Fibromyalgia and its effect on treatment response in early rheumatoid arthritis patients: results from the ESPOIR cohort.

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ABSTRACT

Objective: To evaluate if patients with rheumatoid arthritis (RA) and concomitant fibromyalgia (FM) have an impaired response to treatment measured by traditional activity scores.

Methods: Patients from the ESPOIR cohort were analyzed. This prospective cohort included 813 patients with early arthritis not initially receiving disease-modifying antirheumatic drugs (DMARDs). Among the 697 patients who met RA classification criteria, we studied two groups, one with and the other without FM. The following endpoints were compared at 6, 12 and 18 months using a mixed linear regression model: DAS28, Simple Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and the Health Assessment Questionnaire (HAQ). In addition attainment of low disease activity (LDA) (DAS28<3.2) and remission (DAS28<2.6, SDAI<3.3, CDAI<2.8) at these timepoints were analyzed.

Results: Patients with FM (120) had a higher DAS28, SDAI, CDAI and HAQ than patients with isolated RA (548). DAS28 and other disease activity scores started out higher in subjects with FM and while they improved to a similar extent as in the isolated RA group, they remained consistently higher among FM patients. Achievement of LDA and of remission was significantly less likely in subjects with FM.

Conclusion: Patients with FM and RA will have a similar response to treatment according the decrease in indexes of disease activity but may miss the target of remission or low disease activity.

Keywords:

Rheumatoid arthritis, Therapy, Outcome measures, Disease Activity Scores, Fibromyalgia, Early Rheumatoid Arthritis

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic chronic inflammatory disease that affects 0.5%-1% of the population [1]. The pain and physical limitation it produces severely compromise functioning, generating work disability in 30-50% of patients at 10 years. [2, 3, 4]

A “treat-to-target“ strategy has been shown to improve outcomes and is advocated in early RA to tailor treatment [5]. This strategy is based in the use of activity scores to define remission or low disease activity (LDA) and adjust treatment according to these aims. DAS28 has been the most studied and used score[6] This score gives a particularly high weight to tender joint counts (TJC) versus swollen joint counts (SJC). This may lead to classifying patients as having an active disease based mainly on tenderness.[7] While they do include TJC and SJC, the Simple Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI) do not give differential weights to these joint count measures. [8]

With advances in RA treatment remission is an achievable target. However, regardless of how remission is defined, a majority of patients still have some residual disease activity [9]. Although several factors that predict a poor response to therapy have been identified, there is limited capacity to anticipate who will require aggressive management. [10, 11] Drugs used in RA are associated with important adverse events; therefore it is crucial to determine who will truly benefit from intense therapy. [12, 13, 14]

Fibromyalgia (FM) often coexists with RA. [15] The prevalence of FM in the general population is 2.7-5.1% and in RA it reaches a prevalence of 10-20%.[16, 17, 18, 19]

Concern has been raised regarding the validity of RA disease activity scores in patients with coexistent RA and FM, making a “treat-to-target“ strategy questionable in these patients. [20] Cross-sectional studies have shown that patients have higher DAS28, higher TJC, worse self-reported global health (GH), and worse functional impairment. [21, 21, 23, 24] Moreover, up to 13% of patients who are classified as having “active” RA through DAS28 scores have no swollen joints. [7] Worse disease activity in FM patients with RA could be a consequence of a blunted response to RA treatment or it could be due

to the effect of persistent tenderness and fibromyalgic symptoms on disease activity measures. If response to treatment is poor, then the treat to target approach might need to be reconsidered in this large subset of patients. To our knowledge, no prospective longitudinal studies that follow patients from beginning of treatment have been carried out to address this question.

Tender points are part of the 1990 ACR classification criteria traditionally used to diagnose FM, with a cutpoint of ≥11 tender points. [25] However measuring them is time consuming and not always performed in RA clinics. In addition, it has been argued that a spectrum of FM exists and patients with RA that do not meet FM ACR criteria may still have a type of CWP that can affect their TJC. An index has been developed to identify RA patients with FM or "fibromyalgic RA" using conventional core data set measures instead of tender points. This score was developed in an RA cohort were they showed the relationship of TJC minus SJC had a ROC area under the curve of 0.86 to predict FM, and a TJC-SJC ≥7 predicted the presence of ≥11 tender points with 83% sensitivity and 80% specificity. The score was validated in a replicate cohort with high sensitivity and specificity (72% and 98%) for FM.[26]

In this prospective study, using the TJC vs. SJC index to diagnose the presence of FM or "fibromyalgic RA", we hypothesized that patients with this condition have an impaired response to treatment measured by traditionally used scores. In spite of this, we postulate they do not have increased structural damage.

MATERIALS AND METHODS.

Study Subjects We addressed our questions using the ESPOIR cohort, a prospective multi-centre early arthritis cohort. This cohort included patients aged 18–70 years, with 2 or more swollen joints with a duration of joint swelling of > 6 weeks and < 6 months, no previous disease-modifying drugs (DMARDS), no previous steroids, and no definite diagnosis of a disease other than RA or undifferentiated arthritis.[27] In our study, we included only patients with RA defined by the 1987 ACR and/or the 2010 ACR/EULAR classification criteria. Our inclusion criteria required a subject to meet either of the aforementioned criteria and have a TJC and SJC performed at baseline visit. We excluded participants

classified as having undifferentiated arthritis, missing values of DAS28, SDAI or CDAI at baseline, and patients with missing values of DAS28, CDAI, and SDAI at all follow up visits. The protocol of ESPOIR Cohort study was approved by the ethical committee of Montpellier. All the patients signed an informed consent form before inclusion. The study was in compliance with the Helsinki declaration.

The diagnosis of fibromyalgic RA was defined at baseline as having a TJC–SJC ≥7. [26] Patients were classified into two groups according to the presence or absence FM. Our two study groups for comparison were patients with RA and concomitant FM and patients with RA who did not meet these criteria for FM. We shall label this latter group isolated RA.

At baseline, differences in demographics between these groups were explored including age, gender, race, body mass index (BMI), and smoking status (defined as current or past smokers vs never smokers). BMI was categorized as obese (BMI≥30kg/m^2) vs non-obese (BMI<30kg/m^2). In addition, a comparison of RA characteristics was performed: serologic markers (rheumatoid factor (RF) and anti-cyclic Citrullinated Peptide (anti-CCP), TJC, SJC and presence of erosions (none vs one or more) evaluated in bilateral hands and feet radiographs. RA activity scores including DAS28, CDAI and SDAI were calculated as well as HAQ (Health Assessment Questionnaire) to evaluate functional impairment and the van der Heijde-modified total Sharp radiologic score (mTSS). Drugs were classified as analgesics, non-steroidal anti-inflammatory drugs (NSAIDS), oral corticosteroids, monotherapy with non-biologic DMARDS, combination of non-biologic DMARDS, monotherapy with biologic DMARDS, and combination of non-biologic with biologic DMARDS.

Study outcomes The main outcome of this study was response to treatment in patients with and without FM. All outcomes were compared at six, twelve and eighteen months of follow-up. DAS28 and its core measurements was the main outcome. Also, CDAI, SDAI and HAQ were compared.

As secondary outcomes an analysis was performed of the attainment of low disease activity (LDA) according to DAS28 (DAS28≤3.2) and of remission according to DAS28 (≤2.6), CDAI (CDAI≤2.8) and

SDAI (SDAI≤3.3). Each of the score's components were analyzed including SJC, TJC, physician global health visual analogue scales (phGH) (VAS), patient global health (ptGH) VAS, C-reactive protein and ESR. Additionally, treatment during follow up was compared. Lastly, to evaluate structural damage, mTSS was analyzed.

Power calculation:

We had 99% power to detect a DAS28 difference between groups of 0.5, considering a standard deviation of 1.3 using 120 subjects with FM and 548 without, 3 visits per subject and an intraclass correlation coefficient for repeated measures of DAS28=0.6.

Statistical Analysis: Baseline characteristics are reported as number (%) or mean±SD. A two sample T-Test was used to compare quantitative variables and a χ^2 test (or Fisher's exact test) for categorical variables.

The analysis of continuous outcomes at 6, 12 and 18 months was performed using a mixed linear regression model for repeated measures. We adjusted for the baseline value of the outcome being measured as well as other potential confounders: gender, age and smoking status. This model was used for activity scores as well as score components. An estimation of the adjusted average of outcomes was performed using least square means.

Comparison of categorical variables with repeated measurements was done using a log binomial regression with an estimation of risk ratios (RRs). RRs were obtained using a generalized estimating equation (GEE) model to adjust for multiple observations per subject.

For all analysis a level of significance of 0.05 was used. SAS 9.3 was used to perform all statistical calculations.

RESULTS

Baseline Patient Characteristics

There were 697 subjects with RA at baseline among the 813 ESPOIR cohort participants. Of these patients 24 did not come to any of the follow-up visits and were excluded. We further excluded 5 subjects with all activity scores missing at follow-up. As a consequence 668 subjects were the focus of the analysis. (Figure 1)

Subjects had a mean age of 48.3 years at baseline, 76.1% were females and 92.1% Caucasian. There were 47.3% ever smokers (see table 1). At baseline, patients had active disease with a mean DAS28 of 5.32. Erosions were present in 63.6% of patients.

FM was present in 120 (17.96%) patients. There was no significant difference in baseline demographic characteristics according to the presence of FM (see Table1). However, patients with FM met ACR/EULAR 2010 RA criteria more frequently than patients without FM (p=0.04), with no difference in ACR 1987 criteria (p=0.54). They also had a lower frequency of seropositivity (RF and antiCCP) (p=0.0003).

RA activity scores and HAQ were higher in the FM group. Also, TJC and GH evaluation by the physician and the patient were higher in these patients. On the other hand, ESR and the mTSS score were significantly lower in spite of the presence of higher activity scores. Regarding treatment there was no difference in drugs of any kind (Table 1).

Patients with missing values in any visit did not have significant differences in baseline characteristics from those without missing value**.**

Activity scores in FM patients over time.

In a multivariate analysis incorporating the three study visits, adjusting for the baseline score, we found that patients with FM had a higher DAS28 than patients with isolated RA (p<0.0001). DAS28 scores started out higher in subjects with FM and while they improved to a similar extent as in the isolated RA group, they remained consistently higher among FM patients. In none of the visits in FM patients did the

average DAS28 score reach LDA. (Figure 2). It is noteworthy that although TJC showed an important decrease in both groups after treatment, they remained significantly higher in patients with fibromyalgic RA. Patient and physician global health scores also remained worse in the RA and FM group at follow up. On the other hand, SJC decreased to such an extent in both groups that there was no difference between them during follow up. Regarding inflammatory parameters (ESR and CRP) there was no difference between groups after treatment. (Figure 3)

As shown in Table 2, other activity scores including SDAI, CDAI and HAQ were also higher in the group with concomitant FM. These scores had a similar behavior as DAS28, starting higher and presenting a similar decrease in both groups (data not shown). In contrast, mTSS score was similar between groups during follow up (Table 2).

The overall achievement of LDA was significantly less likely in subjects with FM, with a RR of 0.77 (95% confidence interval CI 0.63-0.94). Also there was less attainment of remission according to DAS28 and SDAI in this study group: RR=0.61 (95%CI 0.46-0.81) and 0.65 (95%CI 0.43-0.97) respectively. FM patients had a modestly lower risk of achieving CDAI remission too: RR=0.70,with a borderline p value=0.06. (Table 3)

Association between FM and therapy.

We did not find an association between FM and analgesic use with an estimated RR=1.12 and a p value=0.0705. Also no association was identified with NSAIDS nor corticosteroids with an RR=1.0 (p value=0.9759) and an RR=1.07 (p value=0.4785), respectively. Non-biologic DMARDS both as monotherapy and combination therapy were also not associated with the presence of FM (RR=0.82, p=0.98 and RR=0.53, p=0.9205. Finally, no difference existed in the use of biologic DMARDS as monotherapy (RR=0.26, p=0.2928) and combined with non-biologic DMARDS (RR=0.52, p=1.222) .

DISCUSSION

In this cohort, patients with RA and FM had higher baseline DAS28, CDAI, SDAI and HAQ than those with isolated RA. In addition, although FM patients improved with treatment to a similar extent as patients without FM, they maintained higher scores after treatment at all time-points. TJC also continued to be higher in patients classified as having fibromyalgic RA. In contrast, swollen joint counts, acute phase reactant levels, and mTSS scores were higher in patients with isolated RA at baseline, but there was no difference between groups in both measures at follow-up. Therefore, both activity scores and core measurements decreased after treatment in both groups, reflecting that a response to therapy existed in all patients, but TJC and activity scores values remained higher in patients with fibromyalgic RA.

In the only other study examining a similar issue in a longitudinal study Andersson et al. addressed the question of response to treatment in RA patients with chronic widespread pain (CWP), a condition in the same spectrum of conditions as FM. They classified patients as having CWP based on self-report of pain in all four body quadrants at nine years of follow-up and retrospectively looked at response to treatment in an earlier five year period. They found patients with CWP had worse activity scores after having been treated.[28] Patients with active RA without FM could have met their definition of chronic widespread pain, and the number of RA patients in this subset in their study was larger than any other subset and much higher than the usual estimate of 10-20% for FM raising questions as to whether all of these patients had either CWP or FM.

Our baseline findings are concordant with previous cross-sectional studies.[21, 22, 23, 24] One important question is if the traditionally used scores reflect more active RA or if scores in patients with concomitant FM do not necessarily measure RA activity, but a mixture of both conditions. Furthermore, the reliability of DAS28 has been shown to be inferior in patients with FM. [29] .

It could be argued that our finding of a higher baseline DAS28 is secondary to our definition of FM. However, while DAS28 gives more weight to TJC than SJC, CDAI and SDAI do not and these two

scores were also higher in patients with FM. Still, all of these scores include TJC and a Global health measure and it has been shown they are influenced by the patient's pain perception.[30]

The HAQ score, which does not include TJC, measures functional limitation and is also higher in patients with FM. This score is probably affected by the symptoms generated by FM per se and not necessarily due to more aggressive RA.

When analyzing response to treatment, at first impression the fact that activity scores continued to be higher in the FM groups can be interpreted as a poor response to therapy. However, the decrease in score was similar in both groups (Figure 2), and patients with FM had higher baseline values. Therefore, patients with FM do respond to treatment, but have persistently higher activity scores. The maintenance of scores could have two explanations. First, because DAS28 weights TJC more than SJC it is more likely that patients with FM would be assessed as continuing to have activity due to pain which may be secondary to FM and not RA. It has been shown that patients with FM and RA can have no clinical evidence of inflammation and still be categorized as active by DAS28. [7] On the other hand, patients with FM have central sensitization that may affect their response to therapy regarding pain control even if pain was secondary to RA. [31, 32, 33] As a consequence, high activity scores may be produced by a diminished response of pain in patients with FM and not necessarily because of a lack of accuracy of scores. In either situation, this instrument could misclassify patients as having inflammation. It is noteworthy that although at study initiation the existence of higher TJC could be related to our definition of FM, during follow up TJC as well as SJC decreased in both groups, showing that they do respond to therapy, but there is residual pain in patients who have a fibromyalgic spectrum that prevents them from reaching LDA or remission. The TJC scores continued to be higher in FM patients at follow-up after controlling for baseline values. The same occurred with the Global Health measure. Nevertheless, there was no difference in SJC and ESR between the two groups after treatment, two elements that do not rely on patient reports to characterize active RA.

Finally, the fact that SHARP scores were not higher in patients with FM supports the hypothesis that patients' activity scores in this group reflect only RA activity, although the follow up period may be too short to evaluate radiologic differences between groups.

Remission and LDA were less frequently achieved in patients with FM. (Figure 2). The classification of patients as having active disease could lead to escalating the intensity of treatment of RA. Treatment for arthritis is aimed at controlling inflammation and in patients with FM these scores may reflect pain and not necessarily inflammation. As a consequence, patients with fibromyalgia and RA may be overtreated using a “treat-to-target” strategy. This would increase the risk of adverse events and cost. Since current target score values are unlikely to be met in FM patients, a less stringent target may need to be established for this group. On the other hand, the drug algorithm that treatment guidelines using “treat-to-target” propose, could be modified in cases that high activity scores are caused by high pain, focusing more on analgesic treatment. [5, 34] McWilliams et al. have created a score called DAS28-P that focuses in TJC and ptGH and that was shown to predict bodily pain at 12 months. [35] Although it needs further validation, this could be used in patients with FM. Similarly, Kristensen et al. showed in a prospective study that a SJC/TJC ratio predicted response to antiTNF in patients refractory to traditional DMARDS. [36] This ratio could represent a way to categorize patients regarding response to treatment in presence of CWP, a condition that shares many properties with FM.

The definition we used of FM could generate misclassification of patients with RA who have high disease activity as having FM, when this is not the case. However, given the diagnostic performance of the TJC-SJC measure [26], it is unlikely especially since there are not many false positives (i.e. the specificity of this approach is high) and the use of TJC-SJC should be a valid representation of persons with FM. Further, even if these patients do not meet strict criteria for FM, they probably are part of the spectrum of fibromyalgic RA.

One limitation of our work is that the activity scores we used may generate misclassification of our outcome. DAS28, in particular, has been shown to allow for inflammation to exist in a state of remission.[37, 38, 39] The new ACR/EULAR remission criteria avoid this misclassification but SDAI, which is an index recommended by these criteria showed the same results as DAS28 in our study. [40] The ACR/EULAR Boolean definition of remission could also generate misclassification in FM patients because patient global assessment has been shown to be the factor that more frequently prevents remission from being attained. [41]

RA may cause central sensitization and therefore FM.[42] This makes it difficult to determine if it is the coexistence of FM that determines less response to treatment or if patients that have an aggressive form of RA develop FM more frequently. The ESPOIR cohort's short duration of disease at baseline makes it less likely, although not impossible, that at baseline a chronic sensitization phenomenon due to RA existed.[43, 44]

Loss to follow up, considered as missing all visits was extremely low (3.6%) and there was no difference between these patients and patients analyzed. Therefore, it is unlikely to represent a source of bias.

Conclusion

In conclusion, our results show patients with FM and RA have a worse response to treatment according to traditional disease activity scores if we consider the final value achieved and not the decrease in score. However, RA inflammation may be responding as the scores drop and the residual activity measured could correspond mainly to residual pain related to FM.

Competing Interests:

There is no personal disclosures for Josefina Duran, Bernard Combe, Nathalie Rincheval, Jingbo Niu and Cecile Gauloux Viala. David Felson was supported by NIH AR47785
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Authors Contributions

JD: Design of study, analysis of data, interpretation of results, draft of manuscript. BC: Design of study, recollection of data, critical revision of the draft. JN: Analysis and interpretation of data, critical revision of the draft, NR: manages original database and participated in analysis of data, critical revision of the draft. CGV: Design of the study, recollection of data, critical revision of the draft. DF: Design of study, interpretation of results, critical revision of the draft. All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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(CDAI), Patient Activity Score (PAS) and Patient Activity Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score Without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA). *Arthritis Care & Research* 2011; 63: S14–S36

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Table 1. Demographic and disease characteristics at inclusion of the 668 patients with rheumatoid arthritis, grouped by fibromyalgia (FM) presence

	All (n=668)	FM (n=120)	No FM (n=548)	P Value*
Female Gender %,	76.1	82.5	74.6	0.068
Age, mean(SD)	48.3 (12.1)	47.6 (12.5)	48.5(12.1)	0.48
Race (Caucasian,%)	92.1	91.7	92.2	0.86
Smokers (%)	47.3	49.2	46.9	0.65
Obesity (%)	14.4	15.8	14.1	0.61
ACR 1987 (%)	83.5	81.7	83.9	0.54
ACR/EULAR2010 (%)	93.4	97.5	92.5	0.045
DAS 28, mean (SD)	5.32 (1.24)	6.02 (0.92)	5.16 (1.25)	<0.0001
CDAI, mean (SD)	28.77(13.33)	37.94 (10.38)	26.76 (13.06)	<0.0001
SDAI, mean(SD)	31.0 (14.45)	39.78 (11.37)	29.09 (14.35)	<0.0001
HAQ, mean (SD)	1.03 (0.69)	1.25 (0.68)	0.98 (0.68)	<0.0001
SJC, mean (SD)	7.99 (5.42)	7.15 (0.37)	8.17 (5.66)	0.02
TJC, mean (SD)	9.36 (7.12)	18.29 (5.01)	7.41 (5.93)	<0.0001
PtGH VAS (cm), mean (SD)	6.13(2.48)	6.73 (2.15)	5.99 (2.53)	0.001
PhGH VAS (cm), mean (SD)	5.34 (6.13)	5.85 (2.11)	5.22 (2.14)	0.004
ESR (mm/h), mean (SD)	30.6 (25.2)	24.9 (20.5)	31.9 (25.9)	0.002
CRP (mg/l), mean (SD)	21.4 (33.6)	17.4 (24.9)	22.3 (35.2)	0.071
RF (%)	54.6	40	57.9	0.0004
CCP (%)	45.7	29.2	49.3	<0.0001
RF + CCP (%)	41.3	26.7	44.5	0.0003
Erosions (%)	63.6	63.7	61.2	0.61
Sharp score (SD)	6.29 (8.07)	5.12 (6.02)	6.54(8.44)	0.038

Analgesics (%)	70.8	75.8	69.7	0.18
NSAIDS (%)	90.7	89.2	91.1	0.52
Corticosteroids (%)	13.0	14.2	12.8	0.68
DMARDS Monotherapy (%)	7.7	7.5	7.7	1.0
Combined DMARDS (%)	0.5	0.6	0	1.0
Biologic DMARDS (%)	0	0	0	1.0

* P values denote the overall significance of differences between groups calculated by a two-sample T-Test or by the chi-squared test.Obesity: (BMI≥30kg/m^2); DAS28: 28-joint Disease Activity Score; the Simplified Disease Activity Index (SDAI) or the Clinical Disease Activity Index (CDAI); HAQ: Health Assessment Questionnaire; SJC: swollen joint counts, TJC: tender joint counts PtGH: patient global health; PhGH: physician global health; VAS: visual analog scale; RF: rheumatoid factor; CCP: Anti-citrullinated protein antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 2. Comparison of rheumatoid arthritis activity scores and radiologic scores over follow up according to the presence of fibromyalgia

	FM	**No FM**	**Difference in Adjusted scores**	**P value***
DAS 28	3.5045	3.0541	0.4505	<0.0001
SDAI	16.0891	11.5378	4.5514	<0.0001
CDAI	14.9819	10.7510	4.2309	<0.0001
HAQ	0.6293	0.4454	0.1739	0.0002
SJC	2.32	2.18	0.14	0.5476
TJC	5.64	3.27	2.37	0.0001
PtGH VAS	3.82	3.01	0.81	<0.0001
PhGH VAS	2.88	2.38	0.51	0.0044
CRP	0.75	0.84	0.09	0.4147
ESR	13.99	15.05	1.06	0.3602
SHARP	7.3315	7.6756	0.341	0.3125

* P values denote the overall significance of a linear regression adjusting for baseline score, gender, age and smoking status. DAS28: 28-joint Disease Activity Score; Simplified Disease Activity Index (SDAI) or the Clinical Disease Activity Index (CDAI); HAQ: Health Assessment Questionnaire; SJC: swollen joint counts, TJC: tender joint counts PtGH: patient global health; PhGH: physician global health; VAS: visual analog scale; RF: rheumatoid factor; CCP: Anti-citrullinated protein antibodies; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

Table 3. Low activity and remission attainment according to Fibromyalgia (FM) groups.

	Risk Ratio (95% Confidence Interval)	**P value***
DAS low activity	0.77 (0.63, 0.94)	0.0101
DAS remission	0.61 (0.46, 0.81)	<0.0007
SDAI remission	0.65 (0.43, 0.97)	0.0366
CDAI remission	0.70 (0.49, 1.01)	0.0581

P values denote the overall significance of a log binomial regression adjusting for baseline score, gender, age and smoking status. DAS28 low activity; DAS28≤3.2; DAS28 remission: DAS28 ≤2.6; CDAI remission: CDAI≤2.8 and of SDAI (SDAI≤3.3).

Figure Legends.

Figure1. Flow diagram documenting number of patients in this study. RA includes patients that meet either ACR 1987 classification criteria or ACR/ EULAR 2010 classification criteria. FM= Fibromyalgia

Figure 2. DAS28 score at different time points grouped by fibromyalgia presence

Figure 3. DAS28 core measures of disease activity at different time points grouped by fibromyalgia presence. A: Erythrocyte Sedimentation Rate (ESR), B: C Reactive Protein (CRP), C: Tender Joint Count (TJC), D: Swollen Joint Count (SJC)

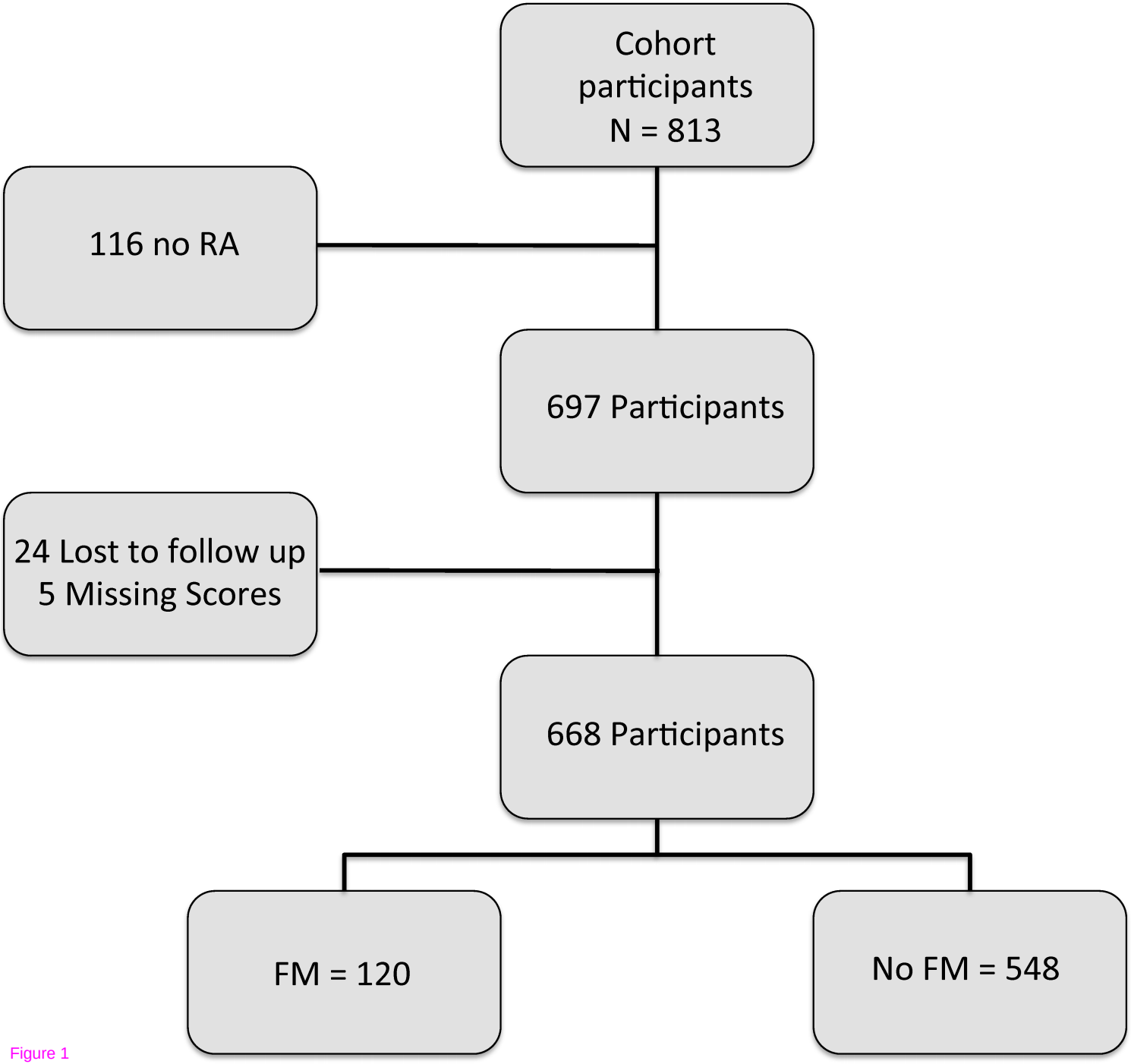
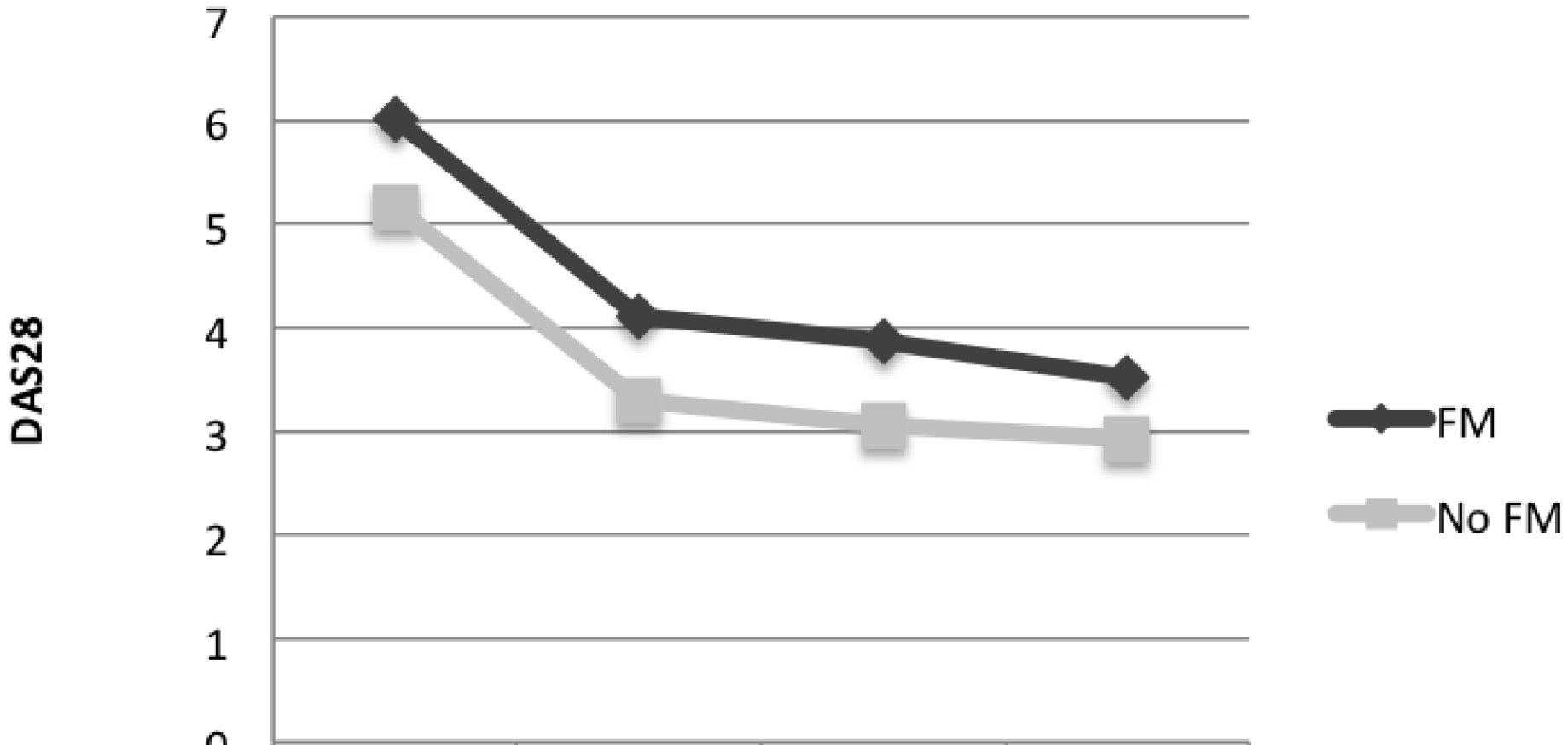

Cohort participants N = 813
116 no RA
697 Participants
24 Lost to follow up
5 Missing Scores
668 Participants
FM = 120
No FM = 548

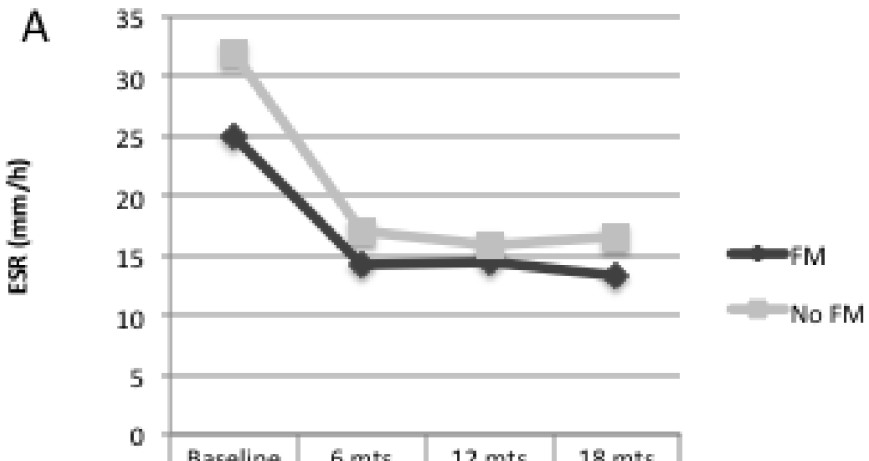
Figure 1



	Baseline	6 months	12 months	18 months
FM	6.02	4.12	3.87	3.52
No FM	5.16	3.31	3.06	2.93

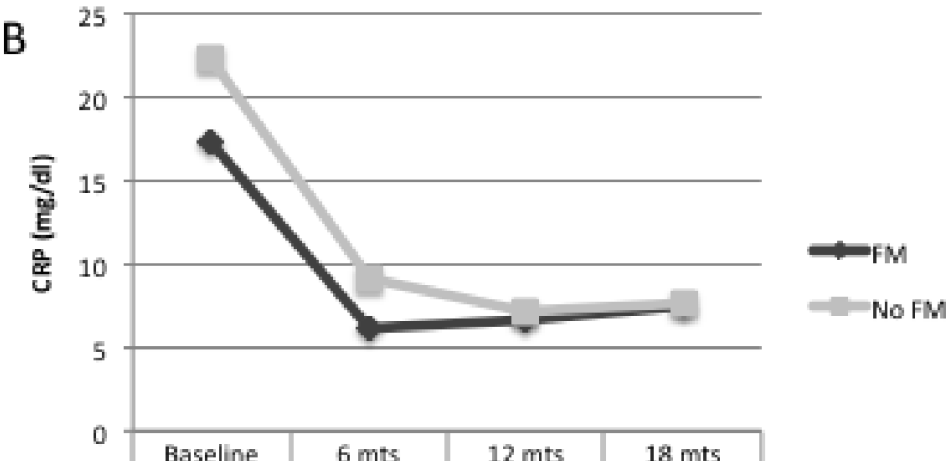
Figure 2

A



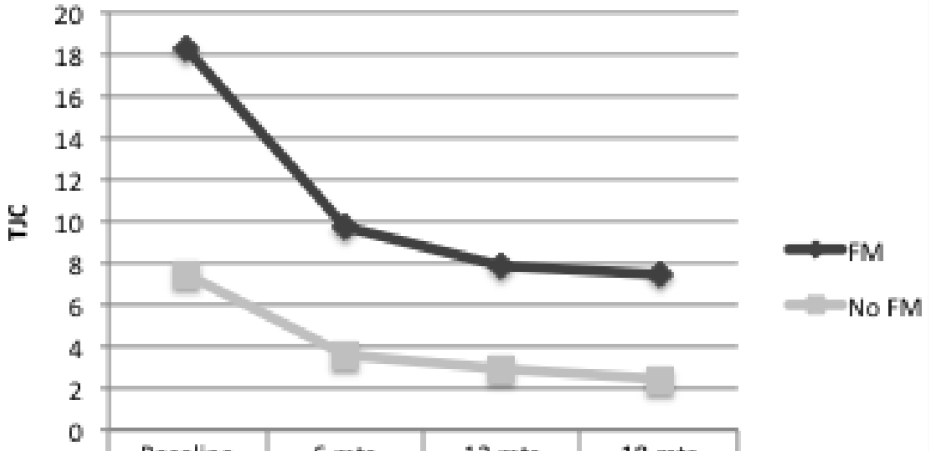
	Baseline	6 mts	12 mts	18 mts
FM	24.91	14.12	14.54	13.2
No FM	31.86	17.05	15.76	16.48

B



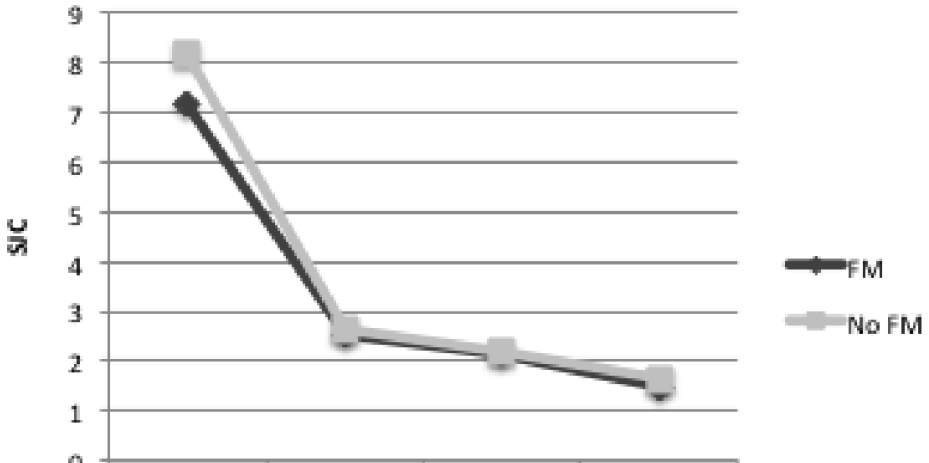
	Baseline	6 mts	12 mts	18 mts
FM	17.38	6.1	6.72	7.54
No FM	22.31	9.22	7.13	7.71

C



	Baseline	6 mts	12 mts	18 mts
FM	18.26	9.67	7.91	7.39
No FM	7.41	3.62	2.97	2.44

D



	Baseline	6 mts	12 mts	18 mts
FM	7.15	2.55	2.16	1.49
No FM	8.17	2.66	2.22	1.66

Figure 3