Epidemiological, pharmacological and sociodemographic characterisation of a population of 386 fibromyalgic patients referred to a tertiary pain centre in Italy

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Received on December 20, 2017; accepted in revised form on March 5, 2018.

Clin Exp Rheumatol 2019; 37 (Suppl. 116): S27-38.

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Key words: fibromyalgia, pain

Competing interests: none declared.

ABSTRACT

Fibromyalgia's prevalence in Italy is about 4%. Apart from widespread pain and the three main conditions related to fibromyalgia that are included in its diagnosis (fatigue, unrefreshing sleep and cognitive disorders disturbances), there are a number of minor symptoms that have been associated to fibromyalgia. The current study aimed to characterise fibromyalgic patients referring to a single tertiary pain centre not only for sociodemographic data, but also with special attention on pharmacological history and "minor" symptoms. "Minor" refers to the group of symptoms that were frequently associated and reported with fibromyalgia in various epidemiological studies but are not required for diagnosis. A retrospective analysis was made on 386 patients with confirmed diagnosis based on the 2010 modified criteria.

Our results partially confirmed known sociodemographic data, but the prevalence of some "minor" symptoms are impressively high in our population.

Introduction

Fibromyalgia (FM) is a debilitating disease characterised by chronic widespread pain, sleep disorders (including unrefreshing sleep), muscle stiffness, fatigue and cognitive disorders (1). FM has historically been called with different names and defined in different ways, due to the variety of symptoms characterising it. Its aetiology is still not completely understood. In 1990 the American College of Rheumatology developed the first diagnostic criteria for FM (ACR criteria 1990) based on the first multicentre study (2). These criteria involved the presence of widespread pain for 3 months (to be considered widespread, pain has to be in both sides, over and under the waist, and summed with axial pain) and a minimum number of 11/18 tender points. The ACR 1990 criteria presented many difficulties in clinical practice: they could not be standardised (3, 4), there where potentially more tender points in women than in men (5, 6) and the correlation of tender points may vary with psychological stress conditions (6-8). More importantly, these criteria did not consider other basic characteristics of the disease, as fatigue, cognitive, visceral and somatic symptoms and could not assess the severity of symptoms in patients with FM (9). Considering the limits of the ACR 1990 criteria, the American College of Rheumatology published the ACR 2010 criteria and the ACR 2010 modified criteria. Both include 3 conditions for the diagnosis of FM (9): WPI (Widespread index) ≥7 and SS (Symptom Severity score) ≥5 or WPI between 3 and 6 and SS ≥9; presence of symptoms for at least 3 months; exclusion of other pathologies that can explain the pain otherwise. These criteria offer the advantage of carrying a quantitative evaluation, that is fundamental in order to compare FM characteristics between different settings and countries (10). Apart from widespread pain and the three main conditions related to FM that are included in its diagnosis (fatigue, unrefreshing sleep and cognitive disorders disturbances), there are a number of minor symptoms that have been associated to FM patients in several studies. These minor symptoms include temporomandibular joint disorders (1, 11), facial pain (12), irritable bowel syndrome (IBS) (13), interstitial cystitis and pain bladder syndrome (1, 11) and several others, such as dysmenorrhea (11) and sexual dysfunction (14, 15).

Aim of the study

The aim of this study is to contribute to the literature on FM, particularly regarding the prevalence of "minor" symptoms and its socio-demographic and pharmacological characterisation.

Design and subjects

Inclusion criteria

All patients diagnosed with FM according to the ACR 2010 modified criteria referred at Pain Therapy Centre of Verona University between January 2013 and December 2016 were included in the analysis. Some data were not available for all patients, so the number of patients for every measured feature is specified.

Methods

Presented epidemiological, physiological and pharmacological data, such as clinical presentation and symptoms, refer to the period of patients' first medical examination. Past medical history has been reconstructed using clinical documentation given by patients themselves. Questionnaire scores were obtained during the first medical examination, and data collected during follow-up were not used. The results are therefore referred to patients' first contact with our Centre. All anamnestic interviews were administered by a member of medical staff of the Pain Therapy Unit and associated clinical features were assessed during interview following a predefined checklist.

Every patient gave verbal or written consent (also in further visits) for using their data and anonymous treatment of data was guaranteed. Data collected were divided in six categories: socio-demographic, physiological, past medical history, pharmacological history, quantitative indexes, and associated clinical features. All options in each category are reported in detail in Table I.

Questionnaire administration and evaluation

Three different questionnaires were administered to every patient: Fibromyalgia Impact Questionnaire (FIQ), Pittsburgh Sleep Quality Index (PSQI) and Healthy Survey 12 (SF-12). The FIQ (16) evaluates three different areas:

Table I. Data collection. For every examined category each field is reported along with every option.

Socio-demographic		
	Age	
	Gender	
	Nationality	
	Residence (state, region)	
	Civil status	Unmarried, married/cohabitant, divorced/separated, widow
	Education level*	primary school, junior high school, secondary school degree that does not give access to university, 53 patients had secondary school degree that does give access to university, 23 patients had a degree, and 2 had a postgraduate degree.
	Job#	Legislator, manager, businessman; intellectual job, scientific job, elevated specialisation; technical job employers; qualified job in marketing and services; artisan, specialised labourer and farmer; vehicle and machinery drivers, machinery labourer; unqualified jobs; army; students
	Current working condition	Employed, unemployed and retired. Housewives were considered as unemployed if they were working before disease onset and had to quit because of the disease. If instead they were housewives even before the disease, their working condition was classified as employed and the job classification was "unqualified job".
	Disability score	Not disable (<33%), disable (34-99%), inable (100%)
Physiological		
	regular physical activity	at least1 hour of physical activity for at least 3 times a week
	diet	varying diet, gluten free diet, vegetarian diet, vegan diet
	smoking	at least 1 cigarette was smoked in the past year
	alcohol abuse	for more than 3 alcoholic unit/die in men and more than 2 alcoholic unit /die in women
	drug abuse	
	previous physical trauma	significant if it was one of the following: needing medical treatment, column trauma needing medical therapy, major surgery, domestic violence
	previous psychological trauma	unresolved mourning, repeated miscarriage or miscarriage later than first trimester, sexual violence, nervous anorexia, personal failure, stalking, childrens' health problems or death, parents' divorce or separation during childhood, malignant cancer
Past medical history		
	psychological condition	anxiety, depression, panic attacks and major psychosis
	relational problems	familial conflicts, working problems, social problems
	respiratory diseases	asthma, COPD, OSAS
	cardiovascular diseases	arrhythmias, valvular heart disease, vascular diseases, and ischemic cardiopathy
	malignancy	
	musculoskeletal diseases	arthritis (including rheumatoid arthritis, psoriasic arthritis, undifferentiated arthritis and others unspecified), arthrosis (polyarthrosis, spondyloarthropathy), joint prosthesis, connective tissue diseases (includes mixed connective tissue disease, undifferentiated connective tissue disease, scleroderma, systemic eritematosus lupus, sjogren syndrome), discopathies (cervical and lumbar hernia were considered only if currently present, whether not treated or unsuccessfully treated), osteoporosis and osteopenia, degenerative lumbar disease, others
	blood or immunity diseases	anemia, immunodeficiency, thrombocytopenia, thrombophilia
	endocrine diseases	diabetes, gestational diabetes, hypovitaminosis D, thyroid disease, obesity, others
		and other diseases

Pharmacological history	
	SSRI
	SNRI
	tricyclic antidepressant
	benzodiazepines
	NSAID
	opioids
	cortisone drugs
	muscle-relaxant drugs
	anticonvulsivants
	non pharmacological acupuncture, balneotherapy, under threshold physical therapies activity, magneto therapy
Quantitative index	WPI
	SS
	VAS
	Tender Points' number
Associated clinical features	chronic fatigue
	concentration difficulties
	short memory disturbances
	Irritable Bowel Syndrome
	gluten intolerance
	intolerance to chemical substances
	lactose intolerance
	hallucination
	headache
	muscle stiffness
	meteoropathy
	work problems
	school problems
	sleep disturbances
	drugs hypersensitivity
	low back pain
	joint symptoms/crackling
	muscle spasm/clonus
	restless leg syndrome
	teeth pain
	urinary burning
	urgency
	abdominal bloating
	numb extremities
	tinnitus
	polydipsia
	dysmenorrhea
	vulvodynia
	dyspareunia
	mouth/nose/eyes dryness
	peripheral edema
	unsteadiness
	nocturnal muscle cramps

*education level was decided upon Italian educational qualification classification (57) available at http://www.istat.it/archivio/6620, all degrees were considered in the same way, without distinguishing between levels, setting and order.
#categorised using Job classification by ISTAT[58], available at http://nup2006.istat.it/

physical impairment, overall impact and symptoms, that contribute respectively to 10, 20 and 70% of total score, and results can vary from a minimum of 0 to a maximum of 100% (worst condition). According to FIQ scores, FM can be classified in three different classes of severity (17): mild (FIQ<39), moderate (39≤FIQ<59) and severe (FIQ ≥59). In our centre we used the FIQ Italian validated version of 2003 by Sarzi-Puttini (18). Every question has a score from 0 to 10. Questions 3 and 4 about working condition can be left unanswered, and the consequent maximum total score of 80 has thus to be proportionally scaled to a 100 base. Pittsburgh Sleep Quality Index is a questionnaire developed by Bracket at the end of 80s, and the Italian translation and validation was done in 2012 by Curcio (19). PSQI is the most used instrument to establish the sleep quality in the previous month (20). It examines seven different sleep properties: quality, latency, duration, effectiveness, sleep and daily disturbances, drug usage to sleep. A score greater than 5 indicates a sleep disturbance (20). SF-12 Health Survey is composed of two indexes: Physical component survey PCS-12 and Mental Component Survey MCS-12. It represents a shorter but equally efficient version of SF-36 questionnaire (21). This study used the simplified Italian version of SF-12. Scores of SF-12 were obtained with online software "SF-12 Health Survey Scoring Demonstration" freely available online at http://www.sf-36.org/demos/SF-12.html. Lower PCS and MCS scores are related to worse health condition, whilst higher values refer to a good health status.

Statistical analysis

The statistical analysis was done with Excel (Microsoft, USA). Age variable, having a nearly Gaussian curve, is illustrated with range, mean and standard deviation. Questionnaire results have a nearly normal distribution and are presented as range, mean and standard deviation. WPI, SS, VAS and TPs variables are presented as median and quartiles because they are not normally distributed. Qualitative variables are presented as absolute frequencies and percentages. As regards to medical past history, some diseases seemed to be more frequent than others, therefore a binomial test has been performed in order to compare the examined disease prevalence among our sample with the prevalence among general population. Psychiatric disease prevalence among general population was extracted by ESEMeD-WMH study (22), developed by Bologna's Mental Health Department, Verona's Medicine and Public Health Department and National Centre of Health Epidemiology, Promotion and Surveillance of National Health Institute. This study was lead in Italy during 2000 upon 4712 subjects, within a larger European project. Comparison between our prevalence and general population prevalence has been done considering lifetime prevalence and assessed on the bases of our sample gender proportion. Regarding mammary tumor malignancy, data were extracted

from AIRTUM report (23), developed thanks to the collaboration of various institutions, including Oncologic Reference Centre of Aviano and Public Health Department and National Centre of Health Epidemiology, Promotion and Surveillance of National Health Institute, using data coming from different Italian regions covering a population of 21 million people.

Results

Socio-demographic data

Data of 386 patients were reviewed (Table II), 358 were women, while 28 were men, with a women to men ratio of 12.8:1. Mean age was 49.3 (± 11,9) years. Considering only women, mean age was 49.5 years; while among men mean age was 47.6 years; 37.6% of sample was in the range 45-54 years. 331 patients lived in Northern Italy (among them 211 came from the Veneto region), 22 came from Central Italy, 15 from Southern Italy and 6 from Italian islands. One patient had foreign residence. Sixty-eight percent were married or cohabitating and 73% had children.

Education level data were available for 122 patients. Among them, 10 (8%) patients had undergone only primary school, 28 (23%) had junior high school degree, 5 (4%) had secondary school degree that does not give access to university, 53 (43%) patients had secondary school degree that does give access to university, 23 (19%) patients had a degree, and 3 (3%) had a postgraduate degree. The most represented job was unqualified job, followed by a nearly equal representation of office workers, business and service employers, and intellectual jobs. Seventy-one percent were employed at first medical contact. The disability data were not available in the questionnaires, we thus decided to use phone interviews on a sample of 100 patients. Among them, 51% did not present any disability, having a disability score <33%; 40% had variable disability (score between 34-99%) and 9 patients were fully disabled (100% disability score).

Physiological history

Only 36% of patients had a regular physical activity and 70% had varying

Table II. Sociodemographic data.

Socio demographic data		n (%)
Gender (386 pts)	Male	28 (7.3%)
	Female	358 (92.7%)
Age (386 pts)	0-19 years	1 (0%)
	20-29 years	22 (6%)
	30-39 years	56 (14%)
	40-49 years	113 (29%)
	50-59 years	120 (31%)
	60-69 years	55 (14%)
	70-79 years	18 (5%)
	≥80 years	2 (1%)
Nationality (382 pts)	italian	368 (96%)
	other	14 (4%)
Marital status (359 pts)	single	52 (14%)
	married or cohabitating	243 (68%)
	separated / divorced	54 (15%)
	widowed	10 (3%)
Childrens (357 pts)	No children	95 (27%)
	1 children	101 (28%)
	2 children	121 (34%)
	3 children	33 (9%)
	>3 children	7 (2%)
Education level (122 pts)	Primary or junior high school	38 (31%)
	Secondary school	58 (48%)
	Graduated	26 (21%)
Job (365 pts)	Legislator, manager, businessman	7 (2%)
	Intellectual job, scientific job, elevated specialisation	59 (16%)
	Technical job employers	47 (13%)
	Office workers	67 (18%)
	Qualified job in marketing and services	55 (15%)
	Artisan, specialised labourer and farmer	27 (7%)
	Vehicle and machinery drivers, machinery labourer	2 (1%)
	Unqualified job	91 (25%)
	Army	1 (0%)
	Students	9 (3%)
Employment (370 pts)	Empoyed	264 (71%)
	Unempoyed	65 (18%)
	Retired	41 (11%)
Disability degree (100 pts)	not disable	51 (51%)
	disable	40 (40%)
	Inable	9 (9%)

Table III. Physiological history.

Physiological history		n (%)
Regular physical activity (292 pts)	Yes	106 (36%)
	No	186 (64%)
Diet (277 pts)	Varying diet	193 (70%)
	Gluten-free	74 (27%)
	Vegetarian diet	9 (3%)
	Vegan	1 (0%)
Smoke (338 pts)	Yes	69 (21%)
	Past smoking	35 (10%)
	No	234 (69%)
Alcohol abuse (338 pts)	Yes	1 (0%)
	Past abuse	1 (0%)
	No	336 (100%)
Drug abuse (338 pts)	Yes	1 (0%)
	No	337 (100%)
Previous physical trauma (368 pts)	Yes	175 (48%)
	No	193 (52%)
Previous psychological trauma (367 pts)	Yes	184 (50%)
	No	183 (50%)
All traumas (368 pts)	Yes	279 (76%)
	No	89 (24%)

Table IV. Psychological history and comorbidities.

Psychological history and comorbidities		n	(%)
Psychological condition	Nothing	136	(33.6%)
(382 pts)	anxiety	212	(55.5%)
	depression	210	(54.9%)
	panic attacks	32	(8.4%)
	major psychosis	9	(2.4%)
Relational problems	no	294	(76.9%)
(381 pts)	familial conflicts	63	(16.5%)
	working problems	23	(6%)
	social conflicts	6	(2%)
Breathing diseases	no	353	(92.6%)
(381 pts)	asthma	13	(3.4%)
	COPD	9	(2.4%)
	OSAS	4	(1%)
	other	2	(0.05%)
Cardiovascular disease	no	346	(91.3%)
(382 pts)	arrhythmias	9	(2.4%)
	valvular disease	8	(2.1%)
	vasculopathy	12	(3.1%)
	Ischemic cardiopathy	6	(1.6%)
Malignancy	no	339	(89%)
(383 pts)	yes	44	(11%)
	breast	16	(36%)
	cervix	6	(14%)
	tyroid	5	(11%)
	central nervous system	3	(7%)
	skin	3	(7%)
	kidney	2	(4,5%)
	hematological	2	(4,5%)
	others	7	(16%)
Musculoskeletal disease (383 pts)	no	243	(63.4%)
	arthritis	26	(6.7%)
	arthrosis	56	(14.6%)
	connective tissue diseases	10	(2.6%)
	discopathies	45	(11.7%)
	osteoporosis and osteopenia	20	(5.2%)
	degenerative lumbar disease	22	(5.7%)
	joint prosthesis	7	(1.8%)
	others	9	(2.3%)
Blood or immunity diseases (383 pts)	no	367	(95.8%)
	anaemia	9	(2.3%)
	immunodeficiency	2	(0.5%)
	thrombocytopenia	2	(0.5%)
	thrombophilia	4	(1%)
Endocrine diseases (383 pts)	no	259	(67.6%)
	diabetes	13	(3.3%)
	gestational diabetes	4	(1%)
	hypovitaminosis D	35	(9.1%)
	thyroid disease	69	(18%)
	obesity	26	(6.7%)
	others	4	(1%)
Others	endometriosis	13	(3.4%)
	multiple chemical sensibility	7	(1.8%)
	chronic viral hepatitis	7	(1.8%)
	past anorexya	6	(1.5%)
	neuropathy	5	(1.3%)
	myalgic encefalitis	4	(1%)
	epilepsy	4	(1%)
	psoriasis	4	(1%)
	ulcerative colitis	3	(0.8%)
	past rheumatic disease	3	(0.8%)
	coeliac disease	2	(0.5%)

diet, 27% patients had gluten free diet, 9 patients followed vegetarian diet and 1 was vegan. Only 21% were smokers at first medical contact, 10% were ex-smokers and 69% had never smoked. One patient had past alcohol abuse and one had current alcohol abuse and one patient used cannabis. Full details are reported in Table III. Forty-eight percent referred at least one significant physical trauma before FM beginning, whilst 193 had never had physical trauma, 50% patients referred psychological trauma. If both traumas were evaluated as positive, 279 (76%) of them referring a trauma experience in their life, preceding FM occurrence, while 89 (24%) did not refer any trauma.

Psychological history and comorbidities

Full data are available in Table IV. Fifty-five percent of patients suffered from anxiety, 54.9% from depression, 8.4% suffered from panic attacks and 2.4% of major psychosis. Given the high presence of anxiety in our sample, we compared our prevalence with the Italian general population prevalence, observing a significant association between FM and anxiety diseases ($p<0.0001$). The same was done for depression diseases, and a significant association between these and FM was found ($p<0.0001$), such as for panic disease ($p<0.0001$). Relational problems were not reported in 76.9% of cases, whilst 16.5% referred familial conflicts, 6% referred working problems and 1% social conflicts. Cardiovascular and breathing diseases: 91.3% did not have any cardiovascular disease, 2.4% had arrhythmias, 2.1% had valvular diseases and 1.6% had ischaemic cardiopathy. Most patients (92.75%) did not have any respiratory disorder, while 3.4% had asthma, 2.4% had COPD, and 1% had OSAS. Eleven percent of patients had malignancy diagnosis during lifetime. Most represented malignancy was breast cancer with 16 patients. Given the high prevalence of breast cancer we compared prevalence data among our sample with prevalence data on general population. We found a significant association between breast cancer and FM ($p<0.001$). Most patients (68%) did not have any endocrine disease, whilst among the remaining patients the most represented endocrine disease was thyroid disease (18%). Musculoskeletal disease: data for 383 patients. 243 (63%) patients had no diagnosed musculoskeletal disease; the most represented were arthrosis (14.6%) and discopathies (11.7%). Less

Table V. Complete drug usage history.

Treatments (n=379)		n (%)
SSRI	actual	61 (16%)
	past	35 (9%)
	no	283 (75%)
SNRI	actual	58 (15%)
	past	81 (22%)
	no	240 (63%)
Tricyclic antidepressant	actual	51 (14%)
	past	69 (18%)
	no	259 (68%)
Benzodiazepines	actual	125 (33%)
	past	32 (8%)
	no	222 (59%)
NSAID	actual	124 (33%)
	past	52 (14%)
	no	203 (53%)
Opioids	actual	94 (25%)
	past	56 (15%)
	no	229 (60%)
Cortisone drugs	actual	29 (8%)
	past	40 (10%)
	no	310 (82%)
Muscle-relaxant drugs	actual	39 (10%)
	past	60 (16%)
	no	280 (74%)
Anticonvulsivants	actual	35 (9%)
	past	69 (18%)
	no	275 (73%)
Balneotherapy	actual	15 (4%)
	past	4 (1%)
	no	360 (95%)
Under threshold physical activity	actual	26 (7%)
	past	18 (5%)
	no	335 (88%)
Acupuncture	actual	7 (2%)
	past	25 (7%)
	no	347 (91%)

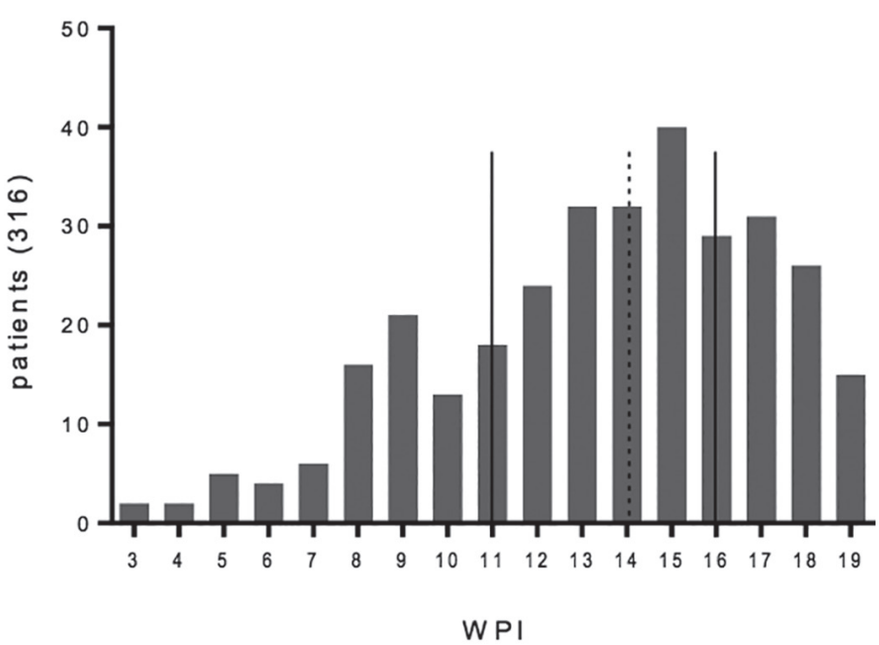

Fig. 1. WPI distribution. Data were available for 316 patients. Solid vertical lines represent first and third quartile, dashed line represents median value.

frequent comorbidities associated with FM were endometriosis (13), multiple chemical sensitivity (7), chronic viral hepatitis (7), previous nervous anorexia (6), chronic fatigue syndrome (5), epilepsy (4), psoriasis (4), ulcerative colitis (3), previous rheumatic disease (3), coeliac disease (2).

Drug usage history and treatments

Complete drug usage history was available for 379 patients on 386 examined (Table V). Most used drugs in our sample were benzodiazepines (33%), NSAIDs (33%) and opioids (25%), both for actual and past use; 23% of patients were not under any drug therapy. Four percent of patients did use balneotherapy while 7% did light workout sessions as therapy and 5% did it previously. Acupuncture was used by 2% of patients while 7% patients had undergone ago-puncture previously.

FM severity indexes

WPI median value was 14 with an interquartile range of 11-16 (Fig. 1); SS first quartile was 8 and third was 11, with a median of 10 (Fig. 2). VAS was initially reported on a 100-scale, but for this analysis it has been brought back to 10-scale. First quartile was 7 and third 8, with a median of 8 (Fig. 3). Only 191 patients were evaluated for tender points (TPs), as these are no more required for the diagnosis; thus the subsequent data refer only to a restricted number of patients, about 50% of the total. First quartile was 9 and third was 16, with a median of 12 (Fig. 4); 65/119 patients (55%) had less than 11 TPs.

Associated clinical features

Available data were 324/386 patients with regard to the symptoms common to both men and women, while they were 298/358 for symptoms referred to only female patients. Most represented symptoms were fatigue (95%), sleep disturbances (93%) and muscle stiffness (93%). Regarding "minor" symptoms, the most reported were concentration and memory disturbances (81% and 80%, respectively) and headache (80%); IBS had a prevalence of 77% and abdominal bloating 73% (Table VI, Fig. 5).

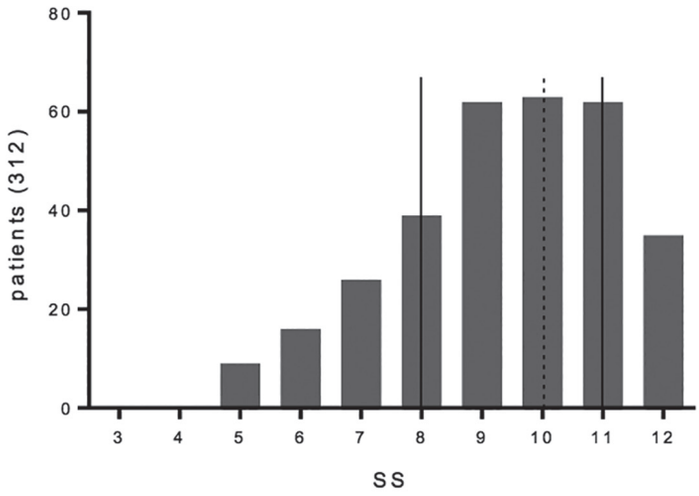

Fig. 2. Severity Score distribution. Data were available for 312 patients. Solid vertical lines represent first and third quartile, dashed line represents median value.

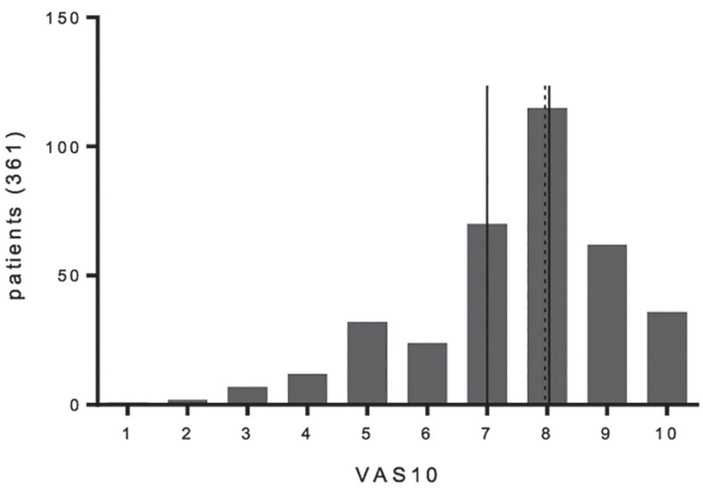

Fig. 3. VAS10 distribution. VAS data were categorised on a 10 base to be represented. Data were available for 361 patients. Solid vertical lines represent first and third quartile, dashed line represents median value.

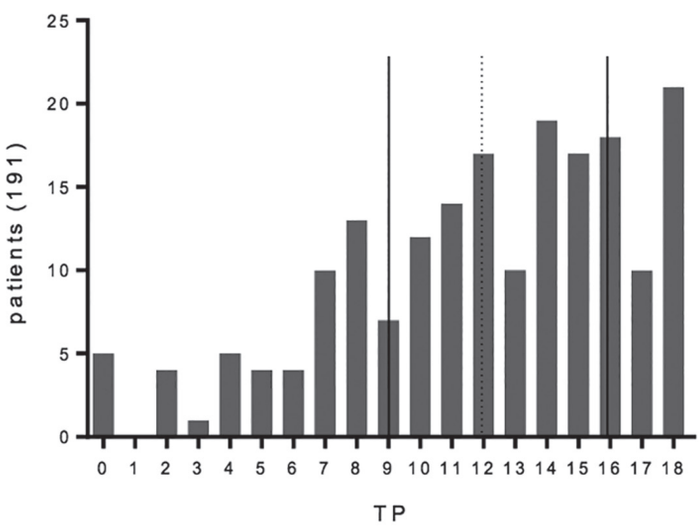

Fig. 4. Trigger points (TP) distribution. Data were available for 316 patients. Solid vertical lines represent first and third quartile, dashed line represents median value.

Questionnaires

FIQ score at first medical examination was available for 302 on 386 patients (Fig. 6). For the other 70 patients FIQ was not administered and 14 did not complete it correctly. Mean FIQ score was 69.4±13.8. Regarding disease severity: 7 (2%) patients had FIQ <39 (mild), 58 (19%) had FIQ between 39 and 58 (moderate) and 237 (79%) patients had FIQ ≥59 (severe). Age and FIQ connection showed a slightly positive correlation (r=0,1). For PSQI, data was available for 270 on 386 patients (Fig. 7). Questionnaire was not administered to 85 patients and 31 patients did not complete it correctly. Mean score was 13.2±3.8. Eight patients on 270 had score less than 5, therefore 262 patients (97%) had sleep disturbances. SF-12 score was available for 283 on 386 patients (Figs. 8, 9). Questionnaire had not been administered to 91 patients, while 12 did not complete it correctly. SF-12_PCS mean score was 27.5±7.1; SF-12_MCS had a mean score of 34.7±9.7.

Table VI. Associated clinical features.

Associated clinical features (n=324 patients)	n (%)
Fatigue	308 (95%)
Concentration difficulties	264 (81%)
short memory disturbances	260 (80%)
Irritable Bowel Syndrome	250 (77%)
Gluten intolerance	84 (26%)
Intolerance to chemical substances	83 (26%)
lactose intolerance	119 (37%)
Hallucination	22 (7%)
Headache	258 (80%)
Muscle stiffness	301 (93%)
Meteoropathy	241 (74%)
Work problems	200 (62%)
School problems	27 (8%)
Sleep disturbances	302 (93%)
Drugs hypersensitivity	106 (33%)
Low back pain	285 (88%)
Joint symptoms/crackling	245 (76%)
Muscle spasm/clonus	197 (61%)
Restless leg syndrome	159 (49%)
Urinary burning	94 (29%)
Urgency	183 (56%)
Teeth pain	138 (43%)
Abdominal bloating	238 (73%)
Numb extremities	234 (73%)
Tinnitus	137 (42%)
Polydipsia	139 (43%)
Mouth/nose/eyes dryness	210 (65%)
Peripheral edema	150 (46%)
Unsteadiness	183 (56%)
Nocturnal muscle cramps	196 (60%)
Dysmenorrhea	126 (42%)
Vulvodynia	82 (28%)
Dyspareunia	101 (34%)

Discussion

Previous studies have separately analysed the prevalence of discrete associated syndromes in FM, but this work is, to the best of our knowledge, the first detailed epidemiological analysis that also includes the analysis of minor symptoms. Compared to the related literature, the average age of our sample

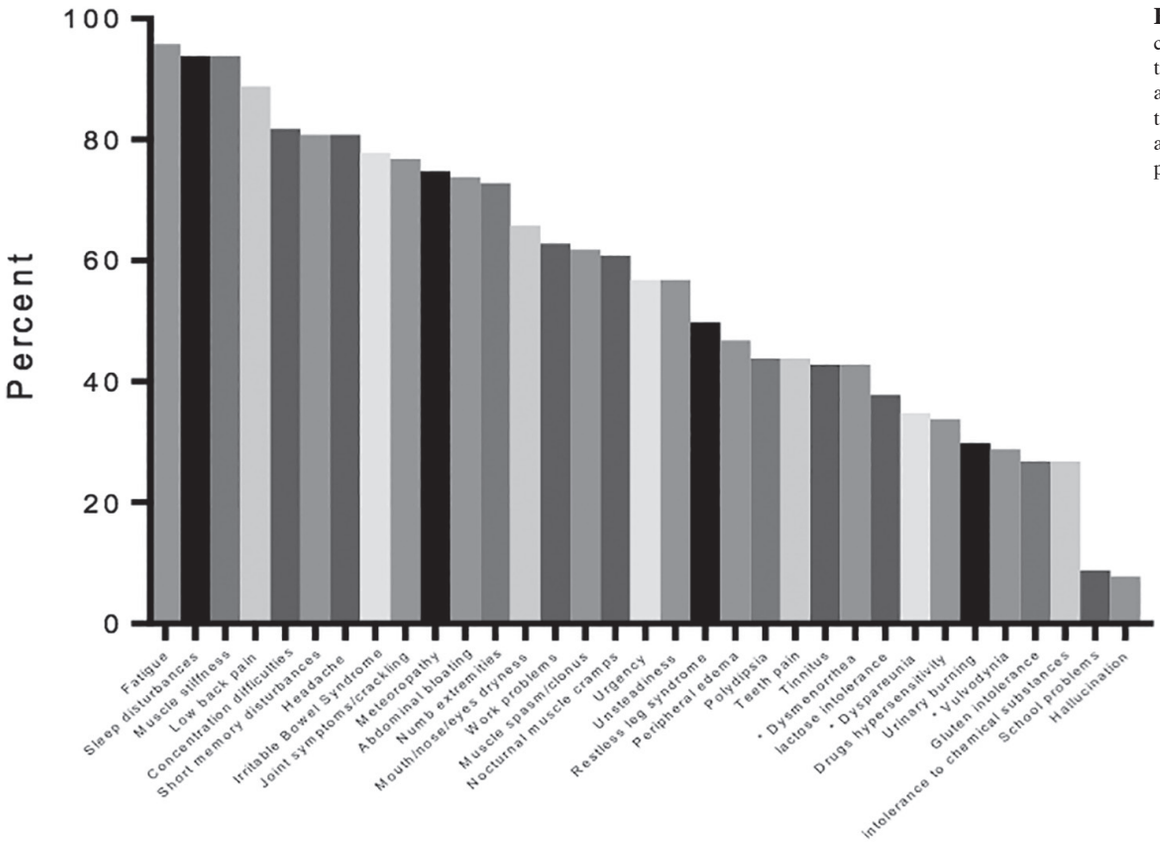

Fig. 5. Associated clinical features distribution. Data were available for 324 patients. Features with asterisk are on 298 patients.

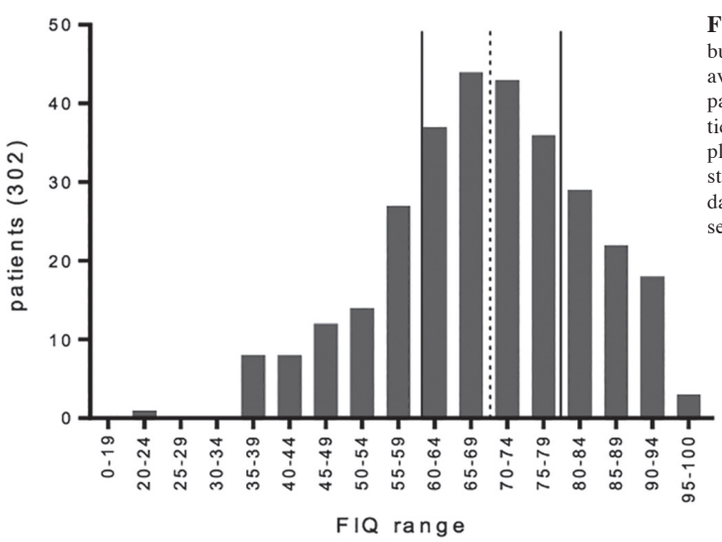

Fig. 6. FIQ distribution. Data were available for 302 patients. Solid vertical lines represent plus or minus 1 standard deviation, dashed line represents mean value.

is comparable to most known epidemiological studies about FM patients (24-28) and our population has a very high female prevalence of 12.8:1. This ratio is much higher than in studies which used ACR 2010 modified criteria, but in line with the ratio found when ACR 1990 criteria were used (10).

Possible association between FM and civil state is controversial : 68% of our patients are married or cohabitant, and have one or more children, while Topbas *et al*. found higher FM prevalence among widows (28), others among married people (30) or among divorced patients (31). Literature data often show a low education level among FM patients (26-28, 31-34), but this is not confirmed in our sample, since 70% of patients had finished secondary school or were graduated. A comparison with general Italian population is not straightforward but, as an example, the Italian National Statistical Institute (ISTAT) has published a report that also covers the education degree in the Italian general population (35), where people aged from 25 to 64 years that had finished secondary school or were graduated were 58.2%. Taking into account only people with comparable age in our sample the new proportion is 73%, thus showing that our population seems more educated than the general Italian population, and apparently more educated than in previous cited studies. This could be probably justified by the fact that our centre is not part of an institutional path of diagnosis and therapy, and only people that are very well informed (for example by internet search) could be addressed to our centre, being thus in some way very selected. Another discordance with previous literature is about employment, since 71% of our patients were currently employed. This finding is higher than data revealed in other studies, which showed that FM patients were mostly unemployed (29, 32, 34), even though our data are similar to those found in

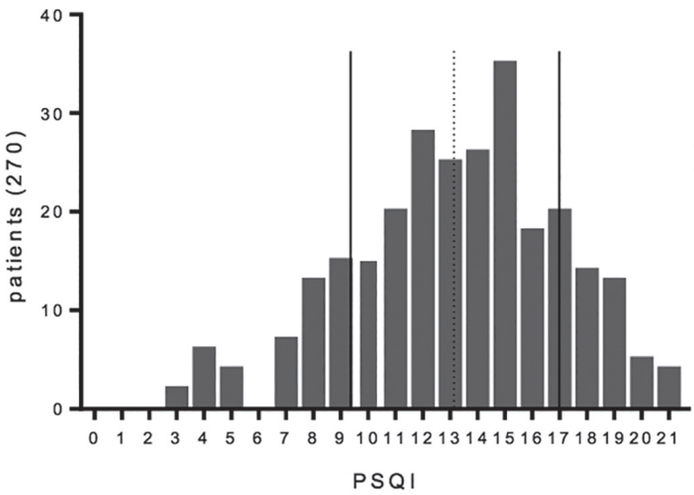

Fig. 7. PSQI distribution. Data were available for 270 patients. Solid vertical lines represent plus or minus 1 standard deviation, dashed line represents mean value.

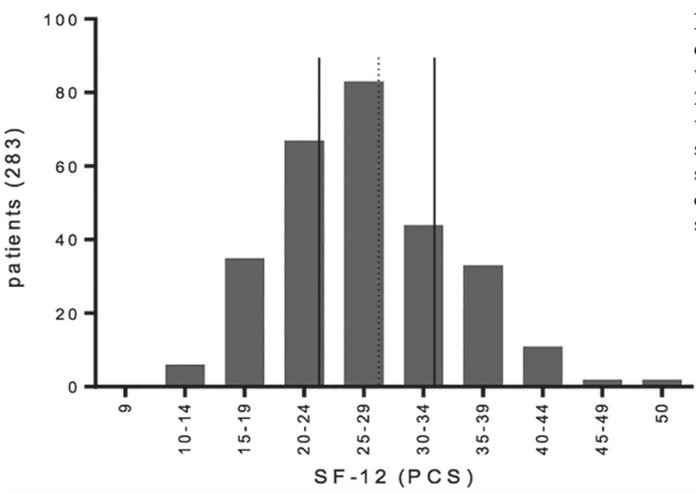

Fig. 8. SF12 PCS distribution. Data were available for 283 patients. Solid vertical lines represent plus or minus 1 standard deviation, dashed line represents mean value.

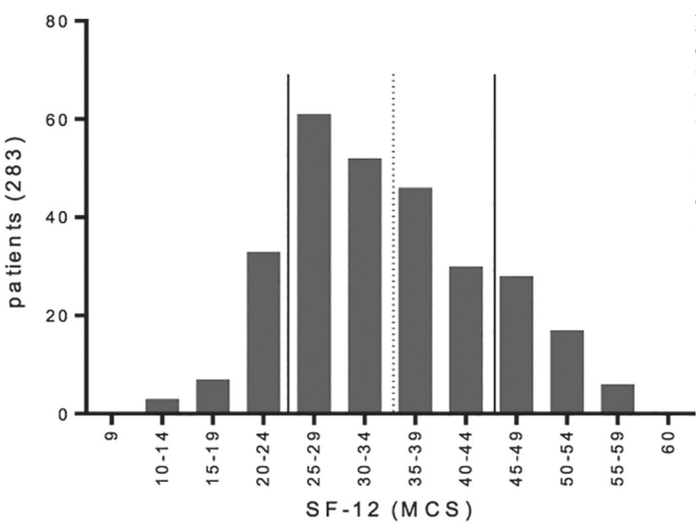

Fig. 9. SF12 MCS distribution. Data were available for 283 patients. Solid vertical lines represent plus or minus 1 standard deviation, dashed line represents mean value.

population suffering from chronic pain (36, 37). The key for interpretation and comparison is the way of classifying jobs. As an example, in the study by Ramos (38), who has also more systematically addressed every job, we do not know whether housewives were included in the "unqualified job" and how they were classified as "employed" or not. In other studies authors had created mixed categories or just reported current working conditions, without a systematical explanation, making a comparison useless without the same measurement method. Another possible explanation of our high employment rate could be related to the fact that 86% of patients came from Northern Italy and particularly 55% from the Veneto region, where unemployment rate is particularly low.

Physiological history showed a strikingly high prevalence of trauma events referred by patients. Trauma events prevalence was 74% according to data referred during the physician's interview. Hauser (39) showed 74.4% of patients referred trauma event and 45.3% post-traumatic stress disease (PTSD) among FM patients. The same study revealed a 17-year delay between the trauma event and chronic diffuse pain onset, with 29.5% of patients referring traumatic events in childhood or adolescence. Although a causative effect could not be demonstrated, these data confirm that psychological o physical trauma could possibly represent an increased risk factor for FM, as also reported by another Italian study (40). These findings focus on the importance of a precise psychiatric evaluation to diagnose PTSD and other psychiatric diseases in FM patients, and therefore address them with an appropriated therapy.

Our data on lifestyle of FM patients are consistent with the study of Mur Martì *et al*. (29), where 21% of patients were smokers and 52% were regularly performing physical activity, while our study showed only 36%. It is interesting to underline that 27% of our patients followed a gluten free diet, even though only two patients were suffering from celiac disease. This behaviour, according to patients' report, is due to a perceived favourable effect of this kind of diet, although this could also be biased by other factors (placebo, advertising, etc.).

Our patients did not present many comorbidities, except for psychiatric disorders. In fact, we found a statistically significant association between FM and anxiety, depression and panic attacks ($p<0.001$ for each of them). Previous works showed a high association between anxiety and depression with FM (29, 34, 38, 41, 42), but never evidenced a cause-effect correlation. A recent Italian study confirmed

a greater presence of psychological distress and psychosomatic syndromes in patients with FM compared to patients with rheumatoid arthritis (43). It is also important to point out that psychiatric diagnosis in our study was mostly referred by patients, and established by a pain physician where a psychiatric diagnosis was missing. In the field of FM specific comorbidities, an interesting figure is the high number of patients affected by breast cancer: 16 of our patients had previously suffered from, or where currently affected by breast cancer, providing a higher prevalence compared to the general female population. It is not the first time that this is highlighted. For example, Akkaya revealed 10 cases of FM on 101 patients, in a study about breast cancer, showing that breast cancer patients could have a higher risk of FM compared to the general population (44). This interesting point could be clarified by larger epidemiological studies.

Main clinical associated symptoms in our sample were similar to what already showed in literature. Fatigue and cognitive disturbances were referred from 80% of patients, in accordance to the literature data (45, 46). Sleep disturbances affected 93% of our patients, similarly to already available data (47). Irritable bowel syndrome and dysmenorrhea had 77% and 42% prevalence among our sample, similar to literature data (48, 49). Headache was surprisingly higher than expected: 80% of our patients suffered from it, while a Mayo clinic study in 2015 revealed a prevalence of only 55.8% among FM patients (50). All presented data may suffer from the pre-selection bias. It is possible that patients who come to the referring centre may represent a subpopulation of FM patients, whose seriousness is higher than average. This hypothesis is supported by FIQ scores, which show 80% of our sample suffering from severe FM, while mean FIQ score in literature is 50 (16). PSQI scores were similar to the literature (51), while there are no available data on mean SF-12 score for FM. Noteworthy, 55% of patients had an under threshold number of TPs according to 1990 criteria, this strikes another time that the research for better diagnostic criteria is probably the most relevant key factor to understand and study FM population.

Relative prevalence of some minor symptoms are impressive. As an example meteoropathy, numb extremities, abdominal bloating, muscle spasm, joint crackling, urgency, mouth/nose/eyes dryness, unsteadiness and nocturnal muscle cramps are present in more than 50% of our sample. In our opinion these symptoms (reported in Table VI), although not mandatory for diagnosis, are part of FM and their impact on global quality of life on FM patients should be checked and taken in account for example in measuring the symptoms severity and monitored to better address therapy.

The analysis of mean SF-12 score in our population could make us understand a little more on the impact of FM on patients comparing our SF-12 scores to those obtained among the general population and on patients suffering from other diseases. ISTAT carried out a study on 140.000 subjects in 1999-2000 to establish the mean SF-12 score in general population and among patients suffering of at least one within diabetes, hypertension, infarction, angina pectoris, arthrosis/arthritis, low back pain, malignancy, headache, COPD, gastric ulcer, prostatic hypertrophy and nervous disturbances (52). Mean SF-12 score found among general population was 53.74±5.98 for PCS and 52.79±7.87 for MCS. Mean SF-12 score for PCS and MCS in our sample were 27.5±7.12 and 34.7±9.74 respectively, much lower than general population. To find a comparable PCS score in the same study we have to look for patients suffering from angina pectoris (36.17±10.82) and the lowest mean MCS score was found among patients suffering from nervous diseases such as Parkinson and Alzheimer (33.76±10.84). Although SF-12 is a self-reported questionnaire, these data underline a key point about the disease, and can give an idea of the impact of FM on patients' quality of life, which is moreover poorly affected by pharmacological therapy. In fact, as previously shown, mostly used drugs, in our sample, were NSAID and benzodiazepine, which are both not recommended by EULAR guidelines. We cannot assert that these drugs are incorrectly prescribed perhaps because of muscle skeletal comorbidities, such as arthritis and arthrosis, and psychiatric disorders such as anxiety and panic attacks that are, probably, poorly addressed and treated. Data on widespread use of NSAID and benzodiazepine were confirmed by a recent study (29), although patients taking them were 60%, compared to 33% in our population. Still about EULAR recommended drugs, the number of patients taking or previously taking SNRI (139/379) or anticonvulsants (104/379) was low in our sample but, for SNRI, the long term dropout rate of our population was high: 81 patients had taken them but were not taking them anymore, while only 58 patients were taking them regularly with a gross long term dropout of 53%. For anticonvulsants the dropout rate in our population is 50%, mostly for adverse effect of the drug, although this sample was smaller. These rates are higher than previously reported in the literature although in many studies it is hard to get precise data on dropout from these therapies. In a study about pregabalin in FM 23% of patients dropped out for adverse effects and the lack of efficacy was 9% (53). It is also worth mentioning that, in comparison, pregabalin and duloxetine both had a dropout rate of 12%, for example, in diabetic neuropathy (54). The "drugs hypersensitivity" was included as a minor symptom in our sample: 106 patients on 324 (33%) shows exaggerated adverse effects to drugs that is: devastating adverse effect (mostly cognitive adverse effect) to regular doses or various adverse effect to very low doses. A possible deduction of these results is that FM patients could be more prone to expect adverse events from pharmacological therapies than other group of patients.

Opioids and SSRI, that no longer indicated in FM (55), are used respectively by 94 patients on 379 (25%) and 61 patients on 379 (16%). The dropout rate from these drugs, 15% for opioids and 9% for SSRI, are lower than SNRI (81 patients on 379, 22%) and anticonvusivants (69 patients on 379, 18%). Both SNRI and anticonvulsivants (namely

pregabalin) gained a "weak for" recommendation by EULAR although, in our sample, more patients left these drugs compared to SSRI and opioids. We did not make a distinction in weak or strong opioids in categorising our patients therapy, this data should be interesting because weak opioids are accepted by EULAR guidelines while strong opioids are discouraged. We also don't know whether dropout was due to inefficacy or adverse effects or if, for example for opioids, a physical dependence was the main reason of the adherence to therapy.

Finally, it is worth highlighting that only a really low number of patients use non-pharmacological therapies such as balneotherapy and light physical activity, which should instead represent first line therapies according to EULAR guidelines, even more so since no substantial changes in the management of fibromyalgia have recently emerged (56). This could be due to under prescription by doctors rather than personal attitude of FM patients towards these therapies, and more effort from scientific societies and National Health Organisations would be probably beneficial on this regard.

Conclusion

FM is an extremely complex disease to understand and diagnose, due to very large symptoms variety and associated features, and still unknown risk factors and complete pathogenesis. There are currently no epidemiological studies on the Italian population in the literature, as for other European states. Moreover, current studies analyse only few features of this disease. This study provides a large and rich set of data for characterising FM patients. Excluding age and sex there are no other features frequently associated to FM, and existing information in literature is often contrasting. This study confirms the already known strong association between FM and psychiatric diseases, such as anxiety, depression and panic attacks. We also showed how FM patients often refer a traumatic event, either psychological or physical, during their lifetime. Patients have a very heterogeneous variety of symptoms, varying from diffuse pain with fatigue and stiffness, to sleep disturbances, cognitive impairment, headache, abdominal pain and bloating, sicca syndrome, urinary disturbances, and others. It is important to notice that all symptoms in this wide range are frequent among FM patients, strongly affecting their quality of life. This aspect is also confirmed by low SF-12 scores found in our population. Despite these features, most of our patients maintain working activities, and are well involved in their familial and social environment. Analysis of prevalence of "minor" symptoms in FM population could be of great value to better understand if different type of FM exists and possibly to understand if the evolution of this syndrome would follow definite patterns in time. Main limit of this study is the absence of a control group, consisting in a cross study.

References

1. BORCHERS AT, GERSHWIN ME: Fibromyalgia: A Critical and Comprehensive Review. *Clin Rev Allergy Immunol* 2015; 49: 100-151.
2. WOLFE F, SMYTHE HA, YUNUS MB *et al*.: The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990; 33: 160-72.
3. JACOBS JW, GEENEN R, VAN DER HEIDE A, RASKER JJ, BIJLSMA JW: Are tender point scores assessed by manual palpation in fibromyalgia reliable? An investigation into the variance of tender point scores. *Scand J Rheumatol* 1995; 24: 243-7.
4. COTT A, PARKINSON W, BELL MJ *et al*.: Interrater reliability of the tender point criterion for fibromyalgia. *J Rheumatol* 1992; 19: 1955-9.
5. WOLFE F, CATHEY MA: The epidemiology of tender points: a prospective study of 1520 patients. *J Rheumatol* 1985; 12: 1164-8.
6. CROFT P, SCHOLLUM J, SILMAN A: Population study of tender point counts and pain as evidence of fibromyalgia. *BMJ* 1994; 309: 696-699.
7. PETZKE F, GRACELY RH, PARK KM, AMBROSE K, CLAUW DJ: What do tender points measure? Influence of distress on 4 measures of tenderness. *J Rheumatol* 2003; 30: 567-74.
8. WOLFE F: The relation between tender points and fibromyalgia symptom variables: evidence that fibromyalgia is not a discrete disorder in the clinic. *Ann Rheum Dis* 1997; 56: 268-71.
9. WOLFE F, CLAUW DJ, FITZCHARLES MA *et al*.: The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. *Arthritis Care Res* (Hoboken) 2010; 62: 600-10.
10. JONES GT, ATZENI F, BEASLEY M, FLÜB E, SARZI-PUTTINI P, MACFARLANE GJ: The prevalence of fibromyalgia in the general population: A comparison of the American College of Rheumatology 1990, 2010, and modified 2010 classification criteria. *Arthritis Rheumatol* 2015; 67: 568-75.
11. CLAUW DJ: Fibromyalgia: a clinical review. *JAMA* 2014; 311: 1547-55.
12. BALASUBRAMANIAM R, DE LEEUW R, ZHU H, NICKERSON RB, OKESON JP, CARLSON CR: Prevalence of temporomandibular disorders in fibromyalgia and failed back syndrome patients: A blinded prospective comparison study. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; 104: 204-16.
13. YANG T-Y, CHEN C-S, LIN C-L, LIN W-M, KUO C-N, KAO C-H: Risk for irritable bowel syndrome in fibromyalgia patients: a national database study. *Medicine* (Baltimore) 2015; 94: e616.
14. SARZI-PUTTINI P, ATZENI F, DI FRANCO M *et al*.: Dysfunctional syndromes and fibromyalgia: a 2012 critical digest. *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S143-51.
15. BAZZICHI L, GIACOMELLI C, ROSSI A *et al*.: Fibromyalgia and sexual problems. *Reumatismo* 2012; 64: 261-7.
16. BURCKHARDT CS, CLARK SR, BENNETT RM: The fibromyalgia impact questionnaire: development and validation. *J Rheumatol* 1991; 18: 728-33.
17. BENNETT R, BUSHMAKIN A, CAPPELLERI J, ZLATEVA G, SADOSKY A: Minimal clinically important difference in the fibromyalgia impact questionnaire. - PubMed - NCBI. *J Rheumatol* 2009; 36: 1304-1311.
18. SARZI-PUTTINI P, ATZENI F, FIORINI T *et al*.: Validation of an Italian version of the Fibromyalgia Impact Questionnaire (FIQ-I). *Clin Exp Rheumatol* 2003; 21: 459-64.
19. CURCIO G, TEMPESTA D, SCARLATA S *et al*.: Validity of the Italian Version of the Pittsburgh Sleep Quality Index (PSQI). *Neurol Sci* 2013; 34: 511-9.
20. BUYSSE DJ, REYNOLDS CF, MONK TH, BERMAN SR, KUPFER DJ: The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; 28: 193-213.
21. WARE JE, KOSINSKI M, KELLER SD: A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. *Med Care* 1996; 34: 220-33.
22. DE GIROLAMO G, POLIDORI G, MOROSINI P *et al*.: La prevalenza dei disturbi mentali in italia. Il progetto ESEMED-WMH. Una sintesi.
23. AIRTUM WORKING GROUP: Italian cancer figures, report 2014: Prevalence and cure of cancer in Italy. *Epidemiol Prev* 2014; 38 (Suppl. 1): 1-122.
24. ASSUMPÇÃO A, CAVALCANTE AB, CAPELA CE *et al*.: Prevalence of fibromyalgia in a low socioeconomic status population. *BMC Musculoskelet Disord* 2009; 10: 64.
25. NAKAMURA I, NISHIOKA K, USUI C *et al*.: An epidemiologic internet survey of fibromyalgia and chronic pain in Japan. *Arthritis Care Res* 2014; 66: 1093-101.
26. BRANCO JC, BANNWARTH B, FAILDE I *et al*.:

Prevalence of fibromyalgia: A survey in five European countries. *Semin Arthritis Rheum* 2010; 39: 448-453.
27. BANNWARTH B, BLOTMAN F, ROUÉ-LE LAY K, CAUBÈRE JP, ANDRÉ E, TAÏEB C: Fibromyalgia syndrome in the general population of France: A prevalence study. *Joint Bone Spine* 2009; 76: 184-187.
28. TOPBAS M, CAKIRBAY H, GULEC H, AKGOL E, AK I, CAN G: The prevalence of fibromyalgia in women aged 20-64 in Turkey. *Scand J Rheumatol* 2005; 34: 140-4.
29. MUR MARTÍ T, LLORDÉS LLORDÉS M, CUSTAL JORDÀ M, LÓPEZ JUAN G, MARTÍNEZ PARDO S: Perfil de pacientes con fibromialgia que acuden a los centros de atención primaria en Terrassa. *Reumatol Clín* 2017; 13: 252-7.
30. COBANKARA V, UNAL UO, KAYA A, BOZKURT AI, OZTURK MA: The prevalence of fibromyalgia among textile workers in the city of Denizli in Turkey. *Int J Rheum Dis* 2011; 14: 390-4.
31. WHITE KP, SPEECHLEY M, HARTH M, OSTBYE T: The London Fibromyalgia Epidemiology Study: the prevalence of fibromyalgia syndrome in London, Ontario. *J Rheumatol* 1999; 26: 1570-6.
32. MOUKADDEM A, CHAAYA M, SLIM ZFN, JAFFA M, SIBAI AM, UTHMAN I: Fibromyalgia: epidemiology and risk factors, a population-based case-control study in Lebanon. *Int J Rheum Dis* 2017; 20: 169-76.
33. MÄKELÄ M, HELIÖVAARA M: Prevalence of primary fibromyalgia in the Finnish population. *BMJ* 1991; 303: 216-9.
34. MAS AJ, CARMONA L, VALVERDE M, RIBAS B, EPISER STUDY GROUP: Prevalence and impact of fibromyalgia on function and quality of life in individuals from the general population: results from a nationwide study in Spain. *Clin Exp Rheumatol* 2008; 26: 519-26.
35. Istat. Bes 2014-Il Benessere Equo e Solidale in Italia. 2014:46. http://www.istat.it/it/files/2014/06/Rapporto_Bes_2014.pdf.
36. JOHANNES CB, LE TK, ZHOU X, JOHNSTON JA, DWORKIN RH: The Prevalence of Chronic Pain in United States Adults: Results of an Internet-Based Survey. *J Pain* 2010; 11: 1230-9.
37. AZEVEDO LF, COSTA-PEREIRA A, MENDONÇA L, DIAS CC, CASTRO-LOPES JM: Epidemiology of chronic pain: A population-based nationwide study on its prevalence, characteristics and associated disability in Portugal. *J Pain* 2012; 13: 773-83.
38. REGAL RAMOS RJ: Epidemiological characteristics of patients evaluated with fibromyalgia in the Assessment of Disability Unit of Madrid. *Semergen* 2017; 43: 28-33.
39. HÄUSER W, GALEK A, ERBSLÖH-MÖLLER B *et al*.: Posttraumatic stress disorder in fibromyalgia syndrome: prevalence, temporal relationship between posttraumatic stress and fibromyalgia symptoms, and impact on clinical outcome. *Pain* 2013; 154: 1216-23.
40. DELL'OSSO L, CARMASSI C, CONSOLI G *et al*.: Lifetime post-traumatic stress symptoms are related to the health-related quality of life and severity of pain/fatigue in patients with fibromyalgia. *Clin Exp Rheumatol* 2011; 29 (Suppl. 69): S73-8.
41. WEIR PT, HARLAN GA, NKOY FL *et al*.: The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th Revision codes. *J Clin Rheumatol* 2006; 12: 124-8.
42. CASTELLI L, TESIO V, COLONNA F *et al*.: Alexithymia and psychological distress in fibromyalgia: prevalence and relation with quality of life. *Clin Exp Rheumatol* 2012; 30 (Suppl. 74): S70-7.
43. GHIGGIA A, TORTA R, TESIO V *et al*.: Psychosomatic syndromes in fibromyalgia. *Clin Exp Rheumatol* 2017; 35 (Suppl. 105): S106-11.
44. AKKAYA N, ATALAY NS, SELCUK ST, ALKAN H, CATALBAS N, SAHIN F: Frequency of fibromyalgia syndrome in breast cancer patients. *Int J Clin Oncol* 2013; 18: 285-292.
45. WOLFE F, HAWLEY DJ, WILSON K: The prevalence and meaning of fatigue in rheumatic disease. *J Rheumatol* 1996; 23: 1407-17.
46. KATZ RS, HEARD AR, MILLS M, LEAVITT F: The prevalence and clinical impact of reported cognitive difficulties (fibrofog) in patients with rheumatic disease with and without fibromyalgia. *J Clin Rheumatol* 2004; 10: 53-8.
47. MOLDOFSKY H: The significance, assessment, and management of nonrestorative sleep in fibromyalgia syndrome. *CNS Spectr* 2008; 13 (Suppl. 5): 22-26.
48. VEALE D, KAVANAGH G, FIELDING JF, FITZGERALD O: Primary fibromyalgia and the irritable bowel syndrome: different expressions of a common pathogenetic process. *Br J Rheumatol* 1991; 30: 220-2.
49. TERZI R, TERZI H, KALE A: Evaluating the relation of premenstrual syndrome and primary dysmenorrhea in women diagnosed with fibromyalgia. *Rev Bras Reumatol* 2015; 55: 334-9.
50. VIJ B, WHIPPLE MO, TEPPER SJ, MOHABBAT AB, STILLMAN M, VINCENT A: Frequency of migraine headaches in patients with fibromyalgia. *Headache* 2015; 55: 860-5.
51. HITA-CONTRERAS F, MARTÍNEZ-LÓPEZ E, LATORRE-ROMÁN PA, GARRIDO F, SANTOS MA, MARTÍNEZ-AMAT A: Reliability and validity of the Spanish version of the Pittsburgh Sleep Quality Index (PSQI) in patients with fibromyalgia. *Rheumatol Int* 2014; 34: 929-36.
52. APOLONE G, MOSCONI P, QUATTROCIOCCHI L, GIANICOLO EAL, GROTH N, WARE JEJ: *Questionario Sullo Stato Di Salute SF-12. Versione Italiana*. Milano; 2005.
53. PAUER L, ATKINSON G, MURPHY TK, PETERSEL D, ZEIHER B: Long-term maintenance of response across multiple fibromyalgia symptom domains in a randomized withdrawal study of pregabalin. *Clin J Pain* 2012; 28: 609-14.
54. TESFAYE S, WILHELM S, LLEDO A *et al*.: Duloxetine and pregabalin: high-dose monotherapy or their combination? The "COMBO-DN study"- a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain* 2013; 154: 2616-25.
55. MACFARLANE GJ, KRONISCH C, DEAN LE *et al*.: EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis* 2017; 76: 318-28.
56. TALOTTA R, BAZZICHI L, DI FRANCO M *et al*.: One year in review 2017: Fibromyalgia. *Clin Exp Rheumatol* 2017; 35 (Suppl. 105): S6-12.
57. Classificazione dei titoli di studio italiani. http://www.istat.it/archivio/6620.
58. Classificazione delle professioni. http://nup2006.istat.it/.