.212	−0.388	−0.806	0.03	0.069
Antidepressant medications (yes vs no)	0.040	0.262	0.147	−0.37	0.665	0.575
Insomnia medications (yes vs no)	−0.001	0.213	−0.004	−0.424	0.416	0.984
Score PHQ-9	0.351	0.022	0.087	0.044	0.13	<0.001
Score ISI	0.382	0.026	0.117	0.066	0.169	<0.001

Continued

Table 2 Continued

Model 3: determinants in the subgroup of hEDS (N=155)
Model 1: the regression model exhibited a significant effect on the dependent variable ($F_{(12)}$=27.036, p<0.001, R^2=54.9%). The close-to-zero mean residuals and the relatively consistent SD suggest that the model reasonably fits the data, and the residuals follow a normal distribution pattern. Model 2: the regression model exhibited a significant effect on the dependent variable ($F_{(11)}$=7.891, p<0.001, R^2=43.0%). The close-to-zero mean residuals and the relatively consistent SD suggest that the model reasonably fits the data, and the residuals follow a normal distribution pattern. Model 3: the regression model exhibited a significant effect on the dependent variable ($F_{(11)}$=11.544, p<0.001, R^2=47.4%). The close-to-zero mean residuals and the relatively consistent SD suggest that the model reasonably fits the data, and the residuals follow a normal distribution pattern. BMI, body mass index; hEDS, hypermobile Ehlers-Danlos syndromes; ISI, Insomnia Severity Index; MFS, Marfan syndrome; PHQ-9, Patient Health Questionnaire-9; Std. B, standardised beta coefficient.

fatigue scores within the MFS and hEDS populations. In the scatterplots of part A obtained by plotting regression coefficients, points that align closely with the dashed line represent determinants with consistent effects across both conditions. For example, the depression scores (PHQ-9) have a relatively stable influence on fatigue regardless of whether the individual has MFS or hEDS. Conversely, points that deviate from the dashed line indicate a differential impact. This is observed with the variable 'Participation in Psychotherapy', which appears to have a disparate effect on fatigue between the MFS and hEDS groups.

With its scatterplots and fitted lines, part B of figure 3 further dissects the relationship between the regression slopes of one model versus another. The slopes and their corresponding confidence intervals (shaded areas) provide a visual estimate of the strength and direction of the relationships. The slope in the scatterplot comparing the regression coefficients from model 1 (overall sample) to model 2 (MFS subgroup) reveals the relationship between the impact of each predictor on fatigue across different patient groups. For some predictors (ie, age, BMI and years from diagnosis), the points plot near the line with a slope of 1 in figure 3, indicating a consistent effect in both the overall sample and the MFS subgroup—these predictors share a common trajectory in influencing fatigue. However, other points diverge from this line, such as sex and participation in psychotherapy, suggesting that these predictors have a differential impact. They appear to be more influential in the overall sample, including MFS and hEDS patients, than in the MFS subgroup alone. This variance underscores the importance of considering the unique interaction of these factors with the specific characteristics of each syndrome when assessing fatigue. A parallel pattern is observed when comparing model 1 with model 3 (hEDS Subgroup). Here, the slope of the fitted line reflects how certain determinants, for example, insomnia medications, have a more substantial influence on fatigue in the hEDS group compared with their impact when considering the entire sample. The comparison between model 2 (MFS subgroup) and model 3 (hEDS subgroup) elucidates the differential impact of predictors on fatigue between the two syndromes. The scatterplots indicate that most predictors have a consistent relationship with fatigue across both subgroups, with the notable exception of the ISI, which shows a divergent pattern, suggesting that it may have a lower influence on fatigue in MFS compared with hEDS patients.

DISCUSSION

This study sheds new light on the multifaceted nature of fatigue in MFS and hEDS, conditions where this symptom has not been described in-depth in recent literature.[12 13 17–21] Distinctive in its approach, the research

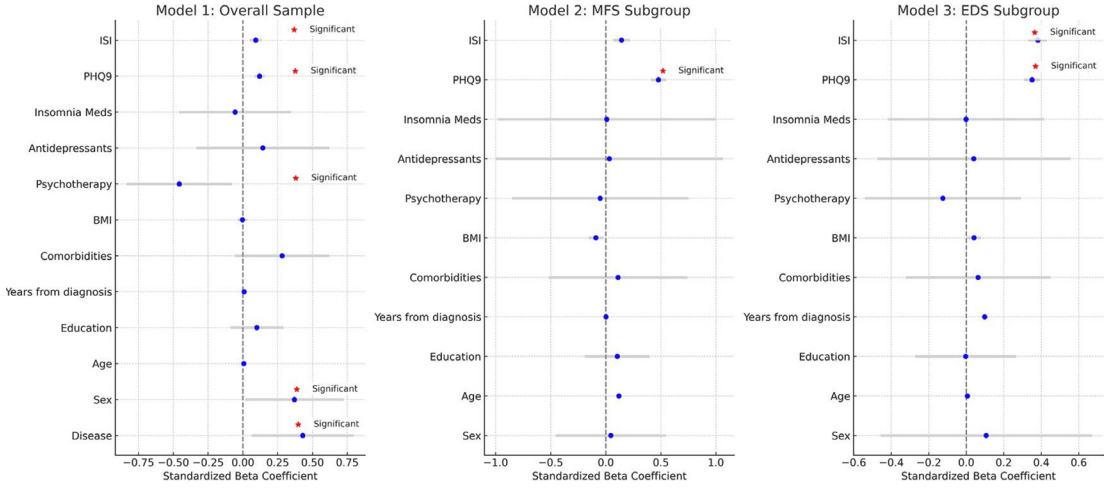

Figure 2 Standardised beta coefficients in model 1, model 2 and model 3. BMI, body mass index; EDS, Ehlers-Danlos syndromes; ISI, Insomnia Severity Index; MFS, Marfan syndrome; PHQ-9, Patient Health Questionnaire-9.

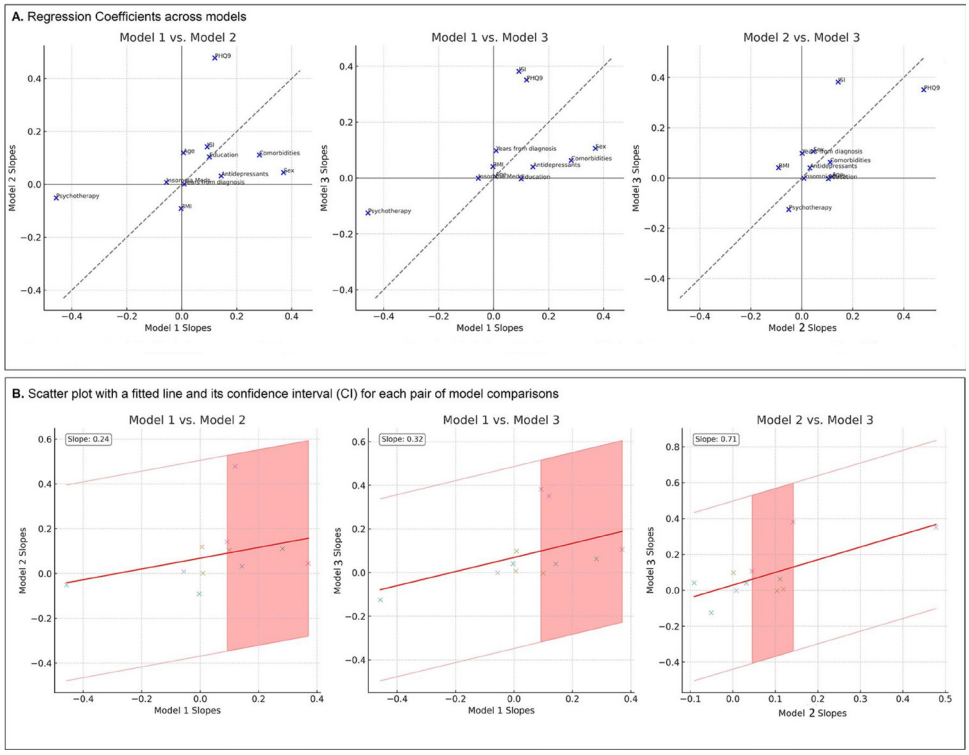

Figure 3 Comparative analysis of regression models. ISI, Insomnia Severity Index; PHQ-9, Patient Health Questionnaire-9. Notes:Points near the dashed line indicate predictors that have a consistent impact on fatigue levels in both models when compared.Points further from the line suggest predictors that differently influence fatigue betwen models

offers a detailed exploration of how fatigue presents and varies within these specific patient groups. Its novelty stems from the simultaneous examination of MFS and hEDS, providing comparative insights that were previously unexplored. Crucially, through regression analyses, the study decodes the array of factors contributing to fatigue, from physical health to psychological well-being, enhancing our understanding of these syndromes and underscoring the need for further investigations.

The findings of this study on the distribution and severity of fatigue in MFS and hEDS populations reveal both corroborations and contrasts with existing literature. Historically, research on fatigue in these populations has been sparse,[12 13 17–21] often overshadowed by more overt physical manifestations of these syndromes. Our study, however, places a spotlight on fatigue, uncovering its significant prevalence and impact in these groups. In line with some prior studies, we observed fatigue as a common symptom among individuals with MFS and hEDS.[1 6 10 12 12 13 13 18–20 30] However, a novel insight from our research is the markedly higher prevalence and severity of fatigue in the hEDS group. This result contrasts with earlier research that typically did not differentiate between the syndromes regarding fatigue severity. The findings suggest that fatigue in hEDS may be more pronounced and debilitating than previously understood, warranting special attention in clinical practice.

Moreover, our study extends the existing knowledge by quantitatively demonstrating these differences, which are adjusted for multiple comparisons performed in the analyses. The use of FSS allowed for a detailed measurement of fatigue levels, showing that hEDS patients experience fatigue more frequently and with greater intensity than their MFS counterparts. This result underscores the need for syndrome-specific considerations in the management of fatigue. These insights are particularly important given the often-overlooked nature of fatigue in the clinical management of MFS and hEDS. The higher prevalence and severity of fatigue in the hEDS group highlight a critical area for intervention and support, suggesting that fatigue management should be an integral part of the therapeutic strategies for these patients.

Given these insights, future research could benefit from incorporating instrumental muscle function and endurance analysis.[31] Such studies could objectively assess muscular capabilities and their correlation with reported fatigue levels. Investigating the physiological underpinnings of fatigue through muscle testing, electromyography, or other relevant measures could offer deeper insights into the mechanisms of fatigue in these syndromes. This approach would enhance the understanding of fatigue in MFS and hEDS and potentially lead to more effective, targeted interventions that address both the subjective experience and the objective physical aspects of fatigue.

The linear regression models and the comparative analyses provide essential insights into how various predictors differentially influence fatigue in MFS and hEDS subgroups. These analyses underscore the importance of considering each syndrome's unique characteristics

when developing intervention strategies. In the overall sample (model 1), factors like sex, disease type, participation in psychotherapy and scores on the PHQ-9 and ISI emerged as significant predictors of fatigue. However, notable differences emerged when these predictors were analysed within the MFS and hEDS subgroups (models 2 and 3). For instance, the PHQ-9 score remained a significant predictor in both subgroups, but its impact was more pronounced in the MFS subgroup. This result suggests that while depression is a key factor in fatigue for both syndromes, its relative influence is greater in MFS patients.

Similarly, the impact of the ISI score on fatigue was significantly stronger in the hEDS subgroup. This finding indicates that insomnia may play a more critical role in fatigue experienced by hEDS patients compared with those with MFS. Such nuanced differences in the influence of predictors between subgroups highlight the necessity of tailored approaches in managing fatigue. hEDS patients, for example, might benefit more from interventions targeting sleep disturbances, while MFS patients might require more focus on managing depressive symptoms.

The comparative analysis also revealed that certain predictors, such as participation in psychotherapy, exhibited divergent effects between the subgroups. This result suggests that the same intervention might have different outcomes in MFS and hEDS patients, emphasising the need for personalised treatment plans.[25] Understanding these differential impacts is crucial for developing effective, syndrome-specific interventions. It enables clinicians to prioritise certain aspects of care based on the unique needs of each patient group. Moreover, these insights inform future research directions, guiding studies toward exploring why certain predictors have varying levels of influence and how interventions can be optimised accordingly.

Recent studies have also highlighted the association between hEDS and psychological factors such as depression and anxiety.[32 33] Halverson *et al* demonstrated a strong link between hEDS and anxiety, suggesting that the psychological burden of the condition, including diagnostic delays and chronic pain, may exacerbate fatigue.[34] Similarly, Bulbena-Cabré *et al* identified anxiety and depression as frequent comorbidities in individuals with hypermobility syndromes, highlighting potential mechanisms such as autonomic nervous system dysfunction and genetic predispositions.[35] These findings align with our results, where psychological factors such as depression emerged as significant contributors to fatigue in both syndromes, with insomnia playing a particularly strong role in hEDS. Integrating these insights into clinical practice underscores the need for multidisciplinary management that addresses the physical and psychological dimensions of fatigue. The higher rates of psychotherapy and antidepressant or insomnia medication use observed in the hEDS cohort further underscore the psychological impact of this condition. These interventions, while reflective of the significant mental health burden, also raise questions about their role in moderating fatigue, suggesting a potential area for targeted interventions. Additionally, the higher proportion of participants with university-level education in the EDS cohort may reflect differences in health-seeking behaviour or awareness of available therapeutic options. This factor could influence the cohort's engagement with mental health services, further shaping the interplay between psychological and physical determinants of fatigue. Understanding how education, psychotherapy and medication use interact with fatigue could provide valuable insights for refining syndrome-specific management strategies.

The insights gained from this study have significant implications for clinical practice. The study highlights the necessity of addressing both physical and psychological aspects of fatigue in these patient populations, advocating for a comprehensive, multidisciplinary approach to treatment.[6 25] For individuals with hEDS, where fatigue is notably more prevalent and severe, interventions may need to focus heavily on managing insomnia and sleep disturbances, as suggested by the strong correlation between insomnia severity (ISI scores) and fatigue. Clinicians should consider routine screening for sleep-related issues in hEDS patients and explore treatment options like cognitive-behavioural therapy for insomnia,[36] sleep hygiene education[37] or pharmacological interventions, depending on individual patient needs, and future research is needed in this regard. In MFS patients, the significant association of depressive symptoms with fatigue implies that mental health support should be an integral part of the treatment plan.[25] Regular assessments for depression using tools like the PHQ-9 can guide clinicians in timely identification and intervention, which may include psychotherapy, pharmacotherapy or a combination of both. Given the differential impact of psychotherapy on fatigue between MFS and hEDS patients, clinicians should tailor psychotherapeutic interventions to each patient's specific psychological profile and fatigue characteristics.[6 25]

While this study offers valuable insights into fatigue in MFS and hEDS, it has limitations. One key limitation is the sample size obtained through a multicentre study involving only two specialised centres: while this approach enhanced the diversity of participants, the recruitment from only two centres may limit the generalisability of the findings. Although adequate for statistical analysis, larger samples from multiple centres would provide more robust data and enhance the generalisability of the findings. Additionally, the study's cross-sectional design limits the ability to establish causality between the identified predictors and fatigue. Longitudinal studies would be beneficial in determining the directionality of these relationships. Another limitation pertains to the reliance on self-reported measures, which can be subject to bias. Future studies might incorporate objective measures like actigraphy to complement self-reported data. Regarding generalisability, the study's findings are predominantly

applicable to the specific populations studied, may not be directly transferable to other groups or settings, and may be undermined by the provenience of patients from a single country (Italy). In addition, excluding patients with cognitive impairments limits the external validity of the study by excluding individuals who may represent an important subgroup with different fatigue profiles. Cognitive impairment could intersect with fatigue or its determinants, such as psychological stress or sleep disturbances, potentially influencing the findings. No subgroup analysis was conducted on the specific hEDS subtypes; hEDS was treated as a single group. This decision was consistent with the original study protocol, which did not include variables to identify the specific hEDS subtypes. This limitation was primarily due to constraints in sample size and the diversity within the subtypes. In rare disease research, particularly for conditions as heterogeneous as hEDS, obtaining a sufficiently large sample size to enable robust subgroup analyses often poses a significant challenge. Consequently, this approach may limit understanding of how different hEDS subtypes individually correlate with fatigue levels. Future studies are encouraged to design methodologies that include detailed subtype classification to comprehensively explore these potential differences.

Future research should focus on addressing these limitations. Larger, more diverse samples and longitudinal designs could provide more comprehensive insights. Investigating the physiological underpinnings of fatigue through muscle testing or metabolic studies could further elucidate the symptom mechanisms in these syndromes. Additionally, exploring interventions by specifically targeting the identified determinants of fatigue holds great promise. Interventional studies examining the effectiveness of tailored psychotherapeutic approaches, sleep management strategies and physical rehabilitation programmes could significantly advance fatigue management in MFS and hEDS. Such studies could also explore the efficacy of multidisciplinary interventions that simultaneously address physical, psychological and lifestyle factors contributing to fatigue.

CONCLUSIONS

This study provides significant insights into the manifestation and determinants of fatigue in individuals with MFS and hEDS. The described findings show that fatigue is a more prevalent and severe symptom in the hEDS population compared with MFS, highlighting the need for syndrome-specific approaches in clinical management. In hEDS, insomnia and depression were particularly strong contributors to fatigue, suggesting the need for interventions targeting sleep quality and mental health. In contrast, fatigue in MFS was more closely associated with depression, emphasising the importance of addressing psychological well-being in this group. Participation in psychotherapy also showed differing effects, indicating the need for tailored mental health strategies in managing fatigue. These findings demonstrate that a one-size-fits-all approach to fatigue management is inadequate, as the determinants and their impacts differ significantly between syndromes. This supports the necessity of a multidisciplinary approach, integrating expertise from cardiology, psychology, sleep medicine and physical rehabilitation to address the unique needs of each patient group. For example, hEDS patients may benefit more from interventions focused on managing insomnia and chronic pain, while MFS patients might require strategies that prioritise cardiovascular monitoring and psychological support. These results carry practical implications for clinicians and healthcare providers, advocating for routine screening of fatigue and its associated factors and the development of tailored interventions to enhance the health-related quality of life for individuals with these syndromes. Furthermore, this study sets the stage for future investigations into the nuanced interplay of factors influencing fatigue, advocating for broader studies to validate these findings and explore syndrome-specific interventions to improve care, diagnosis and prognosis.

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Contributors NU and JT contributed equally and both are considered first authors. They were involved in conceptualisation, methodology, formal analysis, investigation, data curation, writing—original draft preparation, and writing—review and editing. RC and AM performed the analytics. AB, AP, RC, EC, AM, GC, GDA, GP and IB contributed to investigation, data curation, and writing—review and editing. RC, AP, JT, NU were involved in supervision, project administration and funding acquisition. RC acted as the guarantor for this manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and the research protocol, including all aspects related to participant recruitment, data collection, and analysis, received formal approval from the Ethical Committee of Ospedale San Raffaele under protocol number 32/INT/2021. The study's protocol and its implementation were consistent with ethical standards and regulations to protect participants' rights, confidentiality and well-being throughout the research process. Participants in the study provided their consent to participate in the research through digital means included in the platform used to collect data.

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