Onset and temporal sequencing patterns of comorbidity between lifetime major depression, panic disorder and fibromyalgia

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Abstract

Objective

Fibromyalgia (FM) is a syndrome of unknown aetiology characterised by chronic widespread musculoskeletal pain and associated with high rates of psychiatric comorbidities, mainly mood and anxiety disorders.
This study aims to determine the age at onset (AAO) and temporal sequencing patterns of FM and its frequent and distinguishable psychiatric comorbidities, the major depressive episode(s) (MDE), and panic disorder (PD).

Methods

Diagnosis of MDE and PD were assigned using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV). The AAO of FM, MDE, and PD was defined using the event history calendar. All patients completed a sociodemographic data form, self-report questionnaires measuring FM-related symptoms and function, and the Childhood Trauma Questionnaire-28 (CTQ-28).

Results

98 (83%) of the 118 recruited patients with FM had at least one psychiatric comorbidity. Two main temporal patterns were identified among the 83 patients (70.3 %) who could reliably report the age at onset of FM and psychiatric comorbidities. In the concurrent comorbidity pattern (CCP), MDE and/or PD co-occurred with the onset of FM. In the sequential pattern (SP), the patients first developed PD, then MDE, and finally FM. FM patients with SP are overweight and younger than those with a CCP (FM concurrent with MDE and PD) and reported more childhood adversities, mainly sexual abuse. AAO of psychiatric comorbidities significantly differed between the two patterns.

Conclusion

The presence of different temporal comorbidity patterns may suggest prevention/early treatment interventions, especially in patients with childhood adversities and early-onset PD.

Key words

fibromyalgia, major depression episode, panic disorder, childhood maltreatment

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Introduction

Fibromyalgia (FM) is characterised by widespread musculoskeletal pain lasting for more than three months. Patients with FM also present with a wide range of other symptoms, including persistent fatigue, sleep disturbance, and cognitive dysfunction. Although the aetiology of FM is unknown, it is thought that stressful life events, in particular those that occurred during childhood (1), may be involved in its development (2). Previous studies have shown that FM is commonly associated with a high prevalence of psychiatric symptoms and disorders, mainly major depression episode/s (MDE) and panic disorders (PD).

According to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (3), MDE is defined by at least 5 of the following nine symptoms: depressed mood, loss of pleasure or interest, significant appetite disturbance/body weight change, sleep disturbance, loss of energy, psychomotor changes, excessive guilt and/or worthlessness, decreased concentration, and recurring thoughts of death and/or suicide. PD is defined by recurrent unexpected panic attacks and persistent panic attack-related concern, worry, and behavioural change conditions for at least one month. A panic attack, the core feature of PD, is an abrupt surge of fear, apprehension, or anxiety accompanied by at least 4 of the 13 following symptoms: fast heartbeat, sweat, tremor, feeling short of breath, chest pain, dizziness, a sensation of asphyxiation, paresthesia or tingling, choking, hot flashes, nausea or abdominal pain, feeling of detachment, feeling of losing control and/or dying (3). The symptoms reach a peak within minutes and spontaneously decrease until they disappear.

At least one lifetime major depressive episode (MDE) has been described from 20% to 86% of patients with FM (4, 5) with an average rate of 50% (6), and panic disorder (PD) in up to 72% (7, 8).

Three models have been offered to explain this high frequency of co-occurrence. In the first model, depression and/or anxiety cause FM based on an increased or altered perception of somatic sensations. In the second model, distressing physical symptoms and functional limitations produced by FM might cause depression and/or anxiety, and in the third model, shared predisposing factors (biological, psychological and environmental) increase vulnerability to the development of all of them.

While the strong connection of chronic pain with depression and anxiety has been known for a long time, the cause-effect relationship and its directionality are still to be defined. Based on cross-sectional studies, earlier literature found greater evidence that depression is a consequence of pain rather than an antecedent (9). More recent longitudinal clinical (10, 11) and community-based studies (12, 13) provided suggestive evidence for a reciprocal relationship between chronic pain and depression, which is the most extensively studied psychiatric condition.

Few studies have systematically investigated the temporal pattern and timing of the onset of depressive and anxiety disorder when these conditions co-occur with FM. Hudson *et al.* (14) showed that major mood disorders (including major depression and bipolar disorders) and PD began at least one year before the onset of fibromyalgia in 57% and 45% of cases, and within the same year, in 24% and 45%, respectively. These results are in line with the study of Arnold *et al.* (5), who showed that major depressive disorders and anxiety disorders appeared more than one year before the onset of FM in nearly 80% of patients.

The timing of comorbid psychiatric disorders' onset through life in relation to the development of FM could help to understand their inter-relationships, provide clues on aetiology, and suggest preventive strategies.

This study aims to investigate the timing of the most prevalent lifetime comorbid psychiatric disorders with an identifiable onset, namely MDE and PD, compared to the onset of FM. In particular, we aim i) to identify the age at onset (AAO) of FM, MDE, and PD, ii) to describe the temporal sequencing of the onset of FM relative to the onset of comorbid MDE and PD, and iii)

to determine if the onset order of FM, MDE and PD is related to the presence of childhood adversities (such as physical and emotional abuse or neglect, sexual abuse, and parental loss), which display a high prevalence in both FM and depressive/ anxiety disorders.

Materials and methods
Participants
The study involved outpatients referred to the Rheumatology Department of L. Sacco University Hospital in Milan, Italy, between May 2010 and May 2011. The same sample was used in previous studies that had a different aim.
The inclusion criteria were:
a) age: 18–75 years,
b) meeting of the 2009 American College of Rheumatology criteria for fibromyalgia requiring widespread pain for at least three months above and below the waist and on both sides of the body, as well as pain in 11 or more of the 18 "tender points" detected by a pressure of 4 kg/cm² applied for a few seconds.
The exclusion criteria were:
a) inflammatory causes of pain;
b) severe and uncontrolled medical illnesses;
c) lifetime neurological disorders;
d) alcohol/drugs abuse or dependence;
e) current major depression episode and/or Zung Self-rating Depression Scale (SDS) ≥50 (15);
f) any clinical condition that may affect the reliability of the assessment.
All participants provided written informed consent after receiving a complete description of the study. The ethics committee approved the research study at the L. Sacco University Hospital, Milan, Italy (no. 293/2010/26/AP).

Procedure
During a rheumatological visit, the subjects were asked whether they were willing to undergo a psychiatric assessment in the framework of a research study. Clinical and socio-demographic data were collected using interviewer-administered questionnaires and recorded through a structured interview format. In about 70% of cases the collected data was validated using medical records and interviews of family members or close friends.

Psychiatric diagnoses
In a cross-sectional, single assessment study, a senior psychiatrist used the Mood and Anxiety Disorders Modules of Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician Version (SCID-CV) (16), to diagnose lifetime major depression episode (MDE) (current or remitted) as part of major depressive disorder (MDD) or bipolar disorder I/II disorder (BDI/ II), and Panic Disorder (PD). The SCID-CV was modified in a semi-structured interview because the possibility of changing the wording made it possible to check the level of understanding of each patient.

Definition of age-at-onset and temporal relationship
Age-at-onset (AAO) of psychiatric comorbidities was defined as the age at which the patient first met the full DSM-IV-TR criteria for MDE and PD. The definition of AAO of the major depressive episodes (17) as well as of PD (18) has shown to be reliable, even considering the limitation of the retrospective assessment, such as recall bias.
FM AAO was considered when patients first experienced widespread pain for at least three months, above and below the waist and on both sides of the body. In addition, axial skeletal pain (cervical spine, anterior chest, thoracic spine, or low back) must be present.
Due to the period being relatively remote for many participants, the event history calendar (19), a conversational interviewing approach designed to collect retrospective reports of events and the timing of their occurrences, has been used to maximise the accuracy of recall. The patients were asked to reconstruct their geographical, work, and school positions throughout the years so that major events around which memories could be structured may help them to recall the timing of the onset of MDE and/or PD and FM. Since the present study goal had not been planned when the data was recorded, any unintended bias of the interviewer was low.

Measures of childhood adversities
- Childhood trauma
Childhood trauma was measured using the short form of the Childhood Trauma

Questionnaire (CTQ), a 28-item, self-report instrument assessing five types of trauma: emotional abuse (EA), physical abuse (PA), sexual abuse (SA), physical neglect (PN) and emotional neglect (EN) (3, 20). Each type of maltreatment was assessed using five items, and the responses to each item were recorded using a 5-point Likert-type scale in which 1=never true and 5=very often true. Cut-off scores for each type of trauma are provided to define four levels of maltreatment: none, low, moderate, and severe. In this study, we differentiated subjects with and without a history of childhood trauma based on the low cut-off criteria (≥9 for EA, ≥8 for PA, ≥6 for SA, ≥10 for EN, and ≥8 for PN). The participants were identified as having experienced trauma if their scores were equal to or above the cut-off values.
The CTQ also includes a 3-item Minimization/Denial Scale, which is used to identify problematic cases because of potential underreporting of maltreatment. The participants were categorised as minimising if they responded *very often true* to all three items but had none/minimal trauma scores for the other subscales (false-negative trauma reports).

- Childhood parental loss
The parental loss was investigated by a senior psychiatrist and defined as being present if the subject reported that at least one parent (or surrogate parent) had left home because of death or separation (for at least one month) before he/she was 18 years old. The following data was also obtained: time, type (mother/father/surrogate parent), and causes of parental loss. Separations defined as a child being sent away from both parents when there was no obvious socially acceptable reason for the separation were considered. The separation experiences such as parental absence on business, a mother hospitalised because of childbirth, or a child away on holiday were considered "normal" and excluded from the analysis.

Measures of clinical severity of FM
- Fibromyalgia Impact Questionnaire (FIQ)
The Italian version of FIQ (21) is a

Table I. Socio-demographic characteristics of the entire sample.

	FM no comorbidity	FM+PD	FM+MDE	FM+MDE/PD	F or χ2	p
Patients n (%)	20 (16.9)	28 (23,7)	15 (12,7)	55 (46,6)		
Sex-females n (%)	17 (85)	27 (96.7)	13 (86.7)	50 (90.9)	2.147	.542
Age (years)	47.25 ± 9.14	47.25 ± 14.62	47,,5 ± 10.12	47.25 ± 11.9	1.313	.274
Education (years)	12.13 ± 4.6	10.88 ± 3.6	12.27 ± 2.9	11.53 ± 2.9	.675	.570
Marital status n (%)						
Single	5 (25)	6 (21.4)	3 (20)	10 (18.2)		
Married	10 (50)	18 (64.3)	9 (60)	36 (65.5)	1.843	.934
Divorced/Widowed	5 (25)	4 (14.3)	3 (20)	9 (16.4)		
Occupation n (%)						
Manager	2 (10)	4 (14.3)	1 (6.7)	5 (9.1)		
White-collar	9 (45)	7 (7.25)	9 (60)	24 (43.6)	5.834	.756
Blue-collar	6 (30)	10 (15%)	3 (20)	17 (30.9)		
Unemployed	3 (15)	7 (15%)	2 (13.3)	9 (16.4)		

10-item scale measuring FM-related symptoms. The first item contains ten sub-items regarding physical functioning, each rated on a 4-point Likert-type scale. Items 2 and 3 ask the patients to mark the number of days they felt well and the number of days they could not work because of FM symptoms. In items 4–10, the patients have to rate work difficulties, pain, fatigue, morning tiredness, stiffness, anxiety, and depression on horizontal linear scales marked in 10 increments. The maximum possible total score is 100, with higher scores indicating a greater impact of FM.

- *The Fibromyalgia Assessment Status (FAS)*

FAS (22) is an index combining in a single measure (range: 0–10) the patient's assessment of fatigue, sleep disturbances, and pain, evaluated on the basis of 16 non-articular sites.

- *Health Assessment Questionnaire (HAQ)*

HAQ (23) is a 20-item questionnaire investigating difficulties in performing eight daily-life activities categories (dressing and grooming, arising, eating, walking, hygiene, reach, grip, and outside activities). The patient is asked to rate the level of difficulty experienced over the preceding week in performing each activity using a 4-point scale ranging from 0 (no difficulty) to 3 (unable to perform). The final total HAQ score is the average score of the eight categories and ranges from 0 to 3 (the worst score).

Statistical analysis

A descriptive analysis was initially conducted, dividing the entire sample in four groups according to the absence or presence of a single (MDE or PD) or double (MDE+PD) psychiatric comorbidity. Normal data distribution was verified using the Shapiro-Wilk test. Afterward, the temporal relationship between FM and comorbid PD and MDE was identified using the AAO of the single disturbance. Subsequently, differences among the detected temporal pattern were evaluated with one-way analysis of variance (ANOVA) for numeric variables and chi-square analyses for categorical variables. When the differences were significant, pairwise comparisons with Bonferroni's adjustment were used to keep the experimental error rate at ≤0.05 and identify between which groups the differences were significant. All statistics are two-tailed, and significance was set at a *p*-value less than 0.05.

Results

Characteristics of the sample

The analysed sample (n=118 patients with FM) consisted of 107 females (90.7%) and 11 males of Caucasian ethnicity with a mean age of 45.7±12 years. The mean AAO of FM was 35.2±13.2 years, while the mean duration of illness was 128.1±114.6 months.

Psychiatric comorbidities

Overall, psychiatric comorbidity was substantial. Specifically, 43 patients with FM (36.4%) met diagnostic criteria for at least one lifetime disorder

(MDE or PD), and 55 (46.6%) met the criteria for both. MDE occurred only in the context of bipolar II (n=70, 59%) or bipolar not otherwise specified disorders (n=17, 14.4%). In no patient does MDE occur in Major Depressive or Bipolar I disorder.

Temporal sequencing patterns of comorbidities

Of the 118 FM patients analysed, 98 (83%) had psychiatric comorbidity, and of them, 83 (70.3%) could report the AAO of FM and psychiatric comorbidities relative to FM with good reliability. In these patients, two temporal patterns of comorbidity were identifiable. In the first pattern, defined as a concurrent comorbidity pattern (CCP), MDE and/or PD co-occurred simultaneously (within the same year) with the onset of FM. In the second temporal pattern, defined as the sequential pattern (SP), the patients first presented PD, then MDE, and finally FM.

- *Concurrent comorbidity pattern (CCP)*

Of the 83 patients with FM who reliably reported AAO of FM and/or psychiatric comorbidities, 42 (50.6%) presented psychiatric comorbidities co-occurring with FM, as shown in Figure 1.

The simultaneous onset of FM and PD is the most frequent, occurring in more than half of CCP patients (57.1%), followed by the simultaneous onset of FM, PD and MDE detected in more than one-third of them (33.3%) (Fig. 1). Patients in which PD, MDE, or both occurred concurrently with FM did not

differ in socio-demographic and clinical characteristics (Supplementary Table S1).

- Sequential pattern (SP)
A peculiar temporal sequencing pattern emerged in 23 (27.7%) of the 83 patients with FM who reliably reported AAO of FM and/or psychiatric comorbidities. First, patients experienced PD, then MDE, and finally developed FM. The mean AAO of the single disturbances was reported in Table II.
In the remaining 18 patients (21.7%), the onset of FM preceded or followed the beginning of only one psychiatric disorder.

Socio-demographic, clinical and environmental differences in FM comorbidities patterns
The patients with FM without psychiatric comorbidities were compared to SP and CCP patients (considering only the subgroup in which PD, MDE, and FM occurred within the same year) (CCP-PD/MDE/FM). They were compared regarding socio-demographic characteristics, clinical aspects, and childhood adversities (two patients were excluded from the analyses because of probable false-negative childhood trauma reports), and some differences emerged (Table III).
Patients with SP are younger and have lower BMI values than patients with CCP-PD/MDE/FM.
AAO of psychiatric comorbidities significantly differs between the two comorbidity patterns. Conversely, the AAO of FM is similar in patients with SP, CCP-PD/MDE/FM, and in those with FM without comorbidity. In particular, the AAO of PD is significantly earlier (p .001) in SP than in CCP-PD/MDE/FM, as well as the AAO of MDE (p .000) (Table III).
Finally, patients with SP have more childhood trauma (measured as the presence of at least one childhood maltreatment and/or childhood loss) or childhood sexual abuse than those with CCP-PD/MDE/FM and no-comorbid FM.

Discussion
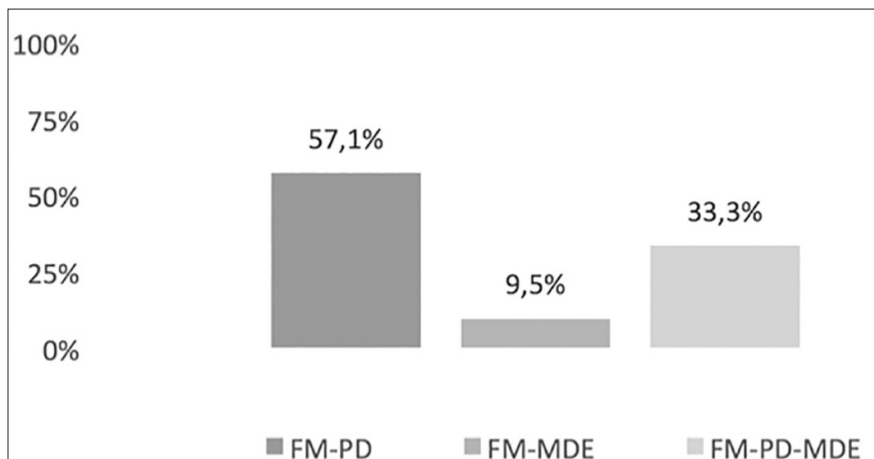The high rate of lifetime MDE and PD detected in this study mirrors the high

Fig. 1. Psychiatric comorbidities with onset concurrent with FM.

Table II. Mean age at onset of the single disturbances in the sequential pattern.

Age at onset of PD (Mean ±SD)	Age at onset of MDE (Mean ±SD)	Age at onset of FM (Mean ±SD)
16.7 ±7.2	25 ±8.9	38 ±10.8
Panic disorder	Major depression episode	Fibromyalgia

comorbidity rate between MDE (primarily if occurring in the context of bipolar spectrum disorders, as in this study sample) and PD, observed in both psychiatric clinical settings (24, 25) and general population surveys (26, 27). Interestingly, a community study based on the National Comorbidity Survey (NCS) data showed that individuals with bipolar-panic comorbidity had significantly higher rates of pain-related syndromes than those with bipolar disorder without panic attacks (arthritis/rheumatism 45.7 *vs*. 7.7% (*p*<0.0001)) (28).
Determining the temporal relationship between PD, MDE, and FM is critical to understanding the mechanisms linking these conditions. A central finding of this study is the identification of two main patterns of psychiatric comorbidity. In patients with FM, the simultaneous psychiatric comorbidity is mainly with PD and less frequently with MDE. Our results agree with the general population's findings: the association between chronic pain and psychopathology emerges more clearly for anxiety than for depressive symptoms, both in children/adolescents (29, 30) and adults (31-33).
The relationship between PD and pain-related conditions has been highlighted

for a long time. Initially, it has been shown that PD and somatisation disorder, a diagnostic category in which many patients with FM may be included, co-occurred both in general and in clinical populations (32). In addition, a number of studies have supported the occurrence of chronic pain in patients with PD. Nearly 40% of consecutively referred patients with PD reported chronic pain, with 7.8% of the total sample using analgesic medications daily (34). In fact, out of 139 patients with PD, about two-thirds reported at least one current pain symptom, and, of them, one-fourth reported joint pain (35).
An explanation for the link between PD and pain is that anxiety leads to increased pain sensitivity. Still, experimental validation of this hypothesis has had inconsistent results so far (36,37). Other studies suggested that anxiety sensitivity, a construct that reflects fear of anxiety-related sensations, represents a common vulnerability factor for the development of anxiety disorders (38), chronic pain (39) and opioid misuse (40).
The SP pattern is characterised by an early onset of PD (16.7±7.2), followed by MDE (exclusively in the context of milder bipolar conditions such as Bipolar II and bipolar disorder not other-

Table III. Socio-demographic, clinical and environmental factors in the different temporal patterns of co-morbidity.

	FM without psychiatric comorbidities	Concurrent comorbidity pattern (CCP-PD/MDE/FM)	Sequential pattern (SP)	F or c^2	p
Patients n (%)	18 (32.6)	14 (25.5)	23 (41.8)		
Sex-females n (%)	15 (83.3)	13 (92.9)	23 (100)	4.160	.125
Age	45.8 ± 8.4	53.21 ± 15.3	43.9 ± 9.5	3.313	0.04*
Education (years)	12.8 ± 3.9	10.5 ± 3	11.8 ± 2.6	1.707	.194
Marital status n (%)					
Single	5 (27.8)	2 (14.3)	6 (26.1)		
Married	9 (50)	10 (71.4)	13 (56.5)	1.634	803
Divorced/Widowed	4 (22.2)	2 (14.3)	4 (17.4)		
Occupation n (%)					
Manager	2 (11.1)	1 (7.1)	1 (4.3)		
White-collar	9 (50)	3 (21.4)	14 (60.9)	6.947	326
Blue-collar	5 (27.8)	6 (42.9)	4 (26.7)		
Unemployed	2 (11.1)	4 (28.6)	4 (17.4)		
BMI	23.6 ± 3.5	25.9 ± 4.9	22.1 ± 2.3	4.012	.026*
Age at onset of FM	39.11 ± 10.4	38 ± 12.9	38 ± 10.8	0.62	.940
Age at onset of PD-		38 ± 12.9	16.7 ± 7.2	13.186	.001*
Age at onset of MDE-		38 ± 12.9	25 ± 8 .9	41.832	.000 *
Childhood adverties					
CTQ total score	39.3 ± 16.2	41.1 ± 12.5	46.6 ± 10.7	1.446	.247
Presence of emotional abuse	3 (20)	2 (15.4)	6 (31.6)	1.272	.530
Presence of sexual abuse	1 (6.7)	1 (7.7)	7 (36.8)	6.453	.040*
Presence of physical abuse	2 (13.3)	1 (7.7)	3 (15.8)	.461	.794
Presence of emotional neglect	5 (33.3)	3 (23.1)	6 (31.6)	.399	.819
Presence of physical neglect	1 (6.7)	4 (3.8)	6 (31.6)	3.446	.179
Presence of childhood loss	3 (20)	6 (42.8)	10 (43.5)	4.085	.130
Presence of childhood adversities (trauma + loss)	7 (38.9)	7 (50)	18 (81.8)	8.22	.016*
FM severity Sscores					
FIQ	78.17 ± 9.8	75 ± 11.2	76.8 ± 10.3	.338	.715
FAS	7.48 ± 1.14	7.8 ± 1.2	7.4 ± 1.42	.432	.652
HAQ	1.02 ± .50	1.09 ± .35	1.03 ± .03	.110	.896

wise specified), and then by FM. This type of temporal sequencing of PD and bipolar depression is similar to those reported by cross-sectional and longitudinal studies in psychiatric clinical settings (41-44) and the general population (28).

Our results are consistent with the National Comorbidity Survey Replication Adolescent Supplement (NCS-A), a US representative survey of 10,148 adolescents (13–18 years), revealing that the most frequent temporal associations were those with the onset of mood and anxiety disorders preceding the onset of chronic pain (45). Similarly, a primary care study showed that in children and adolescents from 8 to 15 years, anxiety disorders were significantly more likely to precede recurrent abdominal pain than to follow them (46).

Our findings of a relationship between SP and childhood adversities, in particular sexual abuse, is in agreement with the previous literature. Cross-sectional community surveys of adults in ten countries demonstrated that multiple childhood adversities, in particular sexual abuse, and early-onset mental disorders, including depressive and anxiety disorders, were independent predictors of several adult-onset chronic pain syndromes (47). Moreover, ten-year longitudinal data obtained from the National Comorbidity Surveys (n=5001) revealed that specific childhood adverse events (*e.g.* verbal and sexual abuse, parental psychopathology, and early parental loss) were associated with increased anxiety and mood disorders. Psychopathology was, in turn, associated with an increase in the number

of painful medical conditions in adulthood (48). Accordingly, a systematic review and meta-analysis of 18 case-control studies revealed a significant association between FM and self-reported physical abuse in childhood (2).

Our results suggest that in individuals with sequential patterns, childhood adversities and an early PD onset can represent risk factors for developing depression and, afterward, FM. In a part of the patients, FM had a progressive nature, thus supporting the existence of early environmental and psychiatric conditions prior to the classic presentation of the illness. This conclusion has implications for the management of FM. The high impact of FM on individual well-being and functioning, along with the partial effectiveness of pharmacological and non-pharmacological treatment, makes the implementation of preventive and early intervention strategies a priority. However, preventive measures applied to an unselected population regardless of the individual susceptibility to the disease development would be expensive and demanding.

Although no study directly investigated this topic, it is possible to hypothesise that early and effective treatment of psychiatric comorbidity could attenuate or even prevent the subsequent FM symptoms (49).

Furthermore, a series of studies suggested that pain in FM can be amplified by the enhanced activity of the sympathetic autonomic nervous system in response to anxiety, fear, and depression and that this would be associated with vasoconstriction. In fact, protracted peripheral sympathetic vasoconstriction can produce muscular ischaemia, with sensitisation of nociceptors and muscular pain (50). Several investigations have reported the effectiveness of physical exercise in sympathoinhibition (51), vasodilation, and inflammatory control (52).

Since a recent review suggested that physical exercise effectively reduces fibromyalgia symptoms (53) and prevents and treats depression (54), it may be considered a preventive intervention in people with early psychiatric and environmental risk factors for FM.

The results of this study should be interpreted in light of several limitations.

The most significant is its cross-sectional nature, which precludes causal inference. The retrospective nature of the AAO data obtained through patients' reports at interview is burdened by a possible recall bias and limits our ability to draw firm conclusions. To avoid the possibility that depression may have interfered with the self-reporting of childhood adversities, we excluded patients with a current MD episode and those with moderate/severe depressive symptoms as assessed by the Zung Self-rating Depression Scale. Moreover, the sample size is small, and it is crucial to investigate this research question with larger samples in a longitudinal design. Finally, as our sample is from a tertiary care clinic, the results may not be generalisable to all populations of individuals with FM.

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