

Fibromyalgia: epidemiology and risk factors, a population-based case-control study in Damascus, Syria.

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Abstract

Background

Fibromyalgia is a chronic disease with a high burden. We aim to be the first to investigate the prevalence of fibromyalgia (FM) in Syria and assess its risk factors.

Methods

a self-reported questionnaire was distributed to the public to identify fibromyalgia patients using the American College of Rheumatology (ACR) 2010 modified criteria. Identified cases were matched using age with controls free from rheumatic disorders that were randomly sampled from the same population.

Results

out of 2966 participants, 350 (11.8%) satisfied the diagnostic criteria. Of these, only 29 (8.2%) were previously diagnosed by a physician, 239 (68.3%) were females, and 69 (19.71%) were diagnosed with depression. Female sex (OR=1.7, CI: 1.3-2.1), unemployment (OR=1.4, CI:1.1 – 1.79), diagnosis of major depressive disorder (OR=3.8, CI: 2.7 – 5.35), generalized anxiety disorder (OR=2.7, CI: 1.95 – 3.72), and irritable bowel syndrome (OR=2.4, CI: 1.78 – 3.17) were significant risk factors for FM.

Conclusion

our study revealed one of the highest prevalence rates of fibromyalgia ever reported in the general population. Efforts must be intensified to increase the awareness about this disease in the Syrian society as well as among healthcare providers.

Background

Fibromyalgia (FM) is a complex disease characterized by chronic (longer than three months) widespread pain combined with tenderness in muscles and joints all over the body.[1] Non-pain-related symptoms of FM include fatigue that can be exaggerated with minor activities, though inactivity for a long period also increases the symptoms,[2] paresthesia with generalized burning and tingling, sleeping disorders with waking up unrefreshed, mood problems, and cognitive disturbances often referred to as “fibro fog” that can interfere with the ability to concentrate, keep attention, and multitasking jobs.[1, 2] Even though patients experience exquisite disabling pain, there is no tissue inflammation. Therefore, there is no risk of tissue damage or deformity.[3] The etiology of FM remains unclear, but many physical and/or emotional stressors have been described as triggers for this condition, including emotional and physical trauma, and infections.[4] Many risk factors have been identified, such as genetic predisposition, family history, female sex, and the presence of other painful conditions.[2] FM can be present with other psychiatric

comorbidities such as anxiety and/or depression with prevalence rates of up to 30 to 50 percent at the time of diagnosis.[5, 6] Finally, FM is associated with gastrointestinal morbidities such as irritable bowel syndrome (IBS) and gastroesophageal reflux disease (GERD).[7, 8]

FM is considered a common disease to encounter in the clinic with a variation in prevalence in the general population in different countries. In Japan, the prevalence of FM was 2.1%, while in Canada, it was estimated at 3.3% (4.9% in women versus 1.6% in men).[9, 10] Branco et al reported the prevalence of FM in 5 European countries and placed it at 4.7%.[11] Another study in Germany estimated the prevalence at 3.8%, with similar rates in men and women, while in Lebanon, Syria's neighboring country, the prevalence of FM was found to be 7%.[12, 13] These differing estimations may reflect differences in study populations, study designs, and measurements. As a result, prevalence estimations can vary, up to 4-folds, depending on the diagnostic criteria applied, which at times exceeded 15% in selected samples. [14, 15]

The lack of a gold standard and objective markers to diagnose FM led to the proposal of many diagnostic criteria that rely on clinical assessment and patient reports. In 1990, Wolfe et al. set the first American College of Rheumatology (ACR) criteria for FM diagnosis.[16] It evaluated 18 body bilateral points and considered the diagnosis of FM to be positive when 11 or more points were positive for pain and tenderness. However, these criteria did not factor in non-pain-related symptoms. Later, the 2010 (ACR) criteria was developed, and then, modified to become self-administered.[1] By 2015, the ACTION-APS Pain Taxonomy (AAPT) criteria was made, but a new study showed that the ACR 2010 modified criteria offered the best concordance with the clinical judgment in comparison to AAPT criteria.[17, 18] The diagnosis of FM could be complex and lengthy, and there is currently no standard treatment algorithm. Together, these make FM a high burden disease with high-cost health care due to increased usage of pain relief medication and outpatient visits per year in both the pre-and post-diagnosis periods. [19] Hence, FM prevalence evaluation has both clinical and economic importance.

The war in Syria, which has lasted more than a decade, has had a profound impact on the population and has created many economic, social, and educational challenges. Damage to health care infrastructure and loss of medical staff have had a major impact on Syria's health care system. As a result, many have been injured, and approximately 511,000 have died.[20] More than 5.6 million have fled the country [21], and nearly 6.2 million have been internally displaced [22], making this event the second-largest immigration in human history after World War II.

As warfare is considered one of the most psychologically stressful events that anyone can experience [23], with catastrophic effects on the population in both long-term and short-term manners, we aim to be the first study, to our knowledge, to determine FM prevalence in a sample of the Syrian population and find its risk factors, in order to help guide the health care interventions.

Patients, And Methods

Inclusion criteria:

We included the participants who were surveyed from April 1 to May 1, 2021, and met the following conditions : (1) 18 years old or older, (2) living in Damascus at least for the last five years.

Out of the 2072 participants who took the in-person survey and 1011 who completed the online survey, 102 and 15 respondents, respectively, were excluded for not meeting the inclusion criteria, resulting in a cohort of 2966 participants.

Study design, setting, and participants:

The sample size was calculated using Cochran's formula. No reference was found that estimated the age of Damascus residents over the age of 18. So, we used the full population number (2079000 people) in Damascus city.[24] To reduce the error margin, we also used a confidence level of 95%, a margin of error of 1%, and a proportion of 7%, as reported previously in a neighboring population.[25] This resulted in a sample size of 2498.

A two-stage population-based study was conducted, to determine the prevalence and risk factor of fibromyalgia in the general population of Damascus, Syria.

Stage one:

Following a two-phase design, a representative sample of Damascus habitants was questioned using a structured self-administered survey from April 1 to May 1, 2021.

In the first phase, we distributed the survey on social media platforms (Facebook[®], Whatsapp[®], and Twitter[®]) as a Google Form[®]. In parallel, in the second phase we met with participants face-to-face, where we handed the questionnaire was handed to patients, their companions, and workers in the outpatient clinics of Damascus Hospital and Ibn Al Nafees Hospital; two major public hospitals in Damascus, Syria.

Measures:

Our survey was composed of two sections:

1. Socio-demographic characteristics

This section covers nine questions about age , gender, marital status, residence (rural or urban), financial status, employment status, educational level, health insurance, current diagnosis of (major depressive disorder, generalized anxiety disorder, Irritable bowel syndrome, Rheumatoid arthritis, Systemic lupus erythematosus, and any other rheumatic disease).

Fibromyalgia questionnaire based on ACR 2010 modified criteria for fibromyalgia diagnosis[26]

This section included questions about Symptom Severity Score (SSS), and widespread pain index (WPI). For SSS, the questions concerned fatigue, waking unrefreshed, and cognitive symptoms (experiencing difficulties thinking or remembering). For each of these symptoms, the participants were asked to rate the level of severity over the past week using the following scale: 0 = No problem; 1 = Slight or mild problems; generally mild or intermittent; 2 = Moderate; considerable problems; often present and/or at a moderate level; 3 = Severe: pervasive, continuous, life-disturbing problems. The survey also included yes and no questions about other symptoms that have occurred within the previous six months such as, headache, lower abdominal pain or cramps, and depression.

For WPI, the questions centered on 19 areas in which the participant may have experienced pain over the last week. There was also a question on whether the participant had a disorder that would otherwise explain the pain. Finally, we included a question about the persistence of the aforementioned symptoms for the last three months

Stage two:

A case-control analysis was designed, as cases were considered the participants who satisfied the modified ACR 2010 fibromyalgia diagnostic criteria (number of cases = 350). Controls were considered the participants who did not meet the criteria of fibromyalgia diagnosis and reported no current diagnosis of rheumatic diseases. In order to optimize the power of the study in detecting any significant associations, four controls per case were selected (number of controls = 1400) randomly from our population sample after matching controls with cases by age group.

Statistical analysis:

We analyzed the data using Statistical Package for Social Sciences version 25.0 (SPSS Inc., Chicago, IL, United States). The maximum total score of the WPI and SSS is 19 and 12, respectively. SSS is the sum of the three symptom severity (fatigue, wakefulness, and cognitive symptoms) plus the sum of the number of the following symptoms that have occurred within the previous six months: headache, lower abdominal pain or cramps, and depression (0-3). A patient was considered meeting the modified ACR 2010 fibromyalgia diagnostic criteria if the following three conditions were met [26] :

- (1) WPI of 7 or more, and $SSS \geq 5$, or WPI between 3-6, and $SSS \geq 9$.
- (2) Symptoms were present at a similar level for at least three months.
- (3) The patient does not have a disorder that would explain the pain.

All variables (including both cases and controls groups) were described using frequency distributions, except for age (the matching variables). Odds ratios (OR), 95% confidence intervals (CI), and P-values

were computed through univariate models Chi-Square. A P-value < 0.05 was considered statistically significant.

Ethical consideration:

The study protocol was approved by the Research Ethics Committee in the Syrian Private University, and the ethical committees in the concerned hospitals. Informed consent was obtained from each participant prior to participation.

Results

Participant's characteristics:

Of the 3083 participants to take part in this study, 2966 answered all the questions and fulfilled the inclusion criteria (response rate 96.2%). Of these, 1315 (44.3%) were males and 1651 (55.7%) were females. Regarding the age groups, most participants [1720 (58%)] were 18–29 years old, 1035 (34.9%) were 30–49 years old, and 211 (7.1%) were \geq 50 years. The majority were singles 1544 (52.1%), and 1422 (48%) were in a relationship. Unemployed individuals represented half of our sample [1502 (50.6%)]. The majority [2548 (85.9%)] did not have health insurance, and 2412 (81.3%) lived in a city. Regarding financial status, 1514 (51.1%), 1452 (49%) were below average, and had average financial status, respectively. When asked about previous medical history, 29 (0.9%) said that they were diagnosed with fibromyalgia, and 30 (1%), 163 (5.5%), 268 (15.3%), and 64 (3.7%) said they have systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), irritable bowel syndrome (IBS) and restless leg syndrome (RLS), respectively. (Table.1)

Table 1
Participants' characteristics.

Variables	Total (2966) N(%)	FM (350) N(%)	Non-FM (2616) N(%)
Age (Years)			
18–29	1720 (58)	250 (71.4)	1470 (56.2)
30–49	1035 (34.9)	84 (24)	951 (36.4)
≥ 50	211 (7.1)	16 (4.6)	195 (7.5)
Gender			
Male	1315 (44.3)	111 (31.7)	1204 (46)
Female	1651 (55.7)	239 (68.3)	1412 (54)
Marital status			
Single	1544 (52.1)	199 (56.9)	1345 (51.4)
In a relationship	1422 (48)	151 (43.1)	1271 (48.6)
employment status			
Unemployed	1502 (50.6)	237 (67.7)	1265 (48.3)
Employed	1768 (59.6)	146 (41.7)	1622 (62)
Do you have health insurance?			
No	2548 (85.9)	266 (76)	2282 (87.2)
Yes	418 (14.1)	84 (24)	334 (12.8)
Current residence			
City	2412 (81.3)	288 (82.3)	2124 (81.2)
Rural	554 (18.7)	62 (17.7)	492 (18.8)
Financial status			
Below average	1514 (51.1)	127(36.2)	1387 (53)
Average and above	1452 (49)	223 (63.7)	1229 (47)
What is your highest education level?			
Elementary	149 (5)	14 (4)	135 (5.2)
Post-university	2817 (94.9)	336 (95.9)	2481 (94.8)
Currently diagnosed with fibromyalgia			
No	2937(99.1)	321(91.7)	2616(100)

Variables	Total (2966) N(%)	FM (350) N(%)	Non-FM (2616) N(%)
Yes	29(0.9)	29(8.2)	0(0)
Currently diagnosed with systemic lupus erythematosus			
No	2936 (99)	346 (98.9)	2590 (99)
Yes	30 (1)	4 (1.1)	26 (1)
Currently diagnosed with rheumatoid arthritis			
No	2803 (94.5)	308 (88)	2495 (95.4)
Yes	163 (5.5)	42 (12)	121 (4.6)
Currently diagnosed with other immune syndromes			
No	2802 (94.5)	309 (88.3)	2493 (95.3)
Yes	163 (5.5)	41 (11.7)	123 (4.7)
Currently diagnosed with major depressive disorder			
No	2741 (92.4)	281 (80.2)	2460 (94)
Yes	225 (7.5)	69 (19.8)	156 (6)
Currently diagnosed with general anxiety disorder			
No	2677 (90.2)	281 (80.2)	2396 (91.5)
Yes	289 (9.7)	69 (19.8)	220 (8.5)
Currently diagnosed with irritable bowel syndrome			
No	2535 (85.4)	260 (74.2)	2276 (87)
Yes	431 (14.5)	90 (25.8)	340 (12.9)
Currently diagnosed with restless legs syndrome			
No	2846 (95.9)	278 (79.4)	2568 (98.1)
Yes	120 (4.1)	72 (20.5)	48 (1.8)

Prevalence of fibromyalgia:

In total, 350 (11.8%) participants were found to meet the modified ACR 2010 criteria. Of these, 239 (68.3%) were females. The majority [250 (71.4%)] were 18–29 years old, single [199 (56.9%)], unemployed [237 (67.7%)], and did not have health insurance [266 (76%)]. Only 62 (17.7%) lived in rural areas. Regarding financial status, 127 (36.2%), 223 (63.7%) were below average, and had average financial status, respectively. When asked about previous medical history, only 29(8.2%) said that they were diagnosed with fibromyalgia, and 4 (1.1%), 41 (11.7%), 90 (25.8%), and 72 (20.5%) said they have

systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), irritable bowel syndrome (IBS) and restless leg syndrome (RLS), respectively. On the other hand, an equal number of participants had the diagnosis of major depressive disorder [69 (19.8%)], and general anxiety disorder [69 (19.8%)], respectively. (Table.1)

When asked about the number of sites that involved any pain problem in the last week, [45 (12.9%)] stated that they had problems in 3 to 6 sites and [305 (87.1%)] had problems in 7 or more sites.

The associations of the study variables among cases and controls:

The final univariable model presented in Table 2 includes the variables that were associated with FM using an odds ratio of $P < 0.05$. Female sex was associated with FM (OR=1.7, CI: 1.3-2.1). Also, being unemployed increased the odds for FM (OR=1.4, CI:1.1 – 1.79). Regarding associated diseases, diagnosis of major depressive disorder (OR=3.8, CI: 2.7 – 5.35), generalized anxiety disorder (OR=2.7, CI: 1.95 – 3.72), irritable bowel syndrome (OR=2.4, CI: 1.78 – 3.17), and restless legs syndrome (OR=8.2, CI: 5.42 – 12.43) were significant risk factors for FM. (Table.2)

Table 2
The associations of the study variables among cases and controls. (n=1750)

Variables	Case (350) N(%)	Control (1400) N(%)	OR (95% CI)	Chi-Square	P-value
Gender					
Male	111 (31.7)	611 (43.6)	0.6 (0.468- 0.769)	16.439	0.000*
female	239 (68.3)	789 (56.4)	1.7 (1.3-2.1)		
Marital status					
Single	199 (56.9)	776 (55.4)	1.1 (0.84- 1.34)	0.232	0.630
Married, in a relationship,	151 (43.1)	624 (44.6)	0.9 (0.75- 1.2)		
Employment status					
Unemployed	208 (59.4)	714 (51)	1.4 (1.1 – 1.79)	7.980	0.005*
Employed	142 (40.6)	686 (49)	0.7 (0.56- 0.9)		
Do you have health insurance?					
No	266 (76)	1234 (88.1)	0.4 (0.32- 0.57)	33.717	0.000*
Yes	84 (24)	166 (11.9)	2.3 (1.75 – 3.15)		
Current residence					
City	288 (82.3)	1127 (80.5)	1.1 (0.83 – 1.53)	0.577	0.448
Rural	62 (17.7)	273 (19.5)	0.9 (0.66 -1.21)		
Financial status					
Bad (Bad, Below average)	127 (36.3)	701 (50.1)	0.6 (0.45 – 0.72)	21.347	0.000*
Good (Average, Good, Excellent)	223 (63.7)	699 (49.9)	1.8 (1.38 – 2.24)		
Highest education level					

Variables	Case (350) N(%)	Control (1400) N(%)	OR (95% CI)	Chi-Square	P-value
Low (elementary or below)	14 (4)	93 (6.6)	0.6 (0.33 – 1.04)	3.407	0.065
High (university, Post-university) /medium (high school)	336 (96)	1307 (93.4)	1.7 (0.96 – 3.03)		
Currently diagnosed with major depressive disorder					
No	281 (80.3)	1315 (93.9)	0.3 (0.19 – 0.37)	64.937	0.000*
yes	69 (19.7)	85 (6.1)	3.8 (2.7 – 5.35)		
Currently diagnosed with general anxiety disorder					
No	281 (80.3)	1283 (91.6)	0.4 (0.27 – 0.51)	38.021	0.000*
Yes	69 (19.7)	117 (8.4)	2.7 (1.95 – 3.72)		
Currently diagnosed with Irritable bowel syndrome					
No	260 (74.3)	1222 (87.3)	0.4 (0.32 – 0.56)	36.487	0.000*
yes	90 (25.7)	178 (12.7)	2.4 (1.78 – 3.17)		
Currently diagnosed with Restless legs syndrome					
No	323 (92.3)	1363 (97.4)	0.1 (0.08 – 0.18)	20.439	0.000*
yes	72 (7.7)	37 (2.6)	8.2 (5.42 – 12.43)		

Discussion

Our study is the first, to our knowledge, to address FM prevalence and the basic characteristics of FM patients and to identify the risk factors in the general population in Damascus, Syria. Our results found that 350 (11.8%) have satisfied the ACR 2010 modified criteria of FM diagnosis, which represents one of the highest prevalence rates of FM in a general population. When considering that many studies showed a psychological predisposition to FM,[2, 27] our finding could be explained by the huge psychological distress experienced by the Syrian population. Syria has been at war for more than a decade now. This led to huge consequences with more than 6 million people being internally displaced to safer areas like Damascus city. Moreover, the economy experienced great damage resulting in 50% of working-age people

becoming unemployed, and more than 90% of people falling under the poverty line. More than 13.4 million Syrian people are in need, 1.1 million of which are in Damascus.[28, 29] Finally, COVID-19 pandemic has had a devastating effect on the Syrian society. The impact of the war on the prevalence of FM was evident in a study conducted on Syrian female refugees in Jordan that revealed a prevalence of severe FM at about 30%.[30]

Undiagnosed FM may result in inadequate treatment and relief of key symptoms like pain, fatigue, and unrefreshed sleep. This will mislead medical decisions to change or escalate the dosage of treatments of the underlying disease rather than addressing FM. In our study, only 29 (8.2%) of the 350 participants who satisfied the ACR 2010 modified criteria were diagnosed by a medical professional. A similar observation was made in a study conducted in Lebanon, as all FM cases were previously misdiagnosed and did not receive a diagnosis of FM.[13] The diagnosis of FM requires the efforts of patients to seek medical care and clinicians who are familiar with the disease and are willing to make the diagnosis, as FM diagnosis is confounded by drug-seeking behavior and malingering.[31]

Our study shows that females have greater odds to have FM (OR=1.7), which goes in line with the literature.[9, 11–13] Having health insurance is shown to be a risk factor in our population, probably because health insurance is not common in Syria, as only 14.1% of our sample have it. In addition, this insurance is offered to the workers in the public sector that have low wages due to economical inflation. One study showed that occupational stress is considered a risk factor for FM,[32] while our results showed that working participants have lower odds of having FM, and unemployment was identified as a risk factor, which was contrary to the results of a Lebanese study that indicated work is a risk factor.[13] This may be due to the bad economic status in Syria, which made it difficult to secure the basics of living, thus making unemployment very stressful. Surprisingly, we found that bad income is correlated with a low probability of FM, and this was inconsistent with what was reported in studies conducted in Europe and Lebanon.[11, 13] This is probably because the question about the financial status has been left subjective to the assessment of the participants, which may vary between the participants according to their opinions, making the results unreliable.

In our study, 225 and 289 of our participants stated that they are diagnosed with major depressive disorder and/or generalized anxiety disorder. However, a recent national study conducted on the general population in Syria found that mental health disorders have reached high rates, with rates of depression and anxiety reaching 83.4% and 69.6%, respectively.[33] This may represent a very concerning proportion, because of the fact that there is growing literature addressing a possible link between FM and.[5, 12, 34] Our study identified major depressive disorder, and generalized anxiety disorder as risk factors with an odds ratio of 3.8 and 2.7, respectively. Similar results were indicated in a US study with depression (OR = 2.85) and anxiety (OR = 3.47) found to be risk ratios for females with FM.[35] Gastrointestinal comorbidities are also common in FM patients. We identified IBS as a risk factor (OR=2.4, CI: 1.78 – 3.17) for FM. A similar finding was found in a study in Norway conducted on IBS patients that identified FM as a risk factor for IBS with an OR of 3.6.[36]

FM is associated with a high burden of illness on patients and the healthcare system, which causes significant disability.[19] We encourage a general awareness program targeting healthcare professionals and the public to help early detection of the disease and ensure a smoother and safer treatment journey specifically directed towards the symptoms of the disease and improvement of patients' quality of life. In addition, Long-term prospective studies should be conducted to address the patterns of treatment, financial burden, and productivity loss among patients.

Conclusion

FM appears to be a very common disease in Damascus, Syria. The lack of knowledge regarding the disease has resulted in many patients suffering due to the lack of recognition of the disease by patients and physicians alike.

Limitation:

We tried to minimize the selection bias by distributing the questionnaire online and in hard copies, and getting a representative sample of people with low economic status, as the online questionnaire may be filled mostly by young age groups with a good economic level. Recall bias is present due to self-reporting. The economic status question was left subjective because the Syrian currency is not stable and is changing dramatically on daily basis. Some aspects that might have accounted for differences in the odds of the disease were not addressed, such as the use of oral contraceptive pills, family history, and body mass index.

Declarations

Availability of data and materials:

The datasets used and/or analyzed during the current study are made available by the corresponding author on a reasonable request.

Competing interests:

The authors declare that they have no competing interests

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Authors' contributions:

M.A.A., M.S., T.A., H.I., S.A., B.S., R.A., and M.K. conceptualized the study, participated in the design, wrote the study protocol, prepared figures, did a literature search, and drafted the manuscript. S.A., A.A., A.T., N.K., participated in the design, distributed the survey face-to-face, did a literature search and revision of the draft. All authors read and approved the final draft.

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