Pain Management Nursing 25 (2024) e336–e345

Contents lists available at ScienceDirect

Pain Management Nursing

journal homepage: www.painmanagementnursing.org

Original Research

Exploring Biopsychosocial Stress Markers in Women With Fibromyalgia

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ARTICLE INFO

Article history:
Received 2 June 2023
Received in revised form 9 April 2024
Accepted 7 May 2024

ABSTRACT

Background: Identification of fibromyalgia has been a challenge for healthcare professionals due to the lack of a clinical biomarker. A well-supported integrative hypothesis holds that this condition is a chronic pain problem partly caused by long-term dysregulation of stress response. Therefore, stress assessment from a biopsychosocial perspective may be a useful approach to recognizing fibromyalgia.
Purpose: A cross-sectional case-control study was conducted to explore stress markers from a multidimensional perspective, including heart rate variability (as a biomarker of stress) as well as psychological distress and social stress.
Methods: Forty-seven women with fibromyalgia were recruited from support groups and another 47 were recruited as matched pain-free controls. Comparison and discriminant function analyses were performed.
Results: The data support the goodness of biopsychosocial stress markers in women with fibromyalgia, resulting in the identification of between 70% and 74.5% of fibromyalgia cases (sensitivity) and 85%-87% pain-free controls (specificity), with medium-high levels of fit ($\lambda = 0.58$ and $\lambda = 0.59$; $p < .00$). Women with fibromyalgia were characterized by high levels of psychological distress, social stress (disorder levels), and autonomic dysregulation. Although distress and social stress had a greater weight in discriminant functions, dysregulation in terms of low parasympathetic activity and high sympathetic activity at rest was also relevant.
Conclusions: A biopsychosocial approach to stress with an objective biomarker such as heart rate variability may be a useful tool to identify and manage FM.

Fibromyalgia (FM) is a heterogeneous and complex syndrome characterized by chronic pain and other symptoms such as fatigue, sleep disturbance, and cognitive and somatic complaints (Wolfe et al., 2016). Diagnosis criteria and prognosis continue to challenge healthcare providers due to the absence of etiological biomarkers. Although current diagnostic criteria have improved this situation (Arnold et al., 2019; Baron et al., 2014; Perrot et al., 2010; Salaffi et al., 2020; Wolfe et al., 2016), they still rely exclusively on patient self-report, which may be subject to bias. Indeed, recent literature indicates that many physicians fail to identify this condition despite using up-to-date criteria (Galvez-Sánchez & Reyes, 2020). Accordingly, misdiagnosis and overdiagnosis of FM are increasingly documented (Häuser et al., 2019; Wolfe et al., 2019), with a greater tendency toward women (Galvez-Sánchez & Reyes, 2020; Srinivasan et al., 2019; Wolfe et al., 2018). Accurate classification or identification is crucial for both patients and healthcare professionals in the context of FM, a condition that is not yet fully understood (Perrot, 2019). FM's etiology involves multiple causes, which further complicates healthcare, social acceptance, and understanding (Perrot, 2019).

An evidence-based integrative biopsychosocial model suggests that stress may be a key factor in the development of FM syndrome. The stress hypothesis, which incorporates the multiple biopsychosocial causes associated with FM, suggests that it is a problem of central sensitization to pain, partly due to a long-term dysfunction of the stress response system ((Hazra et al., 2020; Martins et al., 2021). For decades, stress has been recognized as a critical factor, on several etiological levels, in the symptom development and maintenance process, which is best addressed in a biopsychosocial model (Mezhov et al., 2021). Thus, multidimensional stress assessment could complement current diagnostics to identify FM and provide an important therapeutic value for the dif-

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https://doi.org/10.1016/j.pmn.2024.05.008
1524-9042/

ferent healthcare specialties involved in its management. However, there is a lack of research into the simultaneous assessment of all stress dimensions as a means of identifying FM syndrome.

On one hand, studies on the biological dimension of stress have shown that FM patients have an altered stress system (Martinez-Lavin & Holman, 2021), which is linked to chronic pain and other symptoms (Forte et al., 2022; Reyes-Manzano et al., 2018). In chronic diseases such as FM, where stress systems are under strain over an extended period, there are changes in both psychological and biological processes (Radley & Herman, 2023). In this sense, one of the most studied biological systems involved in stress response is the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenal (HPA) axis (Kim et al., 2018; Leistner & Menke, 2020). In this regard, heart rate variability (HRV) analysis is shown to be the best objective and noninvasive assessment method for identifying the physiological markers of ANS/HPA functioning (Kim et al., 2018; Zetterman et al., 2023). In fact, changes in ANS through HRV analysis have been observed in posttraumatic stress disorder (Schneider & Schwerdtfeger, 2020). In FM, studies evaluating HRV support the existence of stress dysregulation characterized by increased sympathetic and decreased parasympathetic tone at different states (Martinez-Lavin & Holman, 2021). However, findings regarding HRV parameters have been inconsistent, and further investigation is needed to accurately determine dysregulation in this population (Reyes-Manzano et al., 2018).

Studies on psychological and social stress have repeatedly shown its frequent occurrence in FM, which is associated with a worse clinical profile (Wolfe et al., 2019; Maurel et al., 2021). According to the stress approach, distress, as a psychological dimension of stress, can contribute to the development of FM symptoms through a number of different pathways, such as dysregulation of the ANS (Hazra et al., 2020; Pham et al., 2021). HRV, which has become an indirect measure of the ANS function, may also reflect emotional status. Research has shown an association between reduced parasympathetic activity, indicated by HRV indices, and FM. This association may also reflect the chronic psychological distress characteristic of FM (Vreijling et al., 2021).

On the other hand, a recent systematic review of the social stress dimension concludes that childhood sexual and physical abuse, death or illness in the family, and economic problems, among others, are highly prevalent in this population (Kaleycheva et al., 2023). Stressful life events are recognized triggers of FM (Galvez-Sánchez et al., 2019); however, from a diagnostic and clinical perspective, it is important to determine whether these social risks are concurrent over time with a specific psychobiological stress profile.

Therefore, considering that individuals with FM are shown to exhibit ANS dysregulation, high levels of psychological distress, and social stress compared to other populations, this study aims to explore whether these markers of biopsychosocial stress enable women with FM to be identified among women without this diagnosis. To this end, firstly, women with FM were compared with pain-free controls with respect to biological stress (ANS/HPA function through HRV), psychological distress, and social stress. Secondly, a discriminant analysis was performed for the above-mentioned purpose. The focus of this study was on women with FM due to their higher prevalence and diagnostic bias (Galvez-Sánchez & Reyes, 2020; Srinivasan et al., 2019; Wolfe et al., 2018).

Given the complex and heterogeneous clinical and psychosocial characteristics of this population, the identification of biopsychosocial stress markers in women with FM may improve their classification and clinical management (Macfarlane et al., 2017). Furthermore, this multidimensional approach may lead to a better understanding of patients with FM and provide additional insights for the development of more appropriate interdisciplinary care plans.

The strength of this exploratory study is the use of HRV as a biomarker of stress in combination with self-report measures of psychological and social stress. These measures may provide an effective and simple tool for use in clinical and research settings.

Method

Participants

The FM-eligible group consisted of 52 women from the Fibromyalgia Mutual Support Association in the City of Elche, while the control group consisted of 57 female workers from the Miguel Hernández University. All women with fibromyalgia were seen by their primary care physicians, and the diagnosis was subsequently confirmed by a rheumatologist based on the 1990 ACR diagnostic criteria and more recently developed criteria (Wolfe et al., 1990; ACR 2010 and ACR 2016). Importantly, it is assumed that there is concordance or agreement between the ACR 1990, ACR 2010, and ACR 2016 criteria for the diagnosis of FM (Carrillo et al., 2015; Salaffi et al., 2020). FM diagnosis is a requirement for membership in the association. In the study area, the symptoms identification process started with the primary care physician, but for official purposes, only the diagnosis made by a rheumatologist is considered valid. Controls were matched to the group of women with FM based on sociodemographic characteristics (age and education level). Women in both groups were recruited based on the following inclusion criteria: age 25-70 years, normotensive, and without cardiac, pulmonary, neurological, or psychiatric pathologies. Six were excluded from the eligible FM group for hypertension (n = 2) and cardiac, pulmonary, neurological, and psychiatric pathologies diagnosed by a physician or psychologist (n = 4). Ten were excluded from the controls for hypertension (n = 5), cardiac, pulmonary, neurological (n = 3), and psychiatric (n = 2) pathologies. The final sample consisted of 94 women divided into FM (n = 47) and control (n = 47) groups.

Variables and Instruments

Socio-demographic variables (age, marital status, education level, employment status, and economic income) were measured with an ad hoc questionnaire. Physical and hemodynamic variables (body mass index, heart rate, systolic, and diastolic blood pressure) were assessed using a scale, a height meter, a tensiometer, and a pulsometer.

Pain intensity perception was measured by the mean of the maximum, minimum, and usual pain intensity during the past week and pain intensity at the time of the assessment. These four items were answered on an 11-point scale (0 = "no pain at all" and 10 = "the worst pain you can imagine") adapted from Jensen et al. (1996). Higher scores indicate a greater perception of pain intensity. This scale has demonstrated good psychometric properties in women with FM ($\alpha = 0.87$) (López-Roíg et al., 2016). In addition, years since FM diagnosis was collected. The last two variables were only collected from women with FM.

Biological stress was assessed by Heart Rate Variability (HRV) analysis, which is a non-invasive and reliable index for assessing autonomic activity and is widely used as a marker of biological stress (Kim et al., 2018). In this study, short-term (~5 min) HRV was recorded using an electrocardiographic ECG (EC-12R PC-based resting ECG system; Labtech Ltd., Debrecen, Hungary). Three electrodes were placed according to Einthoven's triangle.

Following suggestions from the literature, the following HRV frequency domain parameters were used: the very low frequency (VLF) band (0.0033-0.04 Hz) to reflect HPA activity; the low frequency (LF) band (0.04-0.15 Hz) and the high frequency (HF) band

(0.15-0.4 Hz) to reflect sympathetic and parasympathetic activity, respectively; and the LF/HF ratio as an index of the balance between the sympathetic and parasympathetic nervous systems (Meeus et al., 2013). The analysis method for the frequency domain was the short-time Fourier transform (Griffin & Lim, 1984).

In the time domain, calculations were made of the standard deviation of NN intervals (time between two consecutive heartbeats) (SDNN), the root mean square of successive differences (RMSSD) and the proportion of NN50 divided by the total number of NN intervals (pNN50). HRV time-domain parameters are mainly good indicators of parasympathetic modulation and are therefore used to detect autonomous abnormalities (Rajendra-Acharya et al., 2006). Higher time-domain variability indices mean more parasympathetic influx on the sinus node.

The psychological and social distress variables were assessed using two self-administered questionnaires. The Spanish adaptation (Cabrera et al., 2015) of the Hospital Anxiety and Depression scale (HAD) (Zigmond & Snaith, 1983) was used to assess psychological distress. Fourteen items are divided into two factors: Anxiety and Depression. Patients rate each item on a four-point response scale. High scores indicate greater anxiety or depression, and cut-off scores are ≥12+ and ≥10+/12, respectively. This scale also assesses psychological distress by the total score of both subscales. In this study, the total score for psychological distress and internal consistency was $\alpha = 0.92$. The validity of the HAD scale was demonstrated by confirmatory analysis of its subscales and its relationship with other “gold standard” tools for measuring anxiety and depression (r = 0.40-0.67) (Cabrera et al., 2015).

Social stress was assessed with the Spanish adaptation (De Rivera et al., 1983) of the Social Readjustment Rating Scale (SRRS) (Holmes & Rahe, 1967). This questionnaire consists of 61 items based on a list of life events classified into different domains (health, work, home and family, personal and social, and financial), and the subject is asked to indicate whether each of these events has occurred in the last 12 months. The scale assesses events or experiences that represent a significant change in a person's life. Total social stress experienced is calculated by totaling the weights, or life change units, of the 61 events presented on the SRRS. A higher score indicates greater perceived social stress. There are some general guidelines for scoring, and it is a useful tool for stress researchers and practitioners (Hobson & Delunas, 2001). A total score of 150-299 indicates moderate stress and a 50% chance of developing a stress-related disorder. A total score of 300 or more indicates a high level of stress, and the likelihood of developing a stress-related disorder is approximately 80% (Gerst et al., 1978). The stability of the SRRS over a 2-year period ranges from $r = 0.89$ to $r = 0.96$ (Gerst et al., 1978). Consistency in the absolute weight assigned to various events over time ranges from $r = 0.59$ to $r = 0.83$ for all events (Gerst et al., 1978). The SRSS scale is widely used, and its predictive validity has been demonstrated for certain psychopathologies and physical illnesses (Yoo et al., 2017)

Procedure

In this observational case-control study, the authors endorsed the recommendations from the Strengthening Reporting of Observational Studies in Epidemiology (STROBE), an initiative for assessing quality in the reporting of observational studies in general (Vandenbroucke et al., 2007). More specifically, they also referred to the checklist list published by the National Institute for Health and Care Excellence for adequate protocol in case-control studies (NICE, 2014).

To estimate an appropriate sample size, several criteria were considered, one being that sample size and characteristics should be similar to those found in other FM studies focusing on case-control research (Hernando-Garijo et al., 2022; Piarulli et al., 2021, among others). Each set of matched case-controls consists of one case and one matched control. Therefore, we needed 57 matched sets of subjects, or a total of 114 subjects. Anticipating a 20% dropout rate, we enrolled at least 91 participants in the study (OR $\leq$ 1.5 with 90% power and $\alpha = 0.05$). Additionally, we followed the recommendation that the sample size should be large enough to produce stable estimates for the number of parameters included in this study (Hua et al., 2005). The selection for both groups was based on accessibility to a convenience sample. The authors used the 'matching' technique for cases and controls in the control groups. Matching is a widely used method to ensure comparability between two groups in this type of study (Lazcano-Ponce et al., 2001; Soto & Cvetkovich, 2020). In this study, the final sample sizes of the groups were equivalent, and we ensured that the control group's socio-demographic characteristics matched those of the patient group, as mentioned above.

The women in the sample were recruited through advertisements in two settings (at a mutual support association and at the university). Once they contacted the researchers, they were given an appointment at the Miguel Hernández University. In order to standardize the evaluation according to the availability of the participants, groups of 20 women were scheduled for 1 week, starting each day at 9:00 a.m. They were notified that they should not eat or drink anything in the 2 hours before the visit, only water was allowed. At the time of the visit, first, the research and assessments were explained in a classroom setting, and they were reminded that participation was voluntary, unpaid, and confidential. After signing the consent form, participants completed both self-administered questionnaires (HAD and SRSS). The women then waited in a room (5-20 minutes) and were called to the laboratory where they were assessed for hemodynamic characteristics and short-term (~5 minutes) resting HRV using an electrocardiogram (ECG). To avoid interfering with resting ECG recordings, they were all conducted between 10:00 a.m. and 11 a.m. Temperature was maintained between 21 and 23°C, and noise and disturbances were kept under control. All participants removed clothing and accessories, and while the ECG was recorded, they were in the supine position and were instructed to breathe normally. The physiologist performing the evaluation was blinded to the group, and each individual evaluation took approximately 30 minutes per woman.

Data Analyses

Baseline characteristics of all participants enrolled in this study were analyzed using descriptive statistics. Group differences were assessed using the chi-squared test for dichotomous variables and the Student's *t*-test for continuous variables. Effect size was also calculated using Cohen's d formula. A discriminant function analysis was performed to create a prognostic model for group membership that would discriminate women with FM from the control group according to the stress variables. Normalized and structural coefficients, Wilks' lambda, chi-squared test, eigenvalues, and canonical correlation were calculated for the discriminant function analyses. Statistical significance was set at $p \leq .05$, and all statistical analyses were performed using SPSS software 23.0 (Inc., Chicago, IL, USA). HRV data were processed using Kubios software (Tarvainen et al., 2014).

Results

There were no significant differences between women with FM and controls in sociodemographic and hemodynamic characteristics (all $p > .01$; Table 1). In both groups, the mean age was 55 years, and the body mass index was similar (27 in FM and 26 in

Table 1
Characteristics of the Participants.

	FM ($n = 47$) *Mean* ± *SD*	CG ($n = 47$) *Mean* ± *SD*	*t*	*p*
Age	55.7 ± 7.48	55.35 ± 10.24	−0.19	0.84
Clinical:				
Years since diagnosis	13.83 ± 6.82	-	-	-
Pain	6.38 ± 1.78	-	-	-
Physical/hemodynamic:				
- Body mass index	27.12 ± 4,57	26.74 ± 4.59	−0.4	0.69
- Heart rate	73.19 ± 9,17	73.91 ± 10.02	0.36	0.71
- Systolic blood pressure	126.28 ± 23.19	127.19 ± 15.87	0.34	0.73
- Diastolic blood pressure	77.64 ± 10.16	75.06 ± 9.98	−1.25	0.21
	%	**%**	**χ^2**	***p***
Civil status:				
- Single	8.5	10.6	0.24	0.97
- Married	74.5	70.2		
- Separated/divorced	12.8	14.9		
- Widow	4.3	4.3		
Educational level:				
- Reading and writing	38.3	23.4	2.94	0.40
- Primary studies	29.8	40.4		
- Secondary studies	25.5	25.5		
- University studies	6.4	10.6		
Employment status:				
- Student	6.4	8.5	6.41	0.17
- Working	31.9	36.2		
- Unemployed	17	10.6		
- Housewife	38.3	23.4		
- Retired	6.4	21.3		
Economic income:				
- < NMW	48.9	46.8	0.88	0.97
- Between 1 and 2 NMW	27.7	25.5		
- Between 2 and 4 NMW	4.3	6.4		
- >4 NMW	2.1	2.1		
- Survivor's pension	4.3	2.1		
- Old-age pension	12.8	17		

FM = fibromyalgia; CG = control group; NMW = National Minimum Wage.

Table 2
Comparison of HRV, Psychological Distress and Social Stress Between Women With Fibromyalgia and Controls.

	Mean (*SD*)		*t*	*Cohen's d* (*95% Interval*)
	FM	CG		
HRV				
- SDNN	25.77 (16.18)	23.67 (11.26)	0.732	0.15 (−0.26 to 0.55)
- RMSSD	24.39 (12.81)	24.72 (14.40)	−0.118	−0.02 (−0.43 to 0.38)
- pNN50	6.79 (9.77)	7.24 (11.71)	−0.200	−0.04 (−0.45 to 0.36)
- VLF	8.47 (8.64)	7.4 (7.91)	0.62	0.13 (−0.28 to 0.53)
- LF (%)	51.95 (14.01)	45.32 (16.14)	**−2.28**[a]	**0.44**[c] **(0.03** to **0.84)**
- HF (%)	39.47 (16.71)	47.17 (18.6)	**2.11**[a]	**0.43**[c] (**−0.84** to **[−0.02])**
- LF/HF	1.80 (1.31)	1.44 (1.43)	1.238	0.26 (−0.15 to 0.67)
Psychological distress (0-42)	18.82 (7.62)	7.8 (5.99)	−**7.79**[b]	**1.59**[d] **(1.13** to **2.06)**
Social stress (0-1576)	370.57 (332.11)	232.25 (209.24)	−**2.41**[a]	**0.49**[c] **(0.08** to **0.90)**

FM= fibromyalgia; CG= control group; SDNN= standard deviation of normal-to-normal bits; rmssd= root mean square of successive interval differences; pNN50= percentage of successive RR intervals that differ by more than 50 ms; VLF= very low frequency; LF= Relative power of the low-frequency band; HF= relative power of the high-frequency band; LF/HF= ratio of LF-to-HF power.
[a] p <.05.
[b] p <.01.
[c] Medium size effect.
[d] High size effect.

controls). The heart rate was 76 beats per minute, and systolic and diastolic blood pressures were within normal limits (126 and 77 respectively) and controls (127 and 75 respectively).

The comparative analysis results for HRV and the psychological distress and social stress variables are shown in Table 2. Within HRV parameters, the FM women showed significantly higher scores in LF and lower scores in HF compared to the control group. However, there were no significant differences between groups in the other parameters (see Fig. 1).

For psychological distress and social stress, the FM women showed significantly higher scores in both dimensions compared to the control group (Table 2). The percentages by group for types of social stressors experienced within the past year are shown in Figure 2. In the group of women with FM and in the control group,

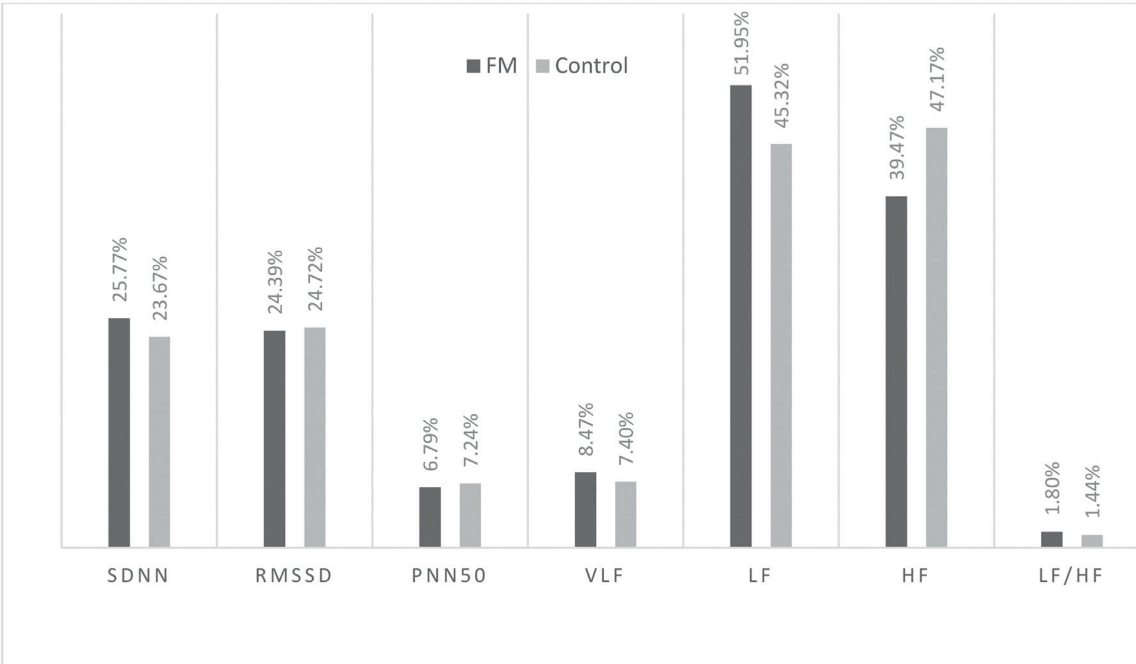

Figure 1. Mean scores for HRV parameters. FM= fibromyalgia; CG= control group; SDNN= standard deviation of normal-to-normal bits; rmssd= root mean square of successive interval differences; pNN50= percentage of successive RR intervals that differ by more than 50 ms; VLF= very low frequency; LF= relative power of the low-frequency band; HF= relative power of the high-frequency band; LF/HF= ratio of LF-to-HF power; *= $p < .05$.

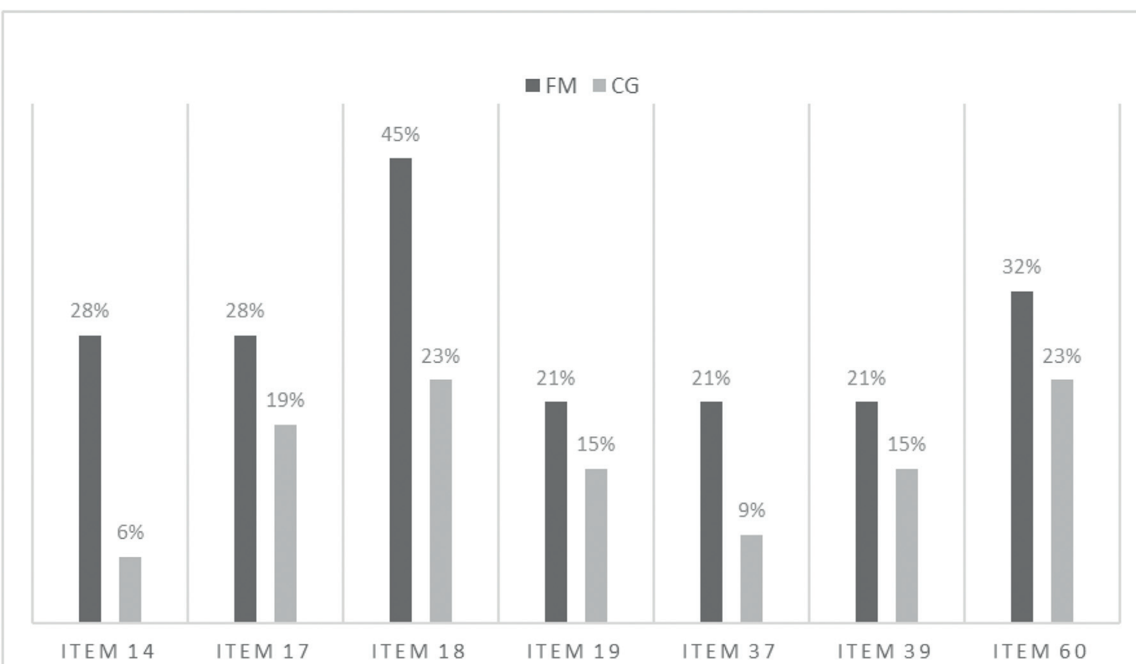

Figure 2. Percentage of types of social stressors reported by group. *Note:* FM= fibromyalgia; CG= control group; Item 14 = "sexual difficulties"; Item 17 = "death of a close member family"; Item 18 = "disease of a close member family"; Item 19 = "incorporation of a new member into the family"; Item 37 = "loan or mortgage of more than 6000 euros"; Item 39 = "income substantially reduced (25%)"; Item 60 = "prolonged illness requiring medical treatment".

the most frequently reported social stressors were the illness of a close family member (item 18: 45% and 23%, respectively), followed by a prolonged illness requiring medical treatment (item 60: 32% and 23%), and the death of a family member (item 17: 28% and 19%). The greatest percentage differences in social stress were found in sexual difficulties (item 14: 28% in the FM group and 8% in the control group).

The results of the discriminant function are shown in Table 3. To perform these analyses, the variables that significantly differentiated the two groups were selected. Three functions were performed including psychological distress and social stress. Among the HRV parameters, only the LF parameter was included in the first function, the HF parameter in the second, and both parameters in the third. As can be seen in Table 3, in the three discrim-

Table 3
Discriminant Analysis of Women With Fibromyalgia and Controls.

	Normalized Coefficients	Structural Coefficients	Function Dates
Function 1			λ = 0.58
LF (%)	0.22	0.26	χ^2 = 48.2; p < .01
Psychological distress	1.01	0.97	Eigenvalue = 0.70
Social stress	−0.13	0.30	CC = 0.64
Function 2			λ = 0.59
HF (%)	−0.13	−0.27	χ^2 = 47.02; p < .01
Psychological distress	1.02	0.98	Eigenvalue= 0.68
Social stress	−0.13	0.30	CC = 0.63
Function 3			λ = 0.58
LF (%)	0.48	0.26	χ^2 = 48.63; p < .01
HF (%)	0.30	−0.26	Eigenvalue= 0.71
Psychological distress	1.03	0.96	CC = 0.65
Social stress	−0.13	0.30	

LF = low frequency; HF = high frequency; λ= lambda coefficient=; χ^2= chi-square; CC= canonical correlation.

Table 4
Results of Groups' Classification.

		Predictor of Group Membership *n* (%)		Centroids
		FM	CG	
Real group	**Function 1**			
	FM	33 (70.2%)	14 (29.8%)	0.83
	CG	6 (12.8%)	41 (87.2%)	−0.83
	Function 2			
	FM	33 (70.2%)	14 (29.8%)	0.82
	CG	7 (14.9%)	40 (85.1%)	−0.82
	Function 3			
	FM	35 (74.5%)	12 (25.5%)	0.84
	CG	6 (12.8%)	41 (87.2%)	−0.84

FM= fibromyalgia; CG= control group.

inant functions, the variable that showed a greater weight in predicting the FM group was psychological distress, followed by social stress, and finally by both LF and HF parameters (Table 3). Wilks lambda coefficient (λ), eigenvalue, and canonical correlation analyses indicate that the predictive ability of the linear functions in discriminating groups was moderate to high (Norris, 2015).

The results for the classification of the groups are shown in Table 4. Women with FM were accurately identified in 70.2% of the cases in the first and second function, and in 74.5% of the cases in the third function with the LH and HF parameters. Controls were identified in 87.2% of the cases in the first function, 85.1% in the second function, and 87.2% in the third function. The mean centroid responses between groups and group assignment was done taking into account the degree of similarity. The distribution centroid scores according to dependent variables are shown in Figures 3–5. All three-group functions were normally distributed and centroids scores indicate that the FM group is more heterogeneous than the controls.

Discussion

This study shows whether markers of biopsychosocial stress (ANS/HPA function through HRV, psychological and social stress) can identify and distinguish women with FM from women without this diagnosis. For biological stress comparisons, ANS/HPA were evaluated at rest (5 minutes) using different HRV parameters. In frequency-domain HRV parameters and comparison with controls, women with FM exhibited higher levels of sympathetic activity (significant differences in LF), and lower levels of parasympathetic activity (significant differences in HF), which is consistent with other studies (Martinez-Lavin & Holman, 2021; Meuus et al., 2013; Vreijling et al., 2021). These results are relevant because LH and HF are the best two principal components on the HRV spectrum that reflect autonomic systems (Shaffer & Ginsberg, 2017). The LH/LF ratio parameter was similar in both groups. However, the literature reviewed underlines that the ratio parameter does not always index autonomic balance because of the complex relationship between both nervous systems.

Contrary to the results of previous studies (Mostoufi et al., 2012; Lerma et al., 2011; Fischer et al., 2016), HPA, assessed by the VLF parameter, revealed similar levels between FM women and controls. A possible explanation is that in previous studies they mainly used 24-hour ambulatory monitoring with ECG (Mostoufi et al., 2012; Lerma et al., 2011) or cortisol levels to demonstrate short-term HPA response to stress (Fischer et al., 2016). In this study, the VLF parameter was assessed at rest to identify basal and long-term HPA function according to the social stress assessment for the previous year. Consequently, in this study, the lack of differences could be explained by the fact that this parameter is predominantly a short-term reflection of sympathetic response, while other authors consider other more representative parameters for evaluating a long-term decrease in parasympathetic activity (Fischer et al., 2016). In addition, the low respiratory rate associated with the resting state could affect the VLF parameter, since its physiological significance is not yet fully understood (Shaffer & Ginsberg, 2017).

The time-domain parameters (SDNN, RMSSD, pNN50) indicate the strength of the ANS at a given time and specifically for the parasympathetic branch (Shaffer & Ginsberg, 2017; Staud, 2008) and as in other studies, no differences were found (Kang et al., 2016). This is possible because the short resting assessment may not detect changes in time-domain parameters. Regarding the SDNN parameter, some authors have suggested that it is more accurate over a 24-hour period (Shaffer & Ginsberg, 2017).

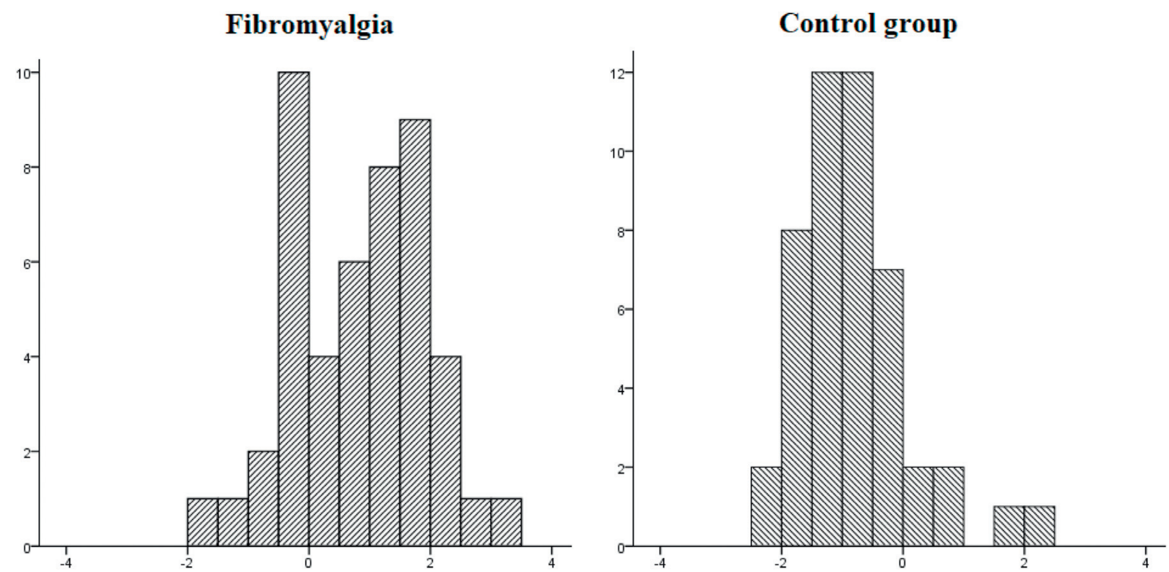

Figure 3. The centroid scores distribution of first discriminant function by groups according to the dependent variables (with psychological distress, social stress and LF parameter).

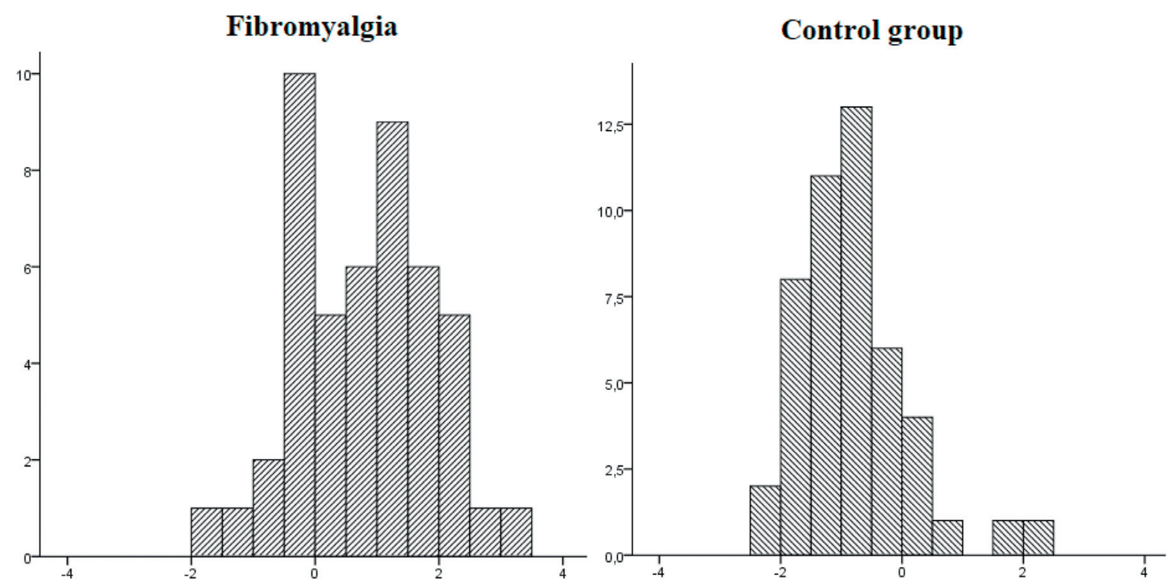

Figure 4. The centroid scores distribution of second discriminant function by groups according to the dependent variables (with psychological distress, social stress and HF parameter).

For the RMSSD parameter, a meta-analysis of chronic pain and FM concluded that there were no significant differences with the control group (Tracy et al., 2016). In addition, in relation to the pNN50 parameter, a recent study in FM patients showed acceptable nighttime accuracy, but not for the 5-minute test (Cao et al., 2022). In conclusion, since previous studies have shown the importance of parasympathetic activity in FM symptoms, further investigation is required to determine the appropriate interval of the ECG signal for HRV analysis (Staud, 2008; Vreijling et al., 2021).

According to the evidence, women with FM show significantly higher levels of psychological distress than controls (Segura-Jiménez et al., 2015). However, compared to other FM studies, the present sample showed lower levels (Wolfe et al., 2019). One explanation could be that the sample studied belongs to a support group where cases tend to be less severe (Boyer et al., 2009), or it could also indicate the effectiveness of the support group in reducing distress.

For social stress, the FM women reported significantly more stressful social life events in the past year than the controls. Given the cut-off scores of the scale used, the FM sample reported social stress levels associated with stress-related disorders (Gerst et al., 1978; Bradley, 2008). The social stressors reported by women with FM were those related to chronic sexual problems, disease processes, and economic difficulties. These findings are consistent with previous studies (Kaleycheva et al., 2023) and underscore that various stressful life experiences or chronic stress in FM are associated with long-term reduced autonomic activity and psychological distress. Social and psychological distress and persistent autonomic dysregulation induce abnormal connections between the autonomic nervous system and other physiological systems, which would explain the symptomatology spectrum of FM beyond pain (Siracusa et al., 2021).

To determine whether this biopsychosocial stress profile can identify women with FM, the discriminant functions classified

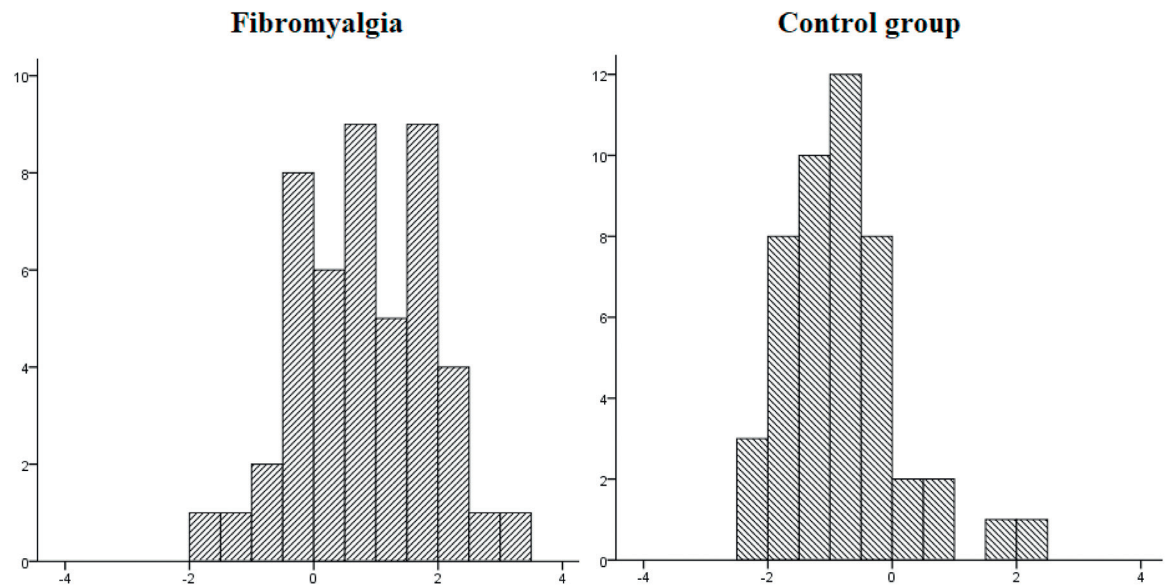

Figure 5. The centroid scores distribution of third discriminant function by groups according to the dependent variables (with psychological distress, social stress, HF and LF parameters).

between 70% and 74% of women with FM (sensitivity) and between 85% to 87% of controls (specificity). In other research with a Spanish FM sample and using modified ACR, Segura-Jiménez et al. (2015) reported a sensitivity of 88.3% and a specificity of 91.8% in the discrimination of FM from healthy controls (2010, 2011). In this study, all functions were tested and psychological distress had the greatest weight, followed by social stress and finally autonomic activity. The findings of this study are relevant because:1) it takes into account the multidimensional stress approach in the context of biopsychosocial markers for a better understanding of the complex process of FM and 2), it is consistent with the 1990 ACR FM criteria, which showed a range of sensitivity and specificity between 70% and 87%, respectively, and modified ACR (2010, 2011) with ranges of 59%-96% and 60%-100%, respectively (Wolfe et al., 2016; Galvez-Sánchez & Reyes, 2020).

In conclusion, this is the first exploratory study to assess stress from a multidimensional perspective, evaluating the severity of each dimension and its predictive power for classification. The data support the reliability of the assessment of all stress dimensions of the biopsychosocial model in the identification of women with FM. Women with FM were characterized by high levels of psychological distress, social stress (stress disorder levels), and ANS dysregulation (assessed by HRV parameters) involving low parasympathetic activity and high resting sympathetic activity. Particularly useful in discriminating FM women from controls were the HF and LF frequency domain parameters (HRV), along with the greater weight of distress and social stress.

Future Research and Implications

For future research, these results imply that FM requires a multidisciplinary approach, and that the assessment of these stress features could also guide health professionals in the screening or case identification and treatment of FM. In addition, this study has shown the implications and advantages of assessing HRV as a stress biomarker in FM. First, it represents a simple noninvasive short-term assessment (5 minutes) with ECG equipment. Second, it can serve as an objective index that reflects the nervous system's capacity to organize an effective homeostatic response to social demands (Appelhans & Luecken., 2006). Third, it provides insights into the potential value of objective information for the treatment of FM patients (Reneau, 2020). Therefore, future studies should follow this line of research to advance and verify the usefulness of biopsychosocial markers in the diagnosis of FM from an integrative perspective.

Limitations

The sample size did not include patients from other settings such as primary care or rheumatology units. Neither did it include a comparison group with rheumatologic pain conditions or conditions that cannot be clearly distinguished from FM (chronic fatigue and irritable bowel syndrome) (Meeus et al., 2013; Wolfe et al., 2019). In addition, the Body Mass Index and age of both groups were high, although both groups were matched. The short at-rest assessment used omitted changes in other HRV parameters that might have been revealed in a longer ambulatory assessment. Finally, the cross-sectional nature of this study limits conclusions regarding casual relationships.

Ethical Committee

The study was reviewed and approved by the Ethics Committee of Miguel Hernández University and supported by MINECO (PSI2016-79566-C2-1-R).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding

Supported by the Spanish Ministry of Economy and Competitiveness (Grant: PSI2016-79566-C2-1-R).

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