Chronic Conditions and Health Problems in Rheumatic Diseases: Comparisons with Rheumatoid Arthritis, Noninflammatory Rheumatic Disorders, Systemic Lupus Erythematosus, and Fibromyalgia

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ABSTRACT. ***Objectives.*** To describe and compare the prevalence of lifetime and current self-reported comorbidity and associated quality of life in 4 rheumatic diseases, and to investigate comorbid conditions in light of the overlap between the index condition and comorbid conditions (CC), and in the context of symptom-type diagnoses.

Methods. We studied comorbidity in 11,704 patients with fibromyalgia (FM), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and noninflammatory rheumatic disorders (NIRD). Patients completed semiannual self-reports relating to 22 present and past illnesses and completed the EuroQol (EQ-5D) utility index.

Results. CC were most common in FM, followed by SLE. FM comorbidity was dominated by depression, mental illness, and symptom-type comorbidity (e.g., gastrointestinal and genitourinary disorders). In SLE, there were substantial increases in hypertension, depression, cataract, fractures, and cardiovascular and cerebrovascular, neurologic, lung, gall bladder and endocrine disorders compared with RA. Any current CC reduced the EQ-5D utility by 0.08 to 0.16 units. The lowest EQ-5D score was noted for current psychiatric illness (0.55) and current depression (0.60).

Conclusion. Four patterns of comorbidity emerged: that associated with aging; that associated with aging but enhanced by the index condition, as in SLE and cardiovascular disease; comorbidity that is part of the symptoms complex of the index condition; and CC that represent lifetime traits or manifestations of the underlying illness. Depression was the most strongly associated correlate of EQ-5D quality of life, and current depression was present in about 15% of patients with RA or NIRD and 34% to 39% of those with SLE and FM. (J Rheumatol First Release January 15 2010; doi:10.3899/jrheum.090781)

Key Indexing Terms:
COMORBIDITY HEALTH PROBLEMS SYSTEMIC LUPUS ERYTHEMATOSUS
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Comorbidity is a signal issue in the care of patients with rheumatic diseases and is equally important in rheumatic disease research. Comorbidity represents the burden carried by the patient, and its presence parallels reduction in quality of life and predicts future utilization of services, additional comorbidity, and mortality[1]. However, defining, ascertaining, and interpreting comorbidity in the outpatient setting is not without problems.

The classic definition of a comorbid condition is a medical condition other than the primary disease itself[2]. A comorbid condition can be unrelated to the primary or index disease, as in breast cancer and rheumatoid arthritis (RA), or can be related to it in a series of causal pathways[3]. In causal models, the index disease or its treatment or consequences increase the risk of the comorbid condition. In addition to this pathway, a common risk factor, for example smoking, can also increase the risk for the index disease as well as the comorbid condition, as in the case of RA and lung cancer. Hudson and colleagues recently pointed out that what may be perceived as a comorbid condition may, in fact, be a manifestation of the index condition[4], as in the case of lupus and renal disease. However, this partitioning and consequent exclusion is problematic when applied to less certain associations, such as RA or systemic lupus erythematosus (SLE, or lupus) and cardiovascular (CV) or cerebrovascular dis-

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ease. For simplicity, we consider all diseases as comorbid, but acknowledge the correctness of excluding manifestations of the index condition, and suggest that readers interpret comorbidity data in light of this distinction.

A second problem in understanding and describing comorbidity is deciding what is a comorbid condition or a comorbid disease. Consider the problem of allergies, asthma, gastrointestinal problems, neurological symptoms, and depression. These problems become a "disease" or a "condition" when they rise to a sufficient level of severity and/or frequency to be identified as a problem by the patient; it would be expected that different patients would have different thresholds for reporting. When health problems such as these are included, comorbid conditions will describe a spectrum that ranges from symptoms, for example allergies, to serious illnesses associated with structural damage, for example myocardial infarction (MI). This problem extends, too, to an index condition such as fibromyalgia (FM), which does not meet the classic definition of disease[5-7].

In addition to the problems of what comorbid means and when symptoms become diseases, a patient's self-report of comorbidity is subject to classification error. But even that is not always clear. Suppose a patient who has had an endoscopic diagnosis of an ulcer begins to have recurrent symptoms. The patient's physician treats the ulcer with antiulcer therapy but does not repeat the endoscopy. Is the patient correct to call the symptoms an ulcer, or correct to not call them an ulcer?

Finally, there is a time component to comorbidity reports that can be important. Conditions may be current or may have occurred in the past. A previous MI or malignancy is medically important to future health, yet may not be present now. However, previous gall bladder disease or cataract may not be medically important. Therefore, comorbidity should have a time component, current or past (ever), lest information be lost.

In our study we describe the prevalence of lifetime and current self-reported comorbidities, and compare comorbidity prevalence and associated quality of life in 4 rheumatic diseases: FM, SLE, RA, and noninflammatory rheumatic disorders (NIRD). Further, we investigate comorbid conditions in light of the overlap between the index condition and the comorbid condition, and in the context of symptom-type diagnoses. We also investigate the use of a comorbidity index we have designed[3]. In contrast to other indices designed to extract data from medical records, the index we describe is used for self-report questionnaires. Both the Charlson Comorbidity Index[8] and the Index of Coexistent Diseases[9] are effective in predicting mortality based on extraction of data from medical records[10]. However, neither of these assessments is designed for self-report, neither includes depression as a comorbid condition, and the Charlson Index omits hypertension.

MATERIALS AND METHODS

Participants. This report concerns 1316 patients with SLE, 2733 with fibromyalgia (FM), 13,722 with RA, and 3623 with NIRD who were participants in the National Data Bank for Rheumatic Diseases (NDB) longitudinal study of rheumatic disease outcomes. Participants in the NDB are generally enrolled from the practices of US rheumatologists and followed longitudinally with semiannual, detailed, 28-page questionnaires, as described[11,12]. Questionnaires were administered by the Internet or by paper questionnaires, depending on the participants' preferences. In this report we analyzed a randomly selected observation from each patient's pool of longitudinal data.

Patients were enrolled continuously beginning in 1999 and ending in July 2008. Rheumatic disease diagnoses were made or confirmed by the patient's rheumatologist. NIRD included diagnoses such as osteoarthritis, back pain syndromes, tendonitis, etc., excluding FM. Patients with SLE were enrolled largely by rheumatologist referral, but also by self-referral after confirmation of the diagnosis of SLE by the patient's rheumatologist[13]. Patients with a physician-confirmed overlap diagnosis of SLE and FM (7.2%) and SLE and RA (13.1%) were assigned to the SLE category. Sensitivity analyses showed that this assignment did not change study results. Patients with RA in the NDB who were enrolled as part of pharmaceutical study registries were excluded from the study so as not to bias the study with more severe patients.

Study variables. Demographic variables included age, sex, education level, ethnicity, and household income.

To determine self-reported comorbidities, we inquired about 22 "health problems," asking patients to indicate if they have the problem "now" and/or "in the past." We then classified these comorbidities as present now or "ever," and we made use of previously collected longitudinal data to aid in the "ever" designation. The conditions inquired about (exact text from the questionnaire) are high blood pressure, heart attack, other heart condition, stroke, depression, mental illness, diabetes, cancer, alcohol or drug problem, kidney problem, lung problem, cataract, asthma, severe allergies, liver problem, gall bladder problem, ulcers, other stomach problem, neurological problem (like seizures, Parkinson's disease, multiple sclerosis, etc.), fractures of the spine/hip/leg, thyroid or endocrine disorder, problems with prostate (men) or uterus, ovaries, etc. (women). We also made several summary variables by combining the above variables (Tables 1 and 2). All Psychiatric combines depression and mental illness; All GI (gastrointestinal) combines GI ulcer, liver, gall bladder, and other stomach; All CV combines MI and other CV disorders; All Lung combines asthma and lung problems; and All Endocrine combines diabetes, thyroid, and endocrine disorders.

We also used these comorbidity variables to compute a composite-derived comorbidity index (range 0–9) composed of 11 present or past comorbid conditions, including pulmonary disorders, MI, other CV disorders, stroke, hypertension, diabetes, spine/hip/leg fracture, depression, GI ulcer, other GI disorders, and cancer[3,14]. The formula is:

Comorbidity index = (2 * (pulmonarynow or pulmonarypast)),
+ 2 if (MInow or MIpast) or (otherCVnow or otherCVpast) or
(CVallnow or CVallpast), plus 1 for each of the following conditions:
(hypertensionnow or hypertensionpast), diabetesnow, (fracturenow
or fracturepast), (depressionnow or depressionpast), (ulcernow or
ulcerpast), (ALLGInow or ALLGIpast), or cancernow

We assessed quality of life using the EuroQol utility index (EQ-5D). The EQ-5D is a 5-item questionnaire that assesses function (3 questions), mood (1 question), and pain (1 question)[15]. Scoring was accomplished using US tariffs (weights)[16,17]. US and European scores are not interchangeable, with US scores being about 0.11 units greater[18]. The EQ-5D ranges from –0.11 to 1. In general, the results may be roughly interpreted as 1 = perfect health, 0 = death, and < 0 representing states worse than death. The EQ-5D was first added to the NDB questionnaire in July 2002

Table 1. Lifetime comorbidity in FM, SLE, RA, and NIRD (continued overleaf).

Condition, Crude Rate (%)	Adjusted Rate (%)	Diagnosis	Condition, Crude Rate (%)	Adjusted Rate (%)
Hypertension			MI	
47.5	24.8 (23.5, 26.1)	RA	8.1	3.9 (3.6, 4.2)
49.5	27.0 (24.4, 29.5)	FM	6.0	4.1 (2.9, 5.3)
55.7**	41.6 (36.5, 46.7)	SLE	7.7*	7.4 (4.6, 10.1)
58.6	30.8 (27.1, 34.5)	NIRD	9.0	3.3 (2.7, 3.9)
CV (other)			Stroke	
18.8	9.5 (8.9, 10.0)	RA	5.8	2.6 (2.3, 2.8)
23.9*	16.0 (14.1, 17.9)	FM	6.4	4.3 (2.8, 5.9)
29.9**	23.2 (18.5, 27.8)	SLE	11.6***	7.5 (5.3, 9.7)
23.1	9.3 (7.5, 11.2)	NIRD	6.3	3.5 (2.1, 4.8)
Depression			Mental illness	
34.4	26.8 (24.2, 29.5)	RA	3.1	2.9 (2.0, 3.8)
67.6***	45.4 (42.8, 47.9)	FM	9.0**	11.9 (9.7, 14.0)
56.9*	33.5 (28.7, 38.2)	SLE	6.8	3.8 (1.8, 5.7)
33.8	27.0 (23.6, 30.5)	NIRD	3.8	3.9 (2.3, 5.5)
Diabetes			Cancer	
11.4	5.9 (5.5, 6.3)	RA	14.7	6.0 (5.6, 6.4)
14.2	9.2 (7.1, 11.3)	FM	14.1	6.7 (5.6, 7.8)
13.8*	8.7 (6.5, 10.8)	SLE	11.6	7.1 (5.0, 9.2)
13.2	6.8 (5.0, 8.7)	NIRD	20.6	6.9 (6.0, 7.7)
Alcohol/drug			Renal	
4.1	4.3 (3.2, 5.3)	RA	11.7	7.1 (6.3, 7.9)
6.1*	4.3 (2.8, 5.8)	FM	16.2*	10.4 (8.5, 12.3)
5.1	3.2 (2.0, 4.4)	SLE	35.3***	30.4 (26.0, 34.9)
3.6	3.1 (2.1, 4.0)	NIRD	12.2	7.7 (5.2, 10.1)
Lung			Cataract	
15.8	8.3 (7.5, 9.1)	RA	27.0	9.9 (9.6, 10.3)
19.1	10.9 (8.9, 12.9)	FM	19.8	9.1 (7.9, 10.2)
30.7**	22.2 (17.2, 27.2)	SLE	20.9**	13.2 (10.3, 16.2)
12.5	7.7 (5.0, 10.3)	NIRD	34.2	9.0 (7.7, 10.3)
Asthma			Severe allergies	
16.6	15.9 (13.3, 18.5)	RA	20.7	15.5 (13.2, 17.9)
30.8*	22.5 (20.1, 25.0)	FM	41.2**	23.3 (20.9, 25.7)
25.4	14.0 (10.4, 17.5)	SLE	30.4	21.3 (16.7, 26.0)
17.3	15.6 (12.0, 19.1)	NIRD	24.2	19.2 (16.0, 22.5)
Liver			Gall bladder	
7.0	8.8 (7.7, 9.9)	RA	19.8	8.8 (8.1, 9.6)
8.8	6.7 (4.9, 8.5)	FM	32.6*	14.1 (12.2, 16.0)
13.4	6.4 (5.0, 7.8)	SLE	25.2*	15.8 (11.5, 20.1)
6.0	3.8 (2.5, 5.2)	NIRD	24.3	11.1 (8.8, 13.4)
GI ulcer			Other stomach	
19.9	14.0 (11.6, 16.4)	RA	30.2	29.7 (27.1, 32.4)
26.5*	16.6 (14.3, 19.0)	FM	54.0**	36.3 (34.0, 0.6)
21.8	13.4 (9.7, 17.1)	SLE	42.1	26.2 (21.9, 30.6)
19.8	12.2 (9.5, 14.8)	NIRD	31.1	18.5 (15.0, 22.0)
Neurologic			Fracture	
5.0	3.5 (2.6, 4.3)	RA	15.1	8.9 (7.8, 9.9)
10.7**	14.0 (12.4, 15.5)	FM	16.7	9.5 (7.8, 11.3)
19.4***	16.7 (11.8, 21.7)	SLE	18.5*	14.2 (10.0, 18.4)
5.5	4.6 (2.9, 6.3)	NIRD	18.1	10.3 (8.1, 12.5)
Thyroid endocrine			GU	
22.3	14.2 (13.4, 14.9)	RA	30.3	15.2 (14.2, 16.3)
?	12.6 (11.1, 14.1)	FM	48.5**	21.5 (19.7, 23.3)
?	16.3 (12.4, 20.1)	SLE	37.4*	18.7 (14.9, 22.4)
26.0	9.1 (8.0, 10.2)	NIRD	37.8	18.9 (16.4, 21.5)
GI (all)			Endocrine (all)	
49.9	42.4 (39.6, 45.1)	RA	30.1	18.3 (17.4, 19.2)
72.1**	45.9 (43.6, 48.2)	FM	39.7*	18.8 (16.5, 21.1)
61.3*	38.0 (33.0, 43.1)	SLE	37.6*	22.7 (18.4, 27.0)
52.6	30.4 (26.6, 34.2)	NIRD	34.8	14.3 (12.2, 16.3)

Table 1. Continued.

Condition, Crude Rate (%)	Adjusted Rate (%)	Diagnosis	Condition, Crude Rate (%)	Adjusted Rate (%)
Psychiatric (all)			CV (all)	
36.0	28.2 (25.5, 30.9)	RA	22.4	11.2 (10.7, 11.8)
68.1***	46.7 (44.2, 49.1)	FM	25.7*	17.8 (15.8, 19.8)
57.7*	34.0 (29.2, 38.7)	SLE	32.1**	26.5 (21.5, 31.5)
35.5	27.9 (24.4, 31.4)	NIRD	26.7	10.5 (8.7, 12.4)
Lung (all)				
25.5	20.2 (17.5, 22.8)			
37.1 *	26.0 (23.5, 28.6)			
42.1**	28.4 (23.0, 33.7)			
23.2	19.8 (16.1, 23.5)			

* OR 1.50–1.99; ** OR 2.00–2.99; *** OR 3.00 for each group compared with RA. FM: fibromyalgia; RA: rheumatoid arthritis; NIRD: noninflammatory rheumatic disorders; CV: cardiovascular; MI: myocardial infarction; GI: gastrointestinal; GU: genitourinary disorder.

and was therefore not available to all study participants. It was used by participants as follows: FM, 1686; SLE, 1231; RA, 7008; and NIRD, 1779.

Statistical methods. Adjusted rates of present and ever comorbid condition are presented per 100 patients (%), adjusted to the age and sex of the estimated 2004 US population. We tested for differences among groups for current and ever comorbid conditions by logistic regression using RA as the comparison group, adjusting for 42 five-year age and sex groups, and clustering on quintiles of databank followup time.

Crude rates (Tables 1 and 2) were analyzed by logistic regression, adjusted to the age and sex of the study sample. Because of the large sample size, small differences are statistically but not clinically significant. We identify differences in Tables 1 and 2 with an EuroQolOR of 1.50-1.99 as *, 2.00-2.99 as **, and ≥ 3.00 as ***.

The ability of individual comorbid conditions to predict EQ-5D scores was analyzed with the area under the receiver operating characteristic curve (AUC; Harrell's c). Data were analyzed using Stata (Stata, College Station, TX, USA) version 10.1. Statistical significance was set at the 0.05 level, and all tests were 2-tailed.

RESULTS

Demographics. The median age of participants was FM, 55.6 years; SLE, 49.9; RA, 61.2; and NIRD, 61.5 years; and the percentage who were men was FM, 4.7%; SLE, 6.0%; RA, 23.0%; and NIRD, 20.9%. The percentage of non-Hispanic whites was FM, 97.4%; SLE, 89.9%; RA, 95.5%; and NIRD, 96.8%. Overall, 7.7% did not graduate from high school. The highest level of educational attainment was high school in 38.2%, post high school without a college degree, 25.8%, and college graduate, 28.2%.

Prevalence of lifetime and current comorbidity. Tables 1 and 2, in columns 2 and 5, display the prevalence of comorbid conditions adjusted to the estimated age and sex distribution of the 2004 US population. Columns 1 and 4 show the crude (unadjusted) prevalence, and asterisks indicate the level of the OR compared with RA for the crude prevalence after adjustment to the mean age and sex in the overall cohort.

To understand comorbidity prevalence, we first present here data on RA, and next use RA as a comparison standard to understand whether FM, SLE, or NIRD has a higher or lower prevalence. Considering crude and adjusted percentages in RA, the highest prevalence of lifetime comorbidity (Table 1) was found for hypertension (47.5%), any GI problem (42.4%), any psychiatric problem (36.0%), depression (34.4%), genitourinary (GU) problems (30.3%), endocrine problems (30.3%), and cataract (27.0%). The percentage of patients with current problems is, expectedly, much less. The most common problems in RA are hypertension (32.5%), any endocrine problem (20.3%), any psychiatric problem (15.9%), any GI problem (15.4%), depression (15.5%), cataract (9.7%), and diabetes (9.1%).

Among problems ordinarily considered to be usually serious and associated with organ damage, the crude lifetime prevalence in RA and NIRD was cancer, 14.7%–20.6%; MI, 8.1%–9.0%; and stroke, 5.8%–6.3%. However, comorbidity prevalence is often a function of age (Figure 1). Results adjusted for US population age and sex for the above variables were cancer, 6.0%–6.9%, MI, 3.9%–3.3%; and stroke, 2.6%–3.5%.

Comparative comorbidity. We used logistic regression to evaluate differences in reported comorbidity for FM, SLE, and NIRD compared with RA. As the large sample sizes result in most differences being statistically significant, we concentrated on significant differences with EuroQolan OR ≥ 1.5 and ≤ 0.66 compared with RA. No differences between RA and NIRD reach an OR ≥ 1.5 or ≤ 0.66. However, major prevalence differences are noted between patients with RA and those with SLE and FM, as shown in Tables 1 and 2.

Two patterns of increased comorbidity emerge in Tables 1 and 2. There is an increase in MI, stroke, all CV diseases, hypertension, pulmonary, and renal and neurologic disease in SLE, as well as an increase in diabetes, fracture, cataract, and GI disease. In FM, 2 group patterns emerge, the first being depression, mental illness, and drug or alcohol problems (psychological issues). The second pattern includes symptom and symptom interpretation-related illnesses, such as asthma, allergies, GI ulcer, GI symptoms, neurologic, and GU symptoms. Of the 27 health symptom categories in Tables 1 and 2, patients with FM reported more conditions

Table 2. Current comorbidity in FM, SLE, RA, and NIRD (continued overleaf).

Condition, Crude Rate (%)	Adjusted Rate (%)	Diagnosis	Condition, Crude Rate (%)	Adjusted Rate (%)
Hypertension			MI	
32.5	15.9 (14.9, 16.8)	RA	0.9	0.5 (0.4, 0.6)
35.1	18.8 (16.4, 21.2)	FM	0.7	0.3 (0.1, 0.6)
37.4*	25.2 (20.6, 29.8)	SLE	1.4**	2.9 (0.5, 5.4)
41.6	20.3 (17.4, 23.1)	NIRD	1.2	0.4 (0.2, 0.5)
CV (other)			Stroke	
7.9	3.7 (3.3, 4.0)	RA	1.0	0.4 (0.3, 0.5)
11.8	9.8 (8.3, 11.3)	FM	1.0	0.5 (0.2, 0.7)
12.0**	8.4 (6.1, 10.7)	SLE	1.4**	1.4 (0.0, 2.9)
10.7	4.0 (2.7, 5.3)	NIRD	0.7	0.2 (0.1, 0.3)
Depression			Mental illness	
15.5	13.1 (10.8, 15.4)	RA	0.9	1.1 (0.3, 1.8)
38.6**	27.9 (25.5, 30.3)	FM	4.6***	5.1 (3.3, 6.9)
33.8**	20.8 (16.9, 24.6)	SLE	2.1*	2.0 (0.1, 3.8)
15.3	12.0 (9.8, 14.1)	NIRD	1.3**	1.5 (0.8, 2.2)
Diabetes			Cancer	
9.1	4.5 (4.2, 4.9)	RA	2.1	0.9 (0.7, 1.0)
10.6	7.0 (5.1, 8.9)	FM	1.7	0.9 (0.4, 1.3)
9.1	6.4 (4.3, 8.4)	SLE	1.4	1.1 (0.3, 1.8)
11.0	5.6 (3.8, 7.4)	NIRD	3.3	1.2 (0.9, 1.5)
Alcohol/drug			Renal	
0.3	0.4 (0.2, 0.5)	RA	2.6	1.6 (1.3, 1.9)
0.4	0.1 (0.0, 0.2)	FM	4.1*	2.8 (1.9, 3.7)
0.5	0.3 (0.0, 0.5)	SLE	13.9***	11.8 (8.1, 15.5)
0.3	0.3 (0.0, 0.6)	NIRD	3.2	2.0 (0.8, 3.1)
Lung			Cataract	
7.0	3.7 (3.0, 4.4)	RA	9.7	3.5 (3.3, 3.8)
7.9	5.0 (3.6, 6.3)	FM	8.5	3.6 (2.6, 4.5)
12.2**	8.1 (5.7, 10.4)	SLE	9.6*	7.0 (4.2, 9.8)
5.5	4.9 (2.3, 7.5)	NIRD	11.1	2.5 (2.3, 2.8)
Asthma			Severe allergies	
7.9	8.8 (6.4, 11.2)	RA	8.0	7.7 (5.4, 10.0)
15.9*	10.7 (8.6, 12.8)	FM	21.0**	13.4 (11.3, 15.5)
13.4*	6.8 (4.1, 9.5)	SLE	14.7*	8.2 (5.8, 10.6)
8.2	9.2 (5.8, 12.6)	NIRD	9.9	9.6 (6.6, 12.6)
Liver			Gall bladder	
1.7	1.5 (0.7, 2.3)	RA	1.2	0.7 (0.5, 0.8)
2.7	2.5 (1.3, 3.8)	FM	1.9	0.8 (0.4, 1.1)
3.6*	1.2 (0.8, 1.5)	SLE	2.2*	1.0 (0.5, 1.4)
1.2	0.8 (0.4, 1.3)	NIRD	1.6	0.9 (0.5, 1.2)
GI ulcer			Other stomach	
2.7	3.1 (1.1, 5.1)	RA	11.8	10.5 (8.0, 12.9)
4.4	2.7 (1.5, 3.9)	FM	29.1**	22.4 (19.8, 24.9)
3.9	2.7 (0.8, 4.5)	SLE	21.2*	15.0 (11.6, 18.4)
2.0	1.9 (0.6, 3.3)	NIRD	13.3	9.9 (6.8, 13.1)
Neurologic			Fracture	
1.9	1.2 (0.9, 1.5)	RA	2.0	1.1 (0.9, 1.3)
5.2**	7.4 (6.1, 8.7)	FM	2.5	1.3 (0.7, 1.9)
7.8***	9.3 (5.0, 13.7)	SLE	2.2	1.1 (0.4, 1.8)
2.3	2.3 (0.8, 3.8)	NIRD	2.0	0.9 (0.5, 1.13)
Thyroid endocrine			GU	
12.9	9.9 (9.2, 10.6)	RA	3.9	3.3 (2.5, 4.2)
*20.5	7.9 (6.7, 9.1)	FM	5.1**	4.9 (3.7, 6.0)
*18.7	9.8 (7.0, 12.7)	SLE	5.6*	5.6 (2.9, 8.3)
14.3	5.0 (4.1, 5.9)	NIRD	4.9	5.4 (3.2, 7.6)
GI (all			Endocrine (all)	
15.4	14.1 (11.6, 16.7)	RA	20.3	13.7 (12.9, 14.5)
33.8**	24.6 (22.0, 27.2)	FM	28.1*	13.4 (11.4, 15.5)
27.0*	17.2 (13.8, 20.6)	SLE	25.5*	15.1 (11.7, 18.5)
16.8	12.8 (9.3, 16.2)	NIRD	22.9	9.7 (7.7, 11.7)

Table 2. Continued.

Condition, Crude Rate (%)	Adjusted Rate (%)	Diagnosis	Condition, Crude Rate (%)	Adjusted Rate (%)
Psychiatric (all)			CV (all)	
15.9	13.4 (11.2, 15.7)	RA	8.6	4.0 (3.6, 4.3)
39.1**	28.1 (25.7, 30.5)	FM	12.1*	10.0 (8.5, 11.5)
34.0**	20.8 (17.0, 24.7)	SLE	12.8**	10.9 (7.7, 14.2)
15.7	12.2 (10.0, 14.3)	NIRD	11.6	4.2 (2.9, 5.6)
Lung (all)				
12.2	10.8 (8.4, 13.1)			
19.0*	12.1 (10.0, 14.3)			
20.8*	12.9 (9.4, 16.4)			
11.2	12.3 (8.7, 15.8)			

* OR 1.50–1.99; ** OR 2.00–2.99; *** OR 3.00 for each group compared with RA. FM: fibromyalgia; RA: rheumatoid arthritis; NIRD: noninflammatory rheumatic disorders; CV: cardiovascular; MI: myocardial infarction; GI: gastrointestinal; GU: genitourinary disorder.

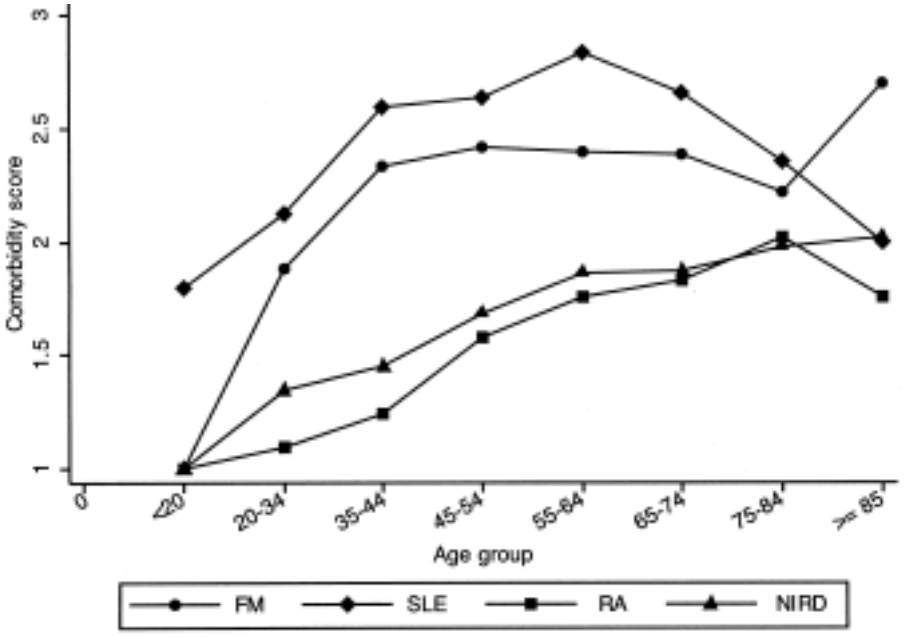

Figure 1. The relation of age to comorbidity score. Rheumatoid arthritis (RA) and noninflammatory rheumatic disorder (NIRD) scores increase with age, but fibromyalgia (FM) and systemic lupus erythematosus (SLE) scores are generally constant for ages 35 through 84 years.

than those with RA in 25 instances in Table 1, and 21 instances in Table 2, after adjusting for age and sex.

We investigated the increases in comorbidity in SLE and FM further using the summary comorbidity index. Age and sex-adjusted comorbidity index scores were 1.7 (95% CI 1.7–1.7) and 1.8 (95% CI 1.7–1.8) for RA and NIRD, respectively, and 2.4 (95% CI 2.4–2.5) and 2.7 (95% CI 2.7–2.8) for FM and SLE, respectively. In addition, Figure 1 shows that there is a smooth increase in the index with age in participants with RA and NIRD. However, the level of the comorbidity index remains about the same in ages 35–84 years in those with FM and SLE.

As the comorbidity index is a summary measure, we studied individual age–comorbidity relationships, and identified 4 patterns. Figure 2, upper left panel, demonstrates a type of comorbidity that increases with age, has little relationship with the underlying rheumatic disease, and is not part of the symptom or manifestation of the underlying disease. Figure 2, upper right, is similar to upper left. However, the increase in MI prevalence in SLE indicates the strong early-in-life relation between SLE and MI. The pattern of Figure 2, lower left, indicates a condition in which the "comorbidity" is part of the symptoms or manifestations of the underlying disease. Finally, Figure 2, lower right panel, describes symptoms or comorbid conditions that represent lifetime traits or manifestation of the underlying illness. The fall-off in this figure with increasing age is an artifact of left-censoring (patients enrolled later in life). These data suggest

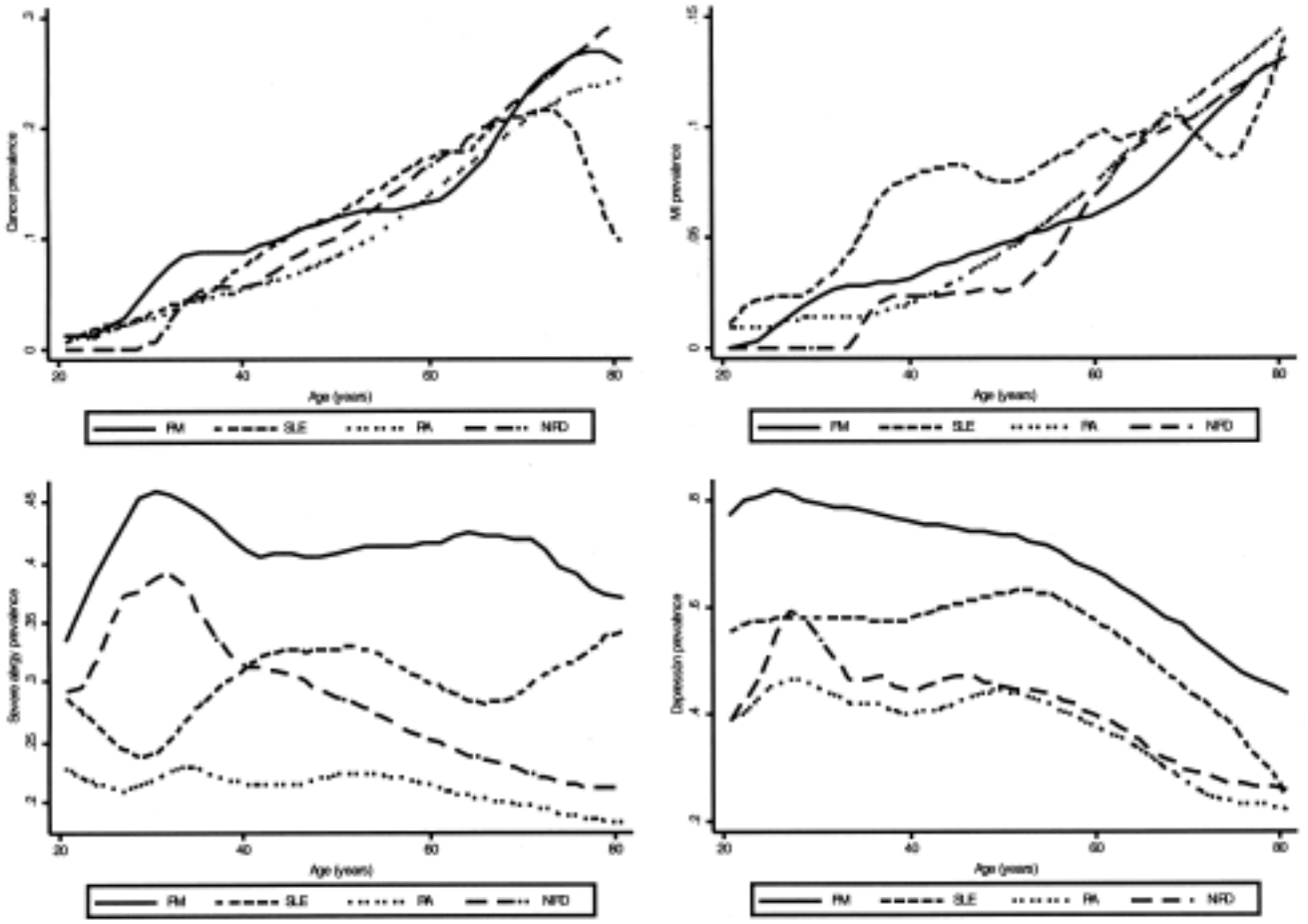

Figure 2. The relation of age to 4 different types of comorbid conditions. Top left, cancer (a condition that increases with age but has little relationship with the underlying rheumatic disease); top right, myocardial infarction (a condition that increases with age and is related to the underlying rheumatic disease); bottom left, severe allergies (a condition that is part of the symptoms or manifestations of the underlying disease); and bottom right panel depression (a condition that represents lifetime traits or manifestations of underlying disease). Y axis represents the proportion reporting the condition.

that comorbidity indices that combine comorbidities should not ordinarily be used across diseases.

Quality of life. To investigate the relation of comorbidity to quality of life, we examined EQ-5D scores for the 4 illnesses by categories of the comorbidity index. Patients with any current comorbid condition had an EQ-5D score that ranged from 0.08 to 0.16 units lower than those without a current comorbidity: FM, –0.13 (95% CI –0.16, –0.10); SLE, –0.16 (95% CI –0.19, –0.13); RA, –0.10 (95% CI –0.11, –0.09); and NIRD –0.08 (95% CI –0.10, –0.06). EQ-5D quality of life score decreased by about 0.04 units for each category (Figure 3). However, scores in FM are always about 0.1 units lower regardless of category.

Different comorbid conditions had variable effects on EQ-5D scores (Table 3). For ease of communication of differences, we present only scores in RA rather than for all 4 groups. Regardless of comorbid condition, current comorbidity always resulted in a lower EQ-5D score than lifetime comorbidity. Among current conditions, EuroQol psychiatric illness (0.55) and depression (0.60) had the most effect on EQ-5D (AUC of 0.745 and 0.747). At EQ-5D scores of 0.61–0.62 were fractures, neurological disorder, and gall bladder conditions (AUC 0.656–0.691). Eight conditions had scores of 0.64. There were fewer discrete levels of EQ-5D scores among lifetime comorbidities. However, depression, neurological disorders, and psychiatric disorder were ranked with the lowest EQ-5D score. The highest AUC was for depression (0.687), psychiatric disorder (0. 681), and GI ulcer (0.661).

DISCUSSION

In agreement with Hudson, *et al*[4], we note that not all coexistent conditions are comorbid. Not unexpectedly, patients with SLE had more renal disease than those with other rheumatic diseases (Tables 1 and 2). In addition, we found substantial increases in age and sex-adjusted current conditions, including EuroQol hypertension, depression, cataract, fractures, and CV and cerebrovascular, neurologic, lung, gall bladder, and endocrine disorders. Some of these increases are, at least in part, manifestations of the underlying illness.

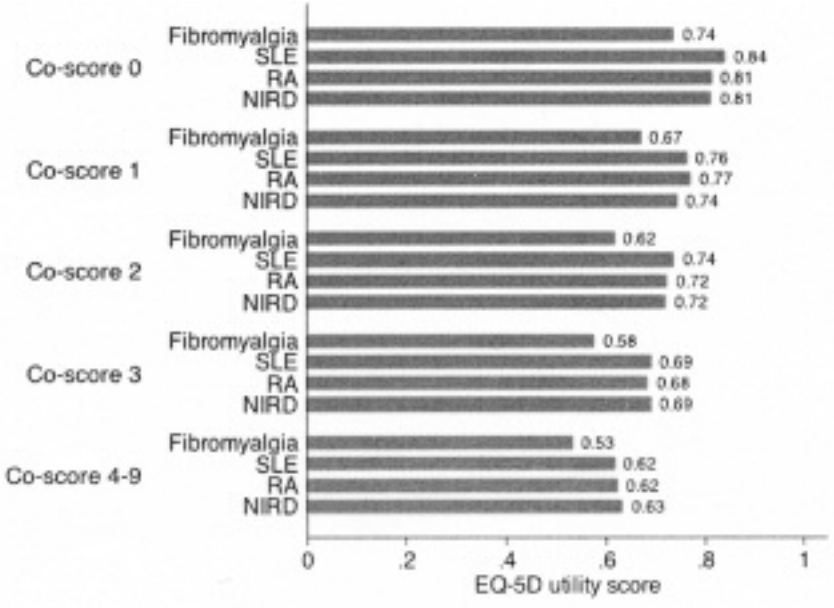

Figure 3. Relation between comorbidity index score (Co-score) and quality of life as measured by the EQ-5D utility score. SLE, rheumatoid arthritis (RA), and noninflammatory rheumatic disorder (NIRD) EQ-5D scores are generally similar at all levels of the comorbidity index and decline by about 0.04 for each increasing comorbidity index category. EQ-5D scores for fibromyalgia (FM) are about 0.1 unit lower at all levels of the comorbidity index.

The literature suggests that SLE is associated with increased CV and cerebrovascular risk[19,20], cancer[21], possibly thyroid disease[22,23], and with multiple organ system involvement as noted in the Systemic Lupus International Cooperating Clinics/American College of Rheumatology damage index[24]. In addition, FM and FM symptoms are common in SLE[13,25], and it also seems possible that increases in fractures, cataract, and GI ulcers could be related to corticosteroid therapy in SLE. Although the prevalence of comorbidity is high, our sample is not a random population sample or an inception cohort, and some of the observed increase might be due to selection bias.

FM also presents special problems. We agree with Wessely and Hotopf, who characterize FM as being "at the extreme end of the spectrum of polysymptomatic distress," and indicate that it overlaps with "...virtually every other medically unexplained syndrome, including tension headache, chemical sensitivity, irritable bowel syndrome, atypical chest pain, gynaecological syndromes, temporomandibular disorders, and mitral valve prolapse"[26], findings that are confirmed in the literature[27]. Therefore it is unclear whether these problems can be classified as being comorbid if they, in fact, help to define the syndrome. The associations noted above explain a large part of the comorbidity increases noted in Tables 1 and 2, including GI and GU disorders. FM is also associated with psychiatric comorbidity and other medically unexplained disorders[26,28,29], and in one report has been associated with increased cancer mortality[30].

We found 2 patterns of involvement in FM. The first set of conditions included depression, mental illness, and drug/alcohol problems (psychological issues). The second pattern included symptom and symptom interpretation-related illnesses, such as asthma, allergies, GI ulcer, GI symptoms, neurologic, and GU symptoms. As noted, of the 27 health symptom categories in Table 1 (lifetime comorbidity) and Table 2 (current comorbidity), patients with FM reported more conditions than those with RA in 25 instances in Table 1, and 21 instances in Table 2, after adjusting for age and sex.

The ascertainment of comorbidity in the self-report research setting is associated with additional problems. As noted, self-reported problems can become a "disease" or a "condition" when they rise to a sufficient level of severity and/or chronicity to be identified as a problem by the patient. In our study we noted an increase in reported conditions in patients diagnosed with FM compared with RA. The greatest increases (OR $\geq$ 1.5) came in 2 areas. The first included depression, mental illness, and drug and/or alcohol problems. The second area included symptom and symptom interpretation-related illnesses, such as asthma, allergies, GI ulcer, other GI, neurologic, and GU problems. GI, neurologic, and GU problems are part of the core FM symptom complex.

We reported similar results in a different set of clinic (not survey) patients more than a decade ago[31]. In that study, we also collected data on the importance that patients attached to their health problems. Compared with patients with RA

Table 3. EQ-5D quality of life utilities associated with lifetime and current comorbidities in rheumatoid arthritis (RA).

Lifetime Comorbidity	(+)	(–)	AUC(c)	Current Comorbidity	(+)	(–)	AUC(c)
Depression	0.67	0.78	0.687	Psychiatric	0.55	0.74	0.745
Neurological	0.67	0.74	0.591	Depression	0.60	0.77	0.747
Psychiatric disorder	0.67	0.78	0.681	Psychiatric disorder	0.60	0.77	0.732
Psychiatric	0.68	0.74	0.582	Fracture	0.61	0.74	0.676
Diabetes	0.68	0.75	0.590	Neurological	0.61	0.74	0.691
Pulmonary	0.68	0.75	0.601	Gall bladder	0.62	0.74	0.656
Fracture	0.68	0.75	0.602	Allergy	0.64	0.75	0.648
Myocardial infarction	0.69	0.74	0.560	Asthma	0.64	0.75	0.640
CVO	0.69	0.75	0.590	Stroke	0.64	0.74	0.663
Stroke	0.69	0.74	0.562	Liver	0.64	0.74	0.650
ETOH	0.69	0.74	0.559	Myocardial infarction	0.64	0.74	0.612
Renal	0.69	0.74	0.582	Pulmonary	0.64	0.74	0.650
Asthma	0.69	0.75	0.592	Ulcer	0.64	0.74	0.648
Allergy	0.69	0.75	0.600	Renal	0.64	0.74	0.645
Liver	0.69	0.74	0.576	GI	0.65	0.75	0.647
Ulcer	0.69	0.75	0.661	Pulmonary disorder	0.65	0.75	0.642
GI	0.69	0.76	0.605	CVO	0.66	0.74	0.629
Heart disorder	0.69	0.75	0.589	GU	0.66	0.74	0.597
Pulmonary disorder	0.69	0.76	0.597	GI disorder	0.66	0.75	0.649
Gall bladder	0.70	0.75	0.571	Heart disorder	0.66	0.74	0.627
GI disorder	0.70	0.77	0.613	Diabetes	0.67	0.74	0.612
Hypertension	0.71	0.76	0.577	ETOH	0.68	0.74	0.606
Cataract	0.71	0.75	0.532	Cataract	0.69	0.74	0.566
GU	0.71	0.75	0.568	Hypertension	0.70	0.76	0.588
Endocrine disorder	0.71	0.75	0.553	Endocrine disorder	0.70	0.75	0.572
Thyroid-endocrine	0.73	0.74	0.524	Cancer	0.71	0.74	0.524
Cancer	0.74	0.74	0.497	Thyroid endocrine	0.72	0.74	0.542

7008 patients with RA, adjusted for age and sex. (+): EQ-5D score for those with comorbid condition. (–): EQ-5D score for those without the comorbid condition. AUC(c): area under receiver operating curve (Harrell's c); CV: cardiovascular; CVO: other cardiovascular; GI: gastrointestinal; GU: genitourinary disorder; ETOH: ethanol.

and osteoarthritis with the same health problems, patients with FM attached a greater "importance" to the health problem. Further, we noted that patients with FM reported more hypertension than other patients, but actually had less hypertension when blood pressure was measured in the clinic[31,32]. The current data on FM suggest an increased sensitivity to reporting symptoms, and further indicate the importance of examining cross-disease comorbid conditions cautiously and often, separately.

Figures 1 and 2 shed some light on comorbidity and the increases noted in SLE and FM. In those conditions, total comorbidity, as measured by the comorbidity index (Figure 1), is greater than in RA and NIRD over the entire time period. Figure 2 offers explanations, showing that different comorbid conditions have different relationships to age and illness duration. FM-type ("symptom") comorbid conditions appear very early and organ involvement somewhat later, and illnesses with weaker or nonexistent associations with the underlying disease appear last. These data illustrate the hazard of comparing total comorbidity across diseases with an index (Figure 1). Instead they address the usefulness of looking at individual comorbid conditions and to using indices only in single or similar diseases.

In addition to comparative comorbidity, the absolute levels of comorbidity are of interest. The literature indicates that the rate of comorbid conditions is increased in RA and osteoarthritis, and increases with time[1]. In addition, MI[12], stroke[33], certain cancers[34], and other disorders are more common in persons with RA[3,35]. We found that hypertension was present in about one-third of all patients, a finding of interest for those with SLE and RA where there is an independent risk of CV and cerebrovascular disease. Depression and psychiatric disease were important comorbidities. Current depression occurred in about 15% of patients with RA and NIRD and in 38.6-33.8% in patients with FM and SLE. It was the variable most strongly associated with substantially reduced quality of life as measured by the EQ-5D (Table 3). Lifetime depression was noted in one-third of patients with RA and NIRD, and in 57%–68% of patients with FM and SLE. As with current depression, it had the strongest correlation with EQ-5D quality of life (Table 3). Also important, multimorbidity is

associated with further decreases in quality of life[36], as we also noted.

It is perhaps useful to note that the levels of current and lifetime comorbidity differed substantially. The reporting of current CV disease and malignancies did not detect previous reports of these conditions. However, past cancers and prior CV disease may be of importance. Lifetime comorbidity, however, was less associated with EQ-5D scores, although depression and mental illness continued to be important correlates using lifetime reports.

This study has a number of limitations. It is not a random population sample or an inception cohort, and the prevalences noted here might be different from those in the underlying population. In addition, some of the comorbid conditions noted here are subject to patient's interpretation. However, in conditions such as FM, self-report defines the illness, and for conditions such as cancer and MI, NDB internal validation studies report concordance between medical records and event reports of about 94%.

Separate patterns of comorbidity are identified in patients with FM, SLE, and RA/NIRD. The patterns include the type of comorbid variables reported and their associations with age and disease duration. Comorbid conditions are most common in FM, followed by SLE. Hypertension and GI disorders are the most common current somatic illnesses, and depression the most common mental illness, with a current depression prevalence of about 15% in RA/NIRD and 34% to 39% in SLE and FM. Depression is the most strongly associated correlate of EQ-5D quality of life.

REFERENCES

1. Gabriel SE, Crowson CS, O'Fallon WM. Comorbidity in arthritis. J Rheumatol 1999;26:2475-9.
2. Kaplan MH, Feinstein AR. The importance of classifying initial co-morbidity in evaluating the outcome of diabetes mellitus. J Chronic Dis 1974;27:387-404.
3. Michaud K, Wolfe F. Comorbidities in rheumatoid arthritis. Best Pract Res Clin Rheumatol 2007;21:885-906.
4. Hudson M, Bernatsky S, Taillefer S, Fortin PR, Wither J, Baron M. Patients with systemic autoimmune diseases could not distinguish comorbidities from their index disease. J Clin Epidemiol 2008;61:654-62.
5. Wessely S. What do you think is a non-disease? Pros and cons of medicalisation. BMJ 2002;324:912.
6. Smith R. In search of "non-disease". BMJ 2002;324:883-5.
7. Morris DB. Illness and culture in the postmodern age. Berkeley and Los Angeles: University of California Press; 1998.
8. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
9. Miskulin DC, Athienites NV, Yan G, Martin AA, Ornt DB, Kusek JW, et al. Comorbidity assessment using the Index of Coexistent Diseases in a multicenter clinical trial. Kidney Int 2001;60:1498-510.
10. Gabriel SE, Crowson CS, O'Fallon WM. A comparison of two comorbidity instruments in arthritis. J Clin Epidemiol 1999;52:1137-42.
11. Wolfe F, Michaud K. A brief introduction to the National Data Bank for Rheumatic Diseases. Clin Exp Rheumatol 2005;23:S168-71.
12. Wolfe F, Michaud K. The risk of myocardial infarction and pharmacologic and nonpharmacologic myocardial infarction predictors in rheumatoid arthritis: A cohort and nested case-control analysis. Arthritis Rheum 2008;58:2612-21.
13. Wolfe F, Petri M, Alarcon GS, Goldman J, Chakravarty EF, Katz RS, et al. Fibromyalgia, systemic lupus erythematosus (SLE), and evaluation of SLE activity. J Rheumatol 2009;36:82-8.
14. 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.
15. EuroQol — a new facility for the measurement of health-related quality of life. The EuroQol Group. Health Policy 1990;16:199-208.
16. Luo N, Johnson JA, Shaw JW, Feeny D, Coons SJ. Self-reported health status of the general adult U.S. population as assessed by the EQ-5D and Health Utilities Index. Med Care 2005;43:1078-86.
17. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care 2005;43:203-20.
18. Johnson JA, Luo N, Shaw JW, Kind P, Coons SJ. Valuations of EQ-5D health states: are the United States and United Kingdom different? Med Care 2005;43:221-8.
19. Nossent J, Cikes N, Kiss E, Marchesoni A, Nassonova V, Mosca M, et al. Current causes of death in systemic lupus erythematosus in Europe, 2000–2004: relation to disease activity and damage accrual. Lupus 2007;16:309-17.
20. van Leuven SI, Franssen R, Kastelein JJ, Levi M, Stroes ES, Tak PP. Systemic inflammation as a risk factor for atherothrombosis. Rheumatology 2008;47:3-7.
21. Bernatsky S, Boivin JF, Joseph L, Manzi S, Ginzler E, Urowitz M, et al. Race/ethnicity and cancer occurrence in systemic lupus erythematosus. Arthritis Rheum 2005;53:781-4.
22. Pyne D, Isenberg DA. Autoimmune thyroid disease in systemic lupus erythematosus. Ann Rheum Dis 2002;61:70-2.
23. Mader R, Mishail S, Adawi M, Lavi I, Luboshitzky R. Thyroid dysfunction in patients with systemic lupus erythematosus (SLE): relation to disease activity. Clin Rheumatol 2007;26:1891-4.
24. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363-9.
25. Gladman DD, Urowitz MB, Gough J, MacKinnon A. Fibromyalgia is a major contributor to quality of life in lupus. J Rheumatol 1997;24:2145-8.
26. Wessely S, Hotopf M. Is fibromyalgia a distinct clinical entity? Historical and epidemiological evidence. Baillieres Best Pract Res Clin Rheumatol 1999;13:427-36.
27. 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. Amsterdam: Elsevier; 2008:555-70.
28. Hudson JI, Goldenberg DL, Pope HGJ, Keck PEJ, Schlesinger L. Comorbidity of fibromyalgia with medical and psychiatric disorders. Am J Med 1992;92:363-7.
29. Weir PT, Harlan GA, Nkoy FL, Jones SS, Hegmann KT, Gren LH, 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.
30. McBeth J, Silman AJ, Macfarlane GJ. Association of widespread body pain with an increased risk of cancer and reduced cancer survival: a prospective, population-based study. Arthritis Rheum

2003;48:1686-92.
31. 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.
32. Wolfe F, Anderson J, Harkness D, Bennett RM, Caro XJ, Goldenberg DL, et al. A prospective, longitudinal, multicenter study of service utilization and costs in fibromyalgia. Arthritis Rheum 1997;40:1560-70.
33. 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.
34. 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.
35. Mikuls TR, Saag KG. Comorbidity in rheumatoid arthritis. Rheum Dis Clin North Am 2001;27:283-303.
36. Perruccio AV, Power JD, Badley EM. The relative impact of 13 chronic conditions across three different outcomes. J Epidemiol Community Health 2007;61:1056-61.