Outcome and Predictor Relationships in Fibromyalgia and Rheumatoid Arthritis: Evidence Concerning the Continuum versus Discrete Disorder Hypothesis

FREDERICK WOLFE and KALEB MICHAUD

ABSTRACT. ***Objective.*** To compare outcome-predictor relationships in fibromyalgia (FM) and rheumatoid arthritis (RA), to provide information regarding the competing hypotheses that FM is a continuum or a discrete disorder.

Methods. We studied 3 outcome variables (work disability, opioid use, depression) and 12 clinical predictor variables in 2,046 patients with FM and 20,374 with RA. We determined whether outcome-predictor relationships were stronger in FM or RA by measuring the areas under the receiver-operating curves. We used fractional polynomial logistic regression to create graphic models for the outcome-predictor relationships.

Results. All measures of status and outcome were more abnormal in FM than in RA. Depression was reported in 33.4% of patients with FM compared with 15.1% of those with RA. The predictor-outcome relationship was significantly stronger in RA in 28 of the 36 tests, and not different in the remainder. The relationship between outcome and predictor variables was generally similar in patients with FM and RA. However, unmodeled depression that was not explained by study variables was noted in FM.

Conclusion. Our data are consistent with the hypothesis that FM is the end of a severity continuum, but that additional psychological factors are an integral part of the syndrome. (First Release Feb 15 2009; J Rheumatol 2009;36:831–6; doi:10.3899/jrheum.080897)

Key Indexing Terms:
FIBROMYALGIA RHEUMATOID ARTHRITIS DEPRESSION ETIOLOGY

There are 3 conceptualizations of fibromyalgia (FM)[1]. The first considers it to be a distinct disorder with an underlying biologic basis (a disorder of central processing with neuroendocrine/neurotransmitter dysregulation). The second model conceptualizes FM as an artificial, if sometimes useful, social construct that describes the end of a pain-distress continuum. A third view sees FM as a kind of unhappiness mixed with medicalization. Similar arguments have surrounded depression with respect to it being a unitary (continuum) or a binary (biologic vs non-biologic) or a medicalized disorder, with current opinion favoring the unitary approach. Recently, regulatory authorities have approved treatments for FM, offering some *de facto* support, although no proof, for FM as a distinct disorder. A model of the key FM variable, widespread pain, based on observed data, is shown in Figure 1.

From the National Data Bank for Rheumatic Diseases and University of Kansas School of Medicine, Wichita, Kansas; and University of Nebraska Medical Center, Omaha, Nebraska, USA.

F. Wolfe, MD, National Data Bank for Rheumatic Diseases and University of Kansas School of Medicine; K. Michaud, PhD, University of Nebraska Medical Center and National Data Bank for Rheumatic Diseases.

Address correspondence to Dr. F. Wolfe, National Data Bank for Rheumatic Diseases, 1035 N. Emporia, Suite 288, Wichita, KS 67214, USA. E-mail: fwolfe@arthritis-research.org

Accepted for publication November 19, 2008.

We hypothesized that if FM was a distinct disorder rather than a continuum of symptoms, the relation between outcome variables and severity variables might be distorted compared with a similar relationship in recognized conditions, such as rheumatoid arthritis (RA). In addition, exploration of outcome and predictor relationships might shed light on how variables perform in FM, regardless of how it is conceptualized.

We chose 3 outcomes to investigate: work disability, uses of opioids, and depression; and we investigated whether a series of 12 predictor variables would perform similarly or differently in FM compared with RA.

MATERIALS AND METHODS

Patient population. We studied participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of rheumatic disease outcomes. NDB participants are diagnosed by United States rheumatologists and are recruited from their practices. Patients are followed prospectively with semiannual, detailed, 28-page questionnaires, as described[2-4]. This report utilized NDB data in a longitudinal cohort analysis of 22,420 adult participants (aged 18–103 yrs), of whom 20,374 had RA and 2,046 had FM. Patients were enrolled continuously beginning in 1999 and ending in January 2008. Rheumatic disease diagnoses were made or confirmed by the patient's rheumatologist. Study variables were assessed at entry into the NDB and at every subsequent semiannual questionnaire. In our report we analyzed one randomly selected observation from each patient.

Study variables. Demographic variables included age and sex. Work and disabled status variables were based on patient self-report. We used

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2009. All rights reserved.

Downloaded on April 15, 2024 from www.jrheum.org

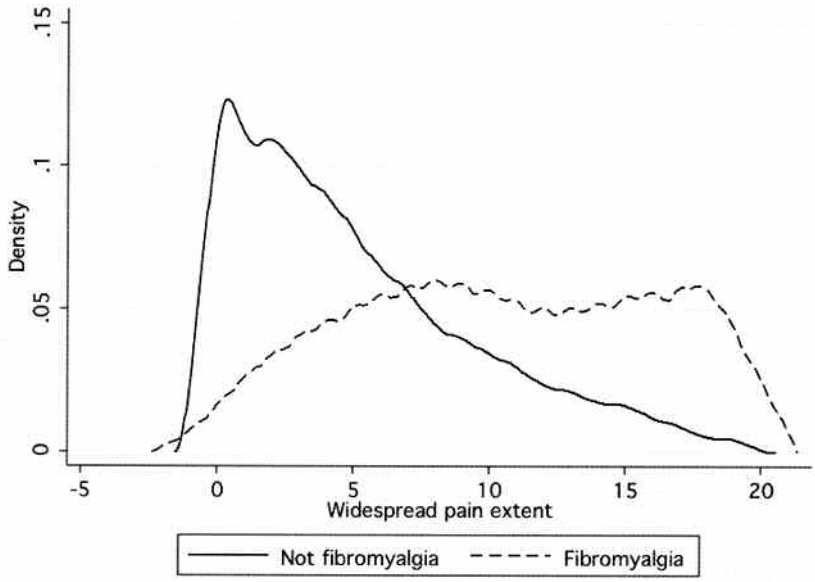

Figure 1. Hypothetical model of the distribution of widespread pain (RPS) in fibromyalgia (FM) and non-FM subjects. FM subjects are the actual patients with FM in our study. Non-FM subjects are the study's patients with rheumatoid arthritis (RA) who have Symptom Intensity Scale scores < 8 (95% of RA subjects). This restriction simulated the distribution of widespread pain in RA with RA patients who had FM removed from the figure.

self-reported disability rather than government social security disability (SSD) awards in order to identify disability status in patients who were not eligible for SSD awards for administrative reasons. Validation studies have demonstrated the reliability of the work and disability assessments[5].

Questions relating to depression and mood included self-reported depression and the Medical Outcomes Study Short-Form 36 (SF-36) mood scale[6]. We assessed self-reported depression by a single question in each semiannual survey (paraphrasing from a table of questions), "Have you had a problem with depression in the last 6 months?".

Comorbidity was measured by a patient-reported composite comorbidity score (range 0–9) comprising 11 present or past comorbid conditions including pulmonary disorders, myocardial infarction, other cardiovascular disorders, stroke, hypertension, diabetes, spine/hip/leg fracture, depression, gastrointestinal (GI) ulcer, other GI disorders, and cancer[7,8]. For the purposes of our study, self-reported depression was omitted from the scale so that it would only assess nondepressive comorbid conditions. As a consequence, its range in our study was 0–8.

Questions related to illness severity included the Health Assessment Questionnaire Disability Index (HAQ)[9,10], visual analog scales (VAS) for pain and patient global severity, the Patient Activity Scale (PAS)[11], the Regional Pain Scale (RPS)[12], and the Symptom Intensity (SI) Scale[13]. The PAS is formed by multiplying the HAQ by 3.33 and then dividing the sum of the VAS pain, VAS global, and HAQ by 3. This yields a 0–10 scale. The PAS is a composite patient measure of RA activity. The RPS is a self-administered count of the number of painful nonarticular regions. The RPS score ranges from 0 to 19. The SI Scale measures the combination of fatigue and pain extent. Derived from the fatigue and RPS, the SI Scale combines these 2 measures in continuous form according to the following formula: [VAS fatigue + (RPS/2)]/2. This yields a scale with a 0 to 9.75 range.

We defined 3 outcome variables: disabled, as a measure of work status; opioid use, as a measure of severe pain outcome; and self-reported depression, as a measure of clinical depression. All of the other clinical variables were used as predictor covariates. Analyses of disabled status were restricted to patients < 62 years of age to avoid confusion in identifying disabled patients who were retired. The sample sizes for these analyses were 10,662 for RA and 1,351 for FM.

Statistical analyses. T-tests and chi-squared tests were used to test whether the groups differed for the study variables (Table 1). Figure 1 is hypothetical model of the distribution of the RPS in FM and non-FM subjects. In this figure, FM subjects are the actual patients with FM in the study. Non-FM subjects are the study's patients with RA who have SI Scale scores < 8 (95% of RA subjects). We imposed this restriction in order to try to remove patients with RA who had FM from the figure.

Graphical inspection of the relation between predictor and outcome variable revealed it to be nonlinear. Therefore, we modeled the relation using fractional polynomial logistic regression, as shown for selected variables in Figures 2-4. To compare the strength of the relation in the groups, we compared the area under the receiver-operation characteristic (ROC) curves derived from the logistic model for the FM and RA patient groups (Table 2).

To be certain that the observed results were not an artifact of the difference in RA and FM sex prevalence (Table 1), we reran all of the study analyses after excluding men from analyses. The results were essentially unchanged.

RESULTS

Covariates and outcomes are more abnormal in FM than RA. Table 1 shows that all clinical variable scores were substantially more abnormal for those with FM compared with RA ($p < 0.001$). We selected 3 binary variables to represent the illness outcomes of depression, pain, and work disability, and we used the outcomes as dependent variables in the analyses of Figures 2-4. For these variables the results were self-reported depression 33.4% versus 15.0%, opioid use 32.0% versus 22.9%, and disabled status 30.5% versus 21.2%, for FM versus RA, respectively. In addition, lifetime depression was 63.9% in FM and 33.0% in RA.

The relation between outcome variables and their predictors in FM compared with RA. We tested whether the modeled relationship between predictor and outcome variables was stronger in RA compared with FM by comparing the respective areas under the ROC curves. As shown in Table 2, the

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2009. All rights reserved.

Downloaded on April 15, 2024 from www.jrheum.org

Table 1. Characteristics of patients with fibromyalgia and rheumatoid arthritis.

Variable	FM, n = 2,046		RA, n = 20,374	
	Mean	SD	Mean	SD
Age, yrs	57.4	12.1	60.5	13.4
Sex, % male	4.9		22.8	
Self-reported depression, %	33.4		15.1	
Self-reported depression, lifetime %	63.9		33.0	
Disabled (age < 62 yrs), %	30.5		21.2	
Ordinary opioids, %	32.0		22.9	
Dissatisfied with health, %	56.1		33.4	
VAS QOL	0.74	0.1	0.78	0.1
Sleep disturbance, 0–10	5.6	3.0	3.8	3.1
Regional Pain Score, 0-10	10.5	5.5	5.7	5.1
Pain, 0–10	5.8	2.6	4.0	2.8
Global severity, 0-10	4.9	2.5	3.7	2.5
HAQ, 0–3	1.3	0.7	1.1	0.7
Patient activity score, 0-10	4.9	2.1	3.8	2.3
Fatigue, 0–10	6.4	2.7	4.5	3.0
Symptom intensity scale, 0–10	5.8	2.3	3.7	2.3
Comorbidity Index, 0–9	1.6	1.4	1.4	1.4
Symptom count, 0–37	13.3	6.6	7.7	6.1
Mental health, SF-36	63.6	21.2	72.5	19.1

Differences for all variables between groups were significant at $p < 0.001$. SD: standard deviation; VAS: visual analog scale; QOL: quality of life: HAQ: Health Assessment Questionnaire; SF-36: Medical Outcomes Study Short-Form 36.

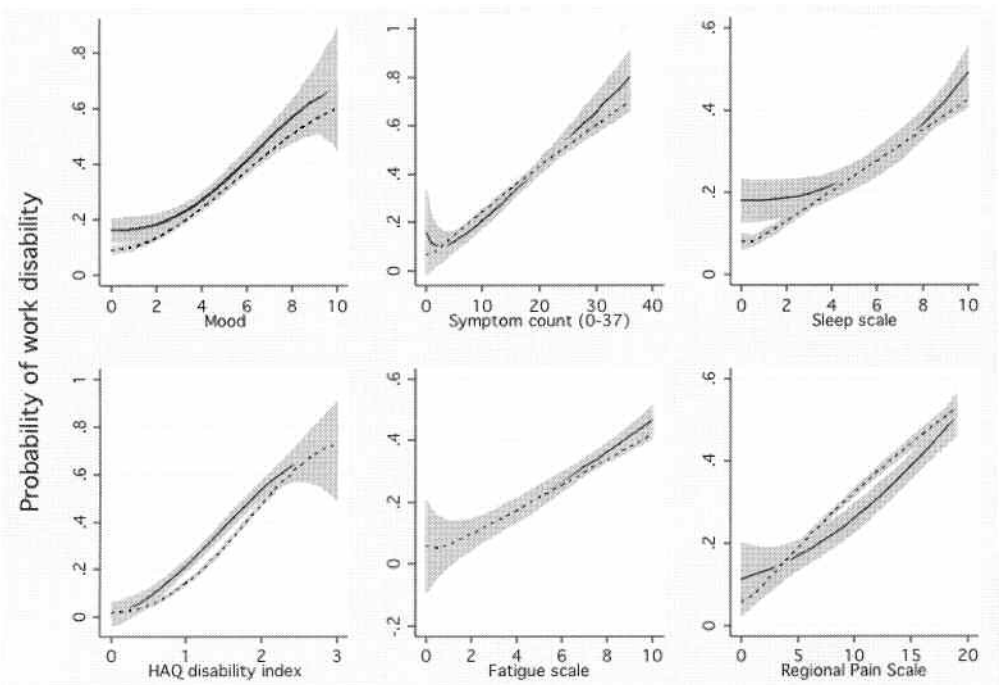

Figure 2. The relation between work disability and selected predictor variables as determined by fractional polynomial regression. Solid line represents FM, broken line RA. Shaded area represents 95% confidence intervals.

predictor-outcome relationship was significantly stronger in RA in 28 of the 36 tests. In the remaining tests, there were no significant differences.

In Figures 2-4, we modeled these relationships using fractional polynomial logistic regression. With respect to work disability, Figure 2, the curves are similar, as are the intercepts, except for the sleep scale. Taken as a whole, these data indicate that patients with FM and RA respond similar-

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2009. All rights reserved.

Downloaded on April 15, 2024 from www.jrheum.org

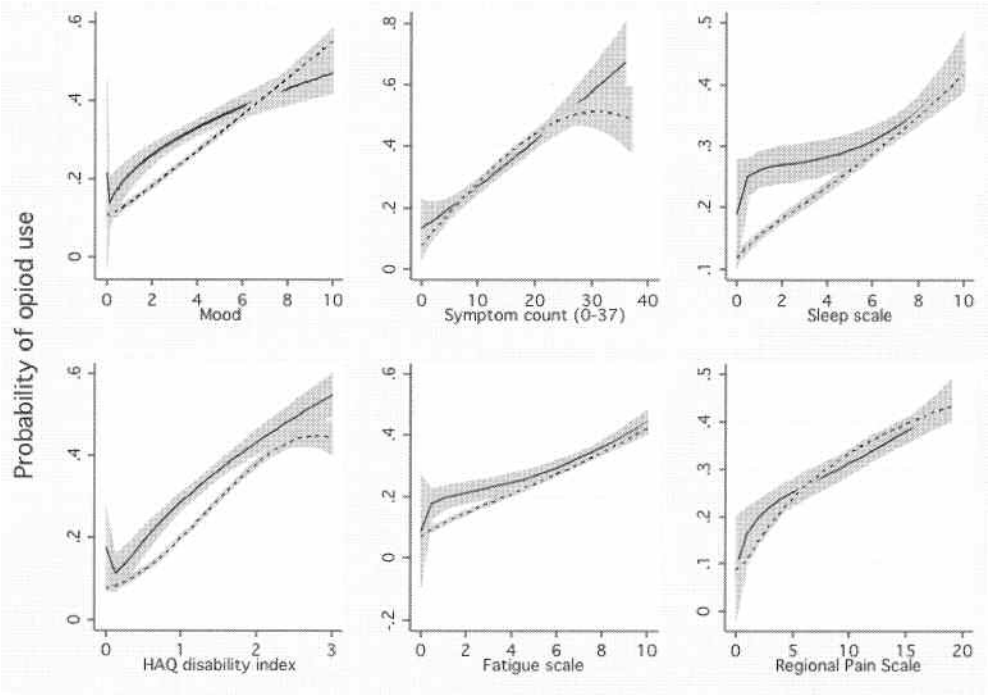

Figure 3. The relation between opioid use and selected predictor variables as determined by fractional polynomial regression. Solid line represents FM, broken line RA. Shaded area represents 95% confidence intervals.

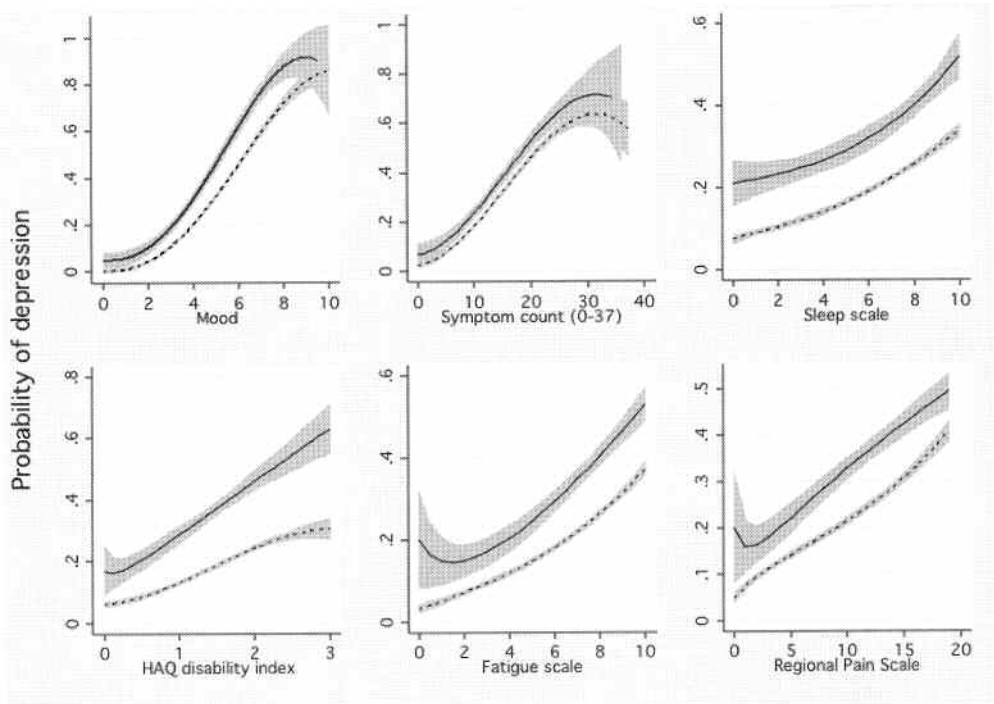

Figure 4. The relation between self-reported depression and selected predictor variables as determined by fractional polynomial regression. Solid line represents FM, broken line RA. Shaded area represents 95% confidence intervals.

ly with respect to work disability; however, the association is weaker (Table 2) in FM than RA.

The curves are also similar for opioid use, a measure of severe pain outcome (Figure 3). However, there is a slight separation of the curves at the lower ranges of mood, HAQ, fatigue, and sleep.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2009. All rights reserved.

Downloaded on April 15, 2024 from www.jrheum.org

Table 2. Area under the receiver operating curve for outcome predictions in patients with fibromyalgia and rheumatoid arthritis.

Predictor		ROC AUC (95% CI) Depression	ROC AUC (95% CI) Disabled	ROC AUC (95% CI) Opioid Use
QOL	FM	0.648 (0.623, 0.673)*	0.700 (0.670, 0.729)*	0.594 (0.568, 0.620)
QOL	RA	0.666 (0.656, 0.677)*	0.724 (0.713, 0.735)*	0.654 (0.645, 0.663)
Sleep	FM	0.618 (0.593, 0.644)	0.636 (0.604, 0.668)	0.578 (0.551, 0.604)
Sleep	RA	0.661 (0.650, 0.671)	0.689 (0.677, 0.701)	0.642 (0.633, 0.651)
RPS	FM	0.635 (0.610, 0.660)	0.669 (0.638, 0.700)	0.605 (0.579, 0.631)
RPS	RA	0.685 (0.675, 0.695)	0.727 (0.715, 0.738)	0.670 (0.661, 0.679)
Pain	FM	0.644 (0.619, 0.669)	0.708 (0.680, 0.737)	0.653 (0.628, 0.678)
Pain	RA	0.685 (0.675, 0.695)	0.747 (0.736, 0.757)	0.703 (0.694, 0.711)
Global	FM	0.666 (0.642, 0.690)*	0.706 (0.677, 0.735)	0.614 (0.588, 0.639)
Global	RA	0.689 (0.679, 0.699)*	0.739 (0.728, 0.750)	0.669 (0.661, 0.678)
HAQ	FM	0.637 (0.612, 0.662)*	0.752 (0.726, 0.778)	0.635 (0.609, 0.660)
HAQ	RA	0.659 (0.649, 0.669)*	0.802 (0.793, 0.812)	0.691 (0.682, 0.699)
PAS	FM	0.677 (0.652, 0.701)	0.760 (0.734, 0.786)	0.659 (0.634, 0.684)
PAS	RA	0.705 (0.695, 0.714)	0.797 (0.788, 0.806)	0.716 (0.708, 0.724)
Fatigue	FM	0.656 (0.632, 0.681)	0.661 (0.631, 0.691)	0.603 (0.577, 0.629)
Fatigue	RA	0.709 (0.699, 0.718)	0.700 (0.688, 0.711)	0.664 (0.655, 0.672)
SI Scale	FM	0.674 (0.650, 0.698)	0.699 (0.669, 0.728)	0.625 (0.599, 0.650)
SI Scale	RA	0.732 (0.723, 0.741)	0.748 (0.737, 0.759)	0.693 (0.684, 0.701)
Comorbidity	FM	0.575 (0.549, 0.600)	0.644 (0.613, 0.675)*	0.576 (0.550, 0.602)*
Comorbidity	RA	0.621 (0.611, 0.632)	0.649 (0.636, 0.661)*	0.601 (0.592, 0.610)*
Symptom count	FM	0.718 (0.695, 0.741)	0.688 (0.657, 0.718)*	0.628 (0.602, 0.654)
Symptom count	RA	0.779 (0.770, 0.787)	0.702 (0.690, 0.714)*	0.675 (0.666, 0.684)
Mood	FM	0.799 (0.779, 0.820)	0.665 (0.633, 0.697)*	0.576 (0.549, 0.602)
Mood	RA	0.827 (0.819, 0.834)	0.658 (0.645, 0.671)*	0.621 (0.612, 0.631)

* = $p > 0.05$. Sleep: sleep disturbance; QOL: quality of life scale; RPS: Regional Pain Scale; Pain: pain scale; Global: global severity; HAQ: Health Assessment Questionnaire Disability Index; PAS: Patient Activity Scale; Fatigue: fatigue scale; SI: scale: Symptom Intensity scale; Comorbidity: comorbidity index; Mood: SF-36 mental health scale.

Figure 4 is concerned with depression. Once again the curves are similar in shape, but the intercepts are different and the curves for FM are shifted upwards substantially, except for symptom count. We interpret the curves of Figure 4 to indicate that unmodeled depression is greater in FM than RA. The data of Figure 3 also suggest that unmodeled opioid use is somewhat greater in FM.

DISCUSSION

We found that illness severity measures are substantially more abnormal in FM than RA. Although this is not new information, the very large sample sizes and range of variables studied make these results robust and informative. Our study also provides information about depression, an area of controversy in FM, and about the interaction of depression with other clinical variables. Specifically, with respect to prevalence, we noted that self-reported depression occurred in 33.4% and lifetime depression in 63.9% compared with 15.0% and 33.0% in RA, respectively. Previous studies of FM have shown depression to be increased in clinic populations[14] and in the general population[15]. Depression exists along a continuum of severity[16], and the prevalences reported here do not distinguish between major depression and subsyndromal and minor depression (subthreshhold depression). However, subsyndromal depression is a medically significant disorder[17].

An important study result was the demonstration that the shape (slope) of the outcome-predictor relationships was similar in FM and RA (Figures 2-4). One can conclude, with respect to outcome-predictor models, that FM has more abnormal outcomes and predictors, as shown in Table 1, but that FM curves are almost superimposable on RA curves. Still, we found that there are some important differences. First, approximately 78% of the associations shown in Table 2 are weaker in FM compared with RA. There are 2 possible explanations for this finding. The first is that FM assessments are "noisier," in effect made with greater error. The literature supports this interpretation with respect to differences between observed performance and stated performance[18], and in overreporting of symptoms[19]. By itself, this suggests that the continuum approach to FM is not fully sufficient, and that other factors partially differentiate FM from other painful conditions.

The relation between depression and predictor variables shown in Figure 4 offers some further insights. The FM curves are shifted upward, with the exception of the symptom-count curve. This suggests that unmodeled depression may be an important feature of FM. By unmodeled depression we mean depression that is present irrespective of covariate status, suggesting perhaps that a key feature of FM is depression that is unrelated to symptom severity. There are several possible explanations for depression that is unre-

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2009. All rights reserved.

Downloaded on April 15, 2024 from www.jrheum.org

lated to covariate severity. The first, and we believe most likely, is that for some proportion of patients with FM, FM is to some extent causally related to depression. The literature suggests an increase in depression in families where the proband has FM[20,21]. The second possibility is that observed FM represents healthcare-seeking behavior and that, in turn, is associated with depression[22]. In addition, the physician may be more likely to consider the diagnosis of FM in those who are depressed.

We noted that there are 2 contrasting hypotheses about FM, the first that it is a distinct disorder, and the second that it represents the end of a continuum of pain and distress. The data of this report are consistent with FM primarily following the continuum theory, but with additional psychological factors an integral part of the syndrome. Wessely and Hotopf carefully, and at length, summarized the issues regarding distinct disorder versus continuum disorder and concluded "that fatigue and myalgia syndromes are arbitrarily created syndromes that lie at the extreme end of the spectrum of polysymptomatic distress"[23].

One should be cautious about extrapolating the result of our study to all patients with FM. No model of FM, whether it is behavioral, genetic, or a disorder of central processing with neuroendocrine/neurotransmitter dysregulation, is capable of explaining more than a small fraction of the FM phenotype. In addition, although this is unlikely, diagnostic differences for FM among referring rheumatologists may have led to heterogeneity among study subjects.

One limitation of our study relates to the definition of depression, which is based on patient self-report rather than formal examinations or a standard scale. However, the area under ROC curve for mood in RA was 0.827 and, in data not shown, was 0.823 for the SF-36 mental component scale, levels that are satisfactory for research.

Despite having more abnormal scores for clinically relevant outcome and predictor variables, the relationship between outcome and predictor variables was generally similar in patients with FM and RA. However, unmodeled depression that was not explained by study variables was noted in FM, and the strength of outcome-predictor relationships was weaker in FM. The data of our report are consistent with the theory that FM is the end of a severity continuum, but that additional psychological factors are an integral part of the syndrome.

ACKNOWLEDGMENT

We thank Prof. J.J. Rasker for his helpful thoughts and manuscript review.

REFERENCES

1. Wolfe F, Rasker JJ. Fibromyalgia. In: Firestein GS, Budd RC, Harris Jr ED, McInnes IB, Ruddy S, Sergent JS, editors. Kelley's textbook of rheumatology. 8th ed. St. Louis: Elsevier; 2008.
2. Wolfe F, Michaud K. Biologic treatment of rheumatoid arthritis and the risk of malignancy: Analyses from a large US observational study. Arthritis Rheum 2007;56:2886-95.
3. Nadareishvili Z, Michaud K, Hallenbeck JM, Wolfe F. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: A nested, case-control study. Arthritis Rheum 2008;59:1090-6.
4. Wolfe F, Michaud K. Prevalence, risk, and risk factors for oral and ocular dryness with particular emphasis on rheumatoid arthritis. J Rheumatol 2008;35:1023-30.
5. Wolfe F, Allaire S, Michaud K. The prevalence and incidence of work disability in rheumatoid arthritis, and the effect of anti-tumor necrosis factor on work disability. J Rheumatol 2007;34:2211-7.
6. Stewart AL, Hays RD, Ware JE. The MOS short-form general health survey. Med Care 1988;26:724-35.
7. Michaud K, Wolfe F. The development of a rheumatic disease research comorbidity index for use in outpatients with RA, OA, SLE and fibromyalgia (FMS) [abstract]. Arthritis Rheum 2007;Suppl 56:S596.
8. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007;21:885-906.
9. Fries JF, Spitz PW, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
10. Wolfe F. A reappraisal of HAQ disability in rheumatoid arthritis. Arthritis Rheum 2000;43:2751-61.
11. Wolfe F, Michaud K, Pincus T. A composite disease activity scale for clinical practice, observational studies and clinical trials: the Patient Activity Scale (PAS/PAS-II). J Rheumatol 2005;32:2410-5.
12. Wolfe F. Pain extent and diagnosis: development and validation of the regional pain scale in 12,799 patients with rheumatic disease. J Rheumatol 2003;30:369-78.
13. Wolfe F, Rasker JJ. The Symptom Intensity Scale, fibromyalgia, and the meaning of fibromyalgia-like symptoms. J Rheumatol 2006;33:2291-9.
14. McBeth J, Silman AJ. The role of psychiatric disorders in fibromyalgia. Curr Rheumatol Rep 2001;3:157-64.
15. Kassam A, Patten SB. Major depression, fibromyalgia and labour force participation: a population-based cross-sectional study. BMC Musculoskelet Disord 2006;7:4.
16. Hybels CF, Blazer DG, Pieper CF. Toward a threshold for subthreshold depression: an analysis of correlates of depression by severity of symptoms using data from an elderly community sample. Gerontologist 2001;41:357-65.
17. Lyness JM, Heo M, Datto CJ, et al. Outcomes of minor and subsyndromal depression among elderly patients in primary care settings. Ann Intern Med 2006;144:496-504.
18. Hidding A, Vansanten M, Deklerk E, et al. Comparison between self-report measures and clinical observations of functional disability in ankylosing spondylitis, rheumatoid arthritis and fibromyalgia. J Rheumatol 1994;21:818-23.
19. Wolfe F, Hawley DJ. Evidence of disordered symptom appraisal in fibromyalgia: Increased rates of reported comorbidity and comorbidity severity. Clin Exp Rheumatol 1999;17:297-303.
20. Arnold LM, Hudson JI, Hess EV, et al. Family study of fibromyalgia. Arthritis Rheum 2004;50:944-52.
21. Raphael KG, Janal MN, Nayak S, Schwartz JE, Gallagher RM. Familial aggregation of depression in fibromyalgia: a community-based test of alternate hypotheses. Pain 2004;110:449-60.
22. Kersh BC, Bradley LA, Alarcon GS, et al. Psychosocial and health status variables independently predict health care seeking in fibromyalgia. Arthritis Rheum 2001;45:362-71.
23. Wessely S, Hotopf M. Is fibromyalgia a distinct clinical entity? Historical and epidemiological evidence. Baillieres Best Pract Res Clin Rheumatol 1999;13:427-36.

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2009. All rights reserved.

Downloaded on April 15, 2024 from www.jrheum.org