Psychosocial Variables and Fatigue: A Longitudinal Study Comparing Individuals with Rheumatoid Arthritis and Healthy Controls

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ABSTRACT. *Objective.* In individuals with rheumatoid arthritis (RA) and healthy controls, at enrollment and one year later, we evaluated relationships between diverse psychosocial characteristics and fatigue in multivariate analyses.
Methods. Participants with RA and controls completed the Fatigue Severity Scale (FSS) at enrollment and again after one year. All participants also completed measures of depressive symptoms, anxiety, role satisfaction, social support, social stress, disability, physical activity, and sleep quality at enrollment.
Results. A total of 122 individuals with RA and 122 controls of similar age, sex, education, employment, and marital status were enrolled. Those with RA had more fatigue compared to controls (FSS scores 4.2 ± 1.2 vs 3.4 ± 1.1; $p < 0.0001$) (possible range 1–7, higher score = more fatigue). In cross-sectional multivariate regression analysis for the RA group, more fatigue was associated with more anxiety, more disability, less social support, and more social stress ($p \leq 0.03$ for each variable, $R^2 = 0.48$). In cross-sectional multivariate regression analysis for controls, more fatigue was associated with more depressive symptoms and more social stress ($p \leq 0.003$ for each variable, $R^2 = 0.31$). Repeat FSS scores at one year also were worse for the RA group (n = 91) compared to controls (n = 89) (4.1 ± 1.3 vs 3.2 ± 1.0; $p < 0.0001$). However, changes in scores from enrollment to followup were not markedly different within patients [0.21 for the RA group ($p = 0.05$) and 0.08 for controls ($p = 0.41$)]. Enrollment variables that were associated with worse fatigue at followup, based on longitudinal multivariate regression analysis, were less help at home, more anxiety, and more disability for the RA group ($p \leq 0.007$ for each variable), and more anxiety and less physical activity for controls ($p \leq 0.006$ for each variable).
Conclusion. Fatigue was relatively stable over time and was common in both the RA group and controls. In addition, fatigue was more closely associated with psychosocial factors in the RA group, and social stress was identified as a relatively unexplored potentially modifiable variable independently related to fatigue in RA. (First Release June 15 2006; J Rheumatol 2006;33:1496–502)

Key Indexing Terms:
RHEUMATOID ARTHRITIS   FATIGUE   HEALTHY CONTROLS
SOCIAL STRESS   LONGITUDINAL

Fatigue is a common and frequent symptom of rheumatoid arthritis (RA), occurring in 73%–100% of patients, and resulting in marked limitations in daily activities[1-4]. Despite its prevalence, the etiology of RA fatigue is not known, but it may be multifactorial and due to inflammation and tissue destruction[1]. In addition, demographic, psychosocial, and clinical characteristics affect RA fatigue. For example, pain, comorbidity, disability, multiple social roles, and low social support have been found to be associated with RA fatigue[1,5–10].

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Given that fatigue is relatively common in the general population, it is challenging to ascertain which aspects of fatigue are unique to RA. It is estimated that 18% of the healthy population and 24%–38% of individuals treated in primary care practices complain of substantial fatigue some of the time[11–14]. Despite its prevalence, the manifestations and sequelae of fatigue are among the least understood clinical issues in healthy individuals[15]. Many of the factors that cause "normal" fatigue (i.e., fatigue that is commonly experienced as part of daily life[11]) also contribute to RA fatigue and are predominantly psychosocial or lifestyle factors, such as depressive symptoms, anxiety, stress, and less physical activity[1,2,11-14,16]. Despite its prevalence, few studies have compared the impact of psychosocial and lifestyle factors on fatigue between persons with RA and controls. In addition, few investigations have studied patterns of fatigue over time and variables associated with fatigue in multivariate analyses. Such studies are necessary to better focus on the unique aspects of fatigue in RA in order to develop RA-specific interventions that will ameliorate this debilitating symptom[10].

Our objectives were to evaluate relationships between diverse psychosocial characteristics and fatigue in multivariate analyses, and to compare these relationships between individuals with RA and controls at enrollment and about one year later.

MATERIALS AND METHODS

Recruitment of participants. Subjects in this study were participants in a larger longitudinal observational study to compare employment issues between individuals with RA and controls[17]. Subjects with RA were identified from the office practices of rheumatologists at the Hospital for Special Surgery, New York City, and from the general internal medicine practices of physicians at Cornell Internal Medicine Associates, New York City. Patients were eligible if they were 18 years of age or older, were fluent in either English or Spanish, were currently working full-time or part-time for salary, and were considered by their physicians to have RA according to American College of Rheumatology (ACR) criteria[18]. Patients were contacted by telephone or in person when they came for routine office visits with their physicians and, if they agreed to participate, were enrolled at that time. Healthy controls, defined as individuals ≥ 18 years of age, were working full-time or part-time for salary, were fluent in English or Spanish, and did not have chronic comorbidity, and were identified by reviewing office records at Cornell Internal Medicine Associates. For this study, not having chronic comorbidity was defined as not having an illness requiring chronic medications and specific followup evaluations with physicians, as outlined in their medical records. Controls were recruited and enrolled when they came for office visits for routine examinations, for example, for a yearly examination, for influenza vaccination, or for other preventive medicine. All participants were enrolled from 1999 to 2000.

Information obtained at enrollment. At enrollment all participants completed a series of questionnaires including measures of fatigue and psychosocial and lifestyle characteristics. A broad array of characteristics were measured in order to reflect those variables currently associated with fatigue in healthy controls and those with chronic illnesses.

Fatigue Severity Scale (FSS). The FSS is a general fatigue scale measuring characteristics and consequences of fatigue during the preceding week, such as causing lower motivation. The FSS has been shown to be valid in healthy controls and in those with diverse chronic diseases, including rheumatic diseases such as systemic lupus erythematosus[19,20]. Respondents rate how strongly they agree or disagree with 9 statements on a 7-point scale. An overall mean score can be calculated, ranging from 1 to 7, with higher scores indicating more fatigue. A score ≥ 4 corresponds to fatigue in those with chronic diseases, and a decrease in score of 0.5 corresponds to a measurable clinical improvement in fatigue[19].

State-Trait Anxiety Inventory (STAI). The STAI is a valid and reliable 2-component scale measuring both a stable personality tendency toward anxiety (trait) and a transitory reaction to current situations (state)[21]. Each component is composed of 20 questions and generates a mean score ranging from 20 to 80, higher scores indicating more anxiety[22]. Participants completed the trait component at enrollment.

Geriatric Depression Scale (GDS). The GDS is a 30-item scale measuring psychological symptoms of depression[23]. Scores can range from 0 to 30, higher scores indicating more depressive symptoms. The GDS is valid and reliable, and has been used in younger adults[24]. It was chosen for this study because it measures only psychological symptoms, as opposed to somatic symptoms, which also can occur because of RA[25].

Duke Social Support and Stress Scale. The Duke scale is a valid and reliable 2-component scale measuring a respondent's perceived amount of emotional social support and social stress[26]. Each component is composed of 11 items and generates a score ranging from 0 to 100. A higher score on the support component indicates more support. A higher score on the stress component indicates more stress.

Paffenbarger Physical Activity and Exercise Index (PAEI). The PAEI is a widely used scale measuring energy expenditure in 3 domains: walking, climbing stairs, and exercise/sports[27]. Respondents indicate how much and how often they performed each activity during the past week. Responses are then converted into kilocalories per week and summed to generate an overall total.

Pittsburgh Sleep Quality Inventory (PSQI). The PSQI is a valid and reliable 19-item scale with 7 components measuring sleep quality[28]. A total composite score ranging from 0 to 21 can be calculated, with a score > 5 indicating poor sleep quality relative to clinical and laboratory measures.

Health Assessment Questionnaire (HAQ) Disability Index. The Disability Index is a component of the HAQ that has been used extensively in patients with rheumatic diseases[29]. The 20-item Disability Index measures function in common daily activities. An overall score can be calculated and can range from 0 (no difficulty) to 3 (unable to perform activities).

Participants also were asked whether they believed they had as much tangible support as they wanted at home during the past 4 weeks, with possible responses ranging from 1 (no, not at all) to 5 (yes, as much as I wanted). Role satisfaction was assessed by asking participants how satisfied they were with their role as spouse, parent, employee, and housekeeper. Questions were modeled after similar items used to measure role strain in patients with systemic lupus erythematosus[30]. Possible responses for each question and an overall composite score can range from 1 to 5, higher scores indicating more dissatisfaction. Pain was assessed by asking participants how much bodily pain they had over the past week, with responses ranging from 1 (none) to 6 (very severe).

Demographic and medical information was obtained from participants and from chart review. Chronic medical conditions were recorded according to the Charlson Comorbidity Index, a well established index that accounts for the spectrum and severity of major conditions[31]. Results are reported from 0 (no comorbidity) to ≥ 4 (severe comorbidity). The comorbidity index was also administered to controls to record any conditions controls thought they might have that were not reported in the medical records. RA characteristics obtained from medical records included the number of ACR criteria fulfilled, current medications, and number and type of extraarticular manifestations associated with RA, specifically nodules, vasculitis, episcleritis/scleritis, anemia, and pleural and pericardial involvement[32].

Information obtained at followup. Roughly one year after enrollment participants were contacted either by telephone or in person when they came for office visits with their physicians. During these followup contacts, participants again completed the FSS.

Data analysis. Frequencies for ordinal and ranked data and means for continuous data were compared between the RA group and controls for all variables. To determine which variables were correlated with fatigue at enrollment, cross-sectional bivariate analyses were carried out with FSS scores and demographic, psychosocial, lifestyle, and clinical variables. Variables related to fatigue with a p value ≤ 0.05 were entered into multivariate regression models with fatigue as the dependent variable. Through a backward stepwise process, variables were then removed one at a time until the final model contained only variables that were related to fatigue with $p ≤ 0.05$[33]. Similar bivariate and multivariate analyses were carried out for the longitudinal analyses with followup FSS scores as the dependent variable and enrollment measurements as the independent variables. Comparisons of fatigue scores between and within groups were measured with t tests and paired t tests, respectively. Additional multivariate analyses were carried out with followup minus enrollment FSS scores as the dependent variable. All analyses were carried out in SAS[34].

This study was approved by the Institutional Review Board at the Hospital for Special Surgery and by the Committee on Human Rights in Research at Weill Medical College of Cornell University.

RESULTS

In total, 122 persons with RA and 122 controls were enrolled; enrollment characteristics are shown in Table 1. Both groups were comparable in age, sex, education, and marital status; 10% in both groups were Latino. All participants were currently employed, with over 70% in each group in profession-

al occupations. The RA group was more likely to have private health insurance compared to controls, who were mostly insured by health maintenance organizations. The number of social roles was comparable between groups, with 69% of those with RA and 63% of controls having 3 or more major social roles (spouse, parent, employee, housekeeper). Overall, both groups were satisfied with their performance in social roles, had low trait anxiety, and had few depressive symptoms. In addition, both groups had similar social support and social stress, but the RA group perceived less tangible support at home, and had more disability, more pain, worse sleep quality, and less physical activity compared to controls. All those with RA received at least one point on the Charlson Comorbidity Index for connective tissue disorder and 15% had an additional significant condition (scored ≥ 2); most controls (94%) had a score of zero (p < 0.0001) based on self-report. Mean duration of RA was 14 ± 10 years and 40% were taking corticosteroids, 49% methotrexate, and 29% etanercept; 81% met ≥ 4 ACR criteria for RA and 47% had extraarticular manifestations of RA.

Fatigue Severity Scale scores are shown in Table 2. The mean fatigue score at enrollment was worse for the RA group compared to controls. All those in the RA group and all but one control reported some fatigue. For the RA group, about 19% scored < 3 (least fatigue), 51% scored 3 to < 5, and 30% scored ≥ 5 (most fatigue). For controls, these values were 38%, 51%, and 11%, respectively. Those with RA scored worse on almost every FSS question compared to controls; in particular, they had more fatigue that interfered with physical

function (p = 0.004), that interfered with carrying out certain duties and responsibilities (p = 0.0008), and that caused frequent problems (p = 0.002).

Cross-sectional analysis. Associations between fatigue and demographic, psychosocial, lifestyle, and clinical variables were determined for each group separately. No relationships were found between fatigue and age, sex, and education in either group. Fatigue was associated, however, with multiple psychosocial and lifestyle characteristics in both groups, and also with measures of disease severity in those with RA. Cross-sectional bivariate relationships between enrollment variables and enrollment FSS scores are shown in Table 3. Variables that were related to FSS scores in bivariate analyses with p ≤ 0.05 were entered into multivariate models with FSS scores as the dependent variable. After backward stepwise elimination, the variables that remained associated with more fatigue were more trait anxiety (r = 0.55), more disability (r = 0.48), more social stress (r = 0.39), and less social support (r = 0.24) (p ≤ 0.03 for each variable). The cumulative variance (R^2) explained by this model was 0.48. Contributions to the cumulative variance from each variable were 0.30 for anxiety, 0.12 for disability, 0.04 for social stress, and 0.02 for social support. In the multivariate model for controls, more depressive symptoms (r = 0.51) and more social stress (r = 0.37) were the only 2 variables that remained significant in multivariate analysis (p ≤ 0.003 for each variable, cumulative variance R^2 = 0.31). Contributions to the cumulative variance from each variable were 0.26 for depressive symptoms and 0.05 for social stress. Thus, the variables considered in this

Table 1. Enrollment characteristics of participants with RA and controls.

Variables	RA Group, n = 122	Controls, n = 122	p
Age, yrs, mean ± SD	49 ± 12	49 ± 10	NS
Women, %	84	91	NS
White, %	71	60	NS
College graduate, %	75	70	NS
Married, %	50	39	NS
Employed as professional, %	73	71	NS
Insurance: self-pay, %	49	28	< 0.0001
Satisfaction with roles, mean ± SD[a]	1.9 ± 0.9	1.8 ± 0.8	NS
Geriatric Depression Scale score, mean ± SD[b]	6.0 ± 4.8	5.5 ± 5.3	NS
State-Trait Anxiety Inventory trait score, mean ± SD[c]	34 ± 10	34 ± 10	NS
Health Assessment Questionnaire Disability Index score, mean ± SD[d]	0.86 ± 0.65	0.08 ± 0.20	< 0.0001
Pittsburgh Sleep Quality Index score, mean ± SD[e]	6.1 ± 3.9	5.2 ± 3.2	0.05
Paffenbarger Physical Activity and Exercise Index, kilocalories/wk, mean ± SD	1474 ± 1198	1958 ± 1940	0.02
Bodily pain, mean ± SD[f]	3.3 ± 1.3	2.9 ± 1.4	0.02
Duke Social Support Scale score, mean ± SD[g]	49 ± 18	52 ± 16	NS
Duke Social Stress Scale score, mean ± SD[h]	18 ± 13	21 ± 13	NS
Had as much help as wanted at home, %	49	62	0.04

Possible ranges: a. 1–5 higher = more dissatisfied. b. 0–30, higher = more depressive symptoms. c. 20–80, higher = more anxiety. d. 0–3, higher = more disability. e. 0–21, higher = worse sleep quality. f. 1–6, higher = more pain. g. 0–100, higher = more support. h. 0–100, higher = more stress. NS: nonsignificant.

Table 2. Fatigue Severity Scale scores from enrollment and followup evaluations.

Time of Evaluation	RA Group*	Controls*	p
Enrollment score, mean ± SD[a]	4.2 ± 1.2	3.4 ± 1.1	< 0.0001
Followup score, mean ± SD[a]	4.1 ± 1.3	3.2 ± 1.0	< 0.0001
Within-patient change (followup minus enrollment score), mean ± SD[b]	–0.21 ± 0.99	–0.08 ± 0.96	
p	0.05	0.41	

* At enrollment n = 122 for both groups; at followup n = 91 RA group, n = 89 controls. a. Fatigue Severity Scale score possible range 1 to 7, higher = worse fatigue. b. Change in score possible range –6 to +6, higher = increasing fatigue.

Table 3. Cross-sectional analysis: enrollment variables associated with worse Fatigue Severity Scale scores at enrollment.

Variables	RA Group, n = 122			Controls, n = 122		
	Correlation Coefficient	Bivariate p	Multivariate Model p	Correlation Coefficient	Bivariate p	Multivariate Model p
Older	0.15	0.10		0.12	0.20	
Women	0.21	0.01		0.10	0.32	
More self-reported comorbidity	0.03	0.79		0.004	0.97	
More trait anxiety	0.55	< 0.0001	< 0.0001	0.45	< 0.0001	
More depressive symptoms	0.53	< 0.0001		0.51	< 0.0001	< 0.0001
More disability	0.48	< 0.0001	< 0.0001	0.18	0.05	
More social stress	0.39	< 0.0001	0.001	0.37	< 0.0001	0.003
Less social support	0.24	0.008	0.03	0.02	0.81	
More bodily pain	0.33	0.0002		0.21	0.02	
Worse sleep quality	0.42	< 0.0001		0.28	0.002	
Less physical activity	0.21	0.02		0.22	0.02	
Less role satisfaction	0.40	< 0.0001		0.41	< 0.0001	
Less perceived home help	0.18	0.04		0.18	0.05	
More ACR criteria	0.21	0.02				
More extraarticular disease	0.20	0.03				
Taking methotrexate	0.16	0.13				

ACR: American College of Rheumatology.

study explained more of the variance in the RA group compared to controls. These results were the same for both groups when controlled for age, sex, and self-reported comorbidity.

Longitudinal analysis. We contacted 113 (93%) in the RA group and 109 (89%) in the control group for the followup. Some of these participants were not able to complete the followup fatigue questions because of lack of time (22 in the RA group and 20 controls). These individuals did not differ from those who did complete the fatigue questions in terms of disability, depressive symptoms, anxiety, social support, or social stress. For the RA group, there also were no differences in demographic characteristics; however, for controls, women and older participants were more likely to respond to the fatigue questions compared to men and younger participants (p ≤ 0.03 for each variable). In total, the FSS was readministered to 91 patients in the RA group at a mean of 13.8 ± 1.6 months, and to 89 controls at a mean of 14.5 ± 3.0 months. Followup FSS scores are shown in Table 2. Similar to the findings at enrollment, those with RA had worse scores at followup compared to controls. Two controls reported no fatigue (i.e., had the lowest possible score) at the followup.

Longitudinal bivariate relationships between enrollment variables and followup FSS scores are shown in Table 4. Variables that were related to FSS scores in bivariate analyses with p ≤ 0.05 were entered into multivariate models with FSS scores as the dependent variable. After backward stepwise elimination, the variables that remained associated with more fatigue in the RA group were less help at home (r = 0.34), more trait anxiety (r = 0.38), and more disability (r = 0.43) (p ≤ 0.007 for each variable). The cumulative variance (R^2) explained by this model was 0.34. Contributions to the cumulative variance from each variable were 0.19 for disability, 0.09 for less help at home, and 0.06 for more anxiety. In the multivariate model for controls, more trait anxiety (r = 0.41) and less physical activity (r = 0.34) remained significant in multivariate analysis (p ≤ 0.006 for each variable, R^2 = 0.24). Contributions to the cumulative variance were 0.17 for anxiety and 0.07 for physical activity. The results were the same for both groups when controlled for age, sex, and self-reported comorbidity.

When compared over time there was little change in scores within groups, with a mean within-patient change in score for the RA group of –0.21 and a mean within-patient change in

Table 4. Longitudinal analysis: enrollment variables associated with worse Fatigue Severity Scale scores at followup.

Variables	RA Group, n = 91 Correlation Coefficient	Bivariate p	Multivariate Model p	Controls, n = 89 Correlation Coefficient	Bivariate p	Multivariate Model p
Older	0.13	0.22		0.15	0.16	
Women	0.21	0.02		0.10	0.13	
More self-reported comorbidity	0.05	0.63		0.08	0.44	
More trait anxiety	0.38	0.0002	0.007	0.41	< 0.0001	0.0004
More depressive symptoms	0.36	0.0004		0.38	0.0003	
More disability	0.43	< 0.0001	0.0006	0.16	0.14	
More social stress	0.19	0.07		0.31	0.003	
Less social support	0.16	0.13		0.09	0.38	
More bodily pain	0.29	0.006		0.18	0.08	
Worse sleep quality	0.33	0.001		0.32	0.003	
Less physical activity	0.19	0.08		0.34	0.002	0.006
Less role satisfaction	0.37	0.0003		0.31	0.004	
Less perceived home help	0.34	0.0008	0.0009	0.07	0.51	
More ACR criteria	0.17	0.11				
More extraarticular disease	0.18	0.21				
Taking methotrexate	0.16	0.38				

ACR: American College of Rheumatology.

score for controls of –0.08 (Table 2). The direction of change in both groups was toward less fatigue. These changes were less than the 0.5 points considered to correspond to a measurable clinical change in fatigue[19]. None of the enrollment demographic, psychosocial, lifestyle, or clinical variables was associated with changes in fatigue scores.

DISCUSSION

Our results showed that although fatigue was common in both the RA and controls groups, it was worse in those with RA, even though these patients were relatively high functioning, with each being actively employed and having diverse social roles. Thus our study provides evidence that fatigue is very much an issue even in individuals with RA who are able to successfully participate in a wide spectrum of demanding daily activities.

Although fatigue was prevalent in both groups, we found differences between groups in psychosocial and clinical factors associated with fatigue. Specifically, for the RA group, more disability, more anxiety, and less social support were independently associated with more fatigue. These variables were not independently associated with fatigue in controls. In contrast, more depressive symptoms remained significant in multivariate analysis for controls, but not for those with RA. One possible reason for this may be that depressive symptoms were more highly correlated with certain critical covariates in the RA group. For example, the correlation coefficients for fatigue and disability were 0.40 for the RA group and 0.21 for controls.

Few studies have assessed fatigue in individuals with RA and controls. In one study, Belza compared fatigue between 51 individuals with RA and 46 social network controls who were identified by the RA group and matched for age and sex[4]. Belza found significant differences in fatigue between groups, but similar bivariate relationships between fatigue and depressive symptoms, pain, disability, and sleep disturbance in both groups. However, multivariate analyses were not carried out in that study to determine which variables were independently associated with fatigue. In another study, Crosby compared fatigue in 2 groups of patients, those having an RA flare and those not having a flare, to controls who were matched by age and sex[7]. Fatigue was markedly worse in patients having a flare compared to the other 2 groups, with no significant differences between controls and non-flare patients. This was a small study, however, with only 15 patients with RA and 12 controls.

Among the variables considered in our study, social stress was the only variable found to be independently correlated with fatigue in both groups. We measured social stress primarily as emotional stress caused by various members of one's social network. Participants reported both the size of the network providing social stress, for example family members (parents, children, in-laws) and non-family members (friends, co-workers, neighbors), as well as the amount of stress provided by each source. It was described as stress caused by the circumstances and actions of others who then make things harder or cause problems for the recipient[26]. Social stress is a psychosocial construct distinct from social support and is not necessarily inversely correlated with social support. Specifically, someone who provides a great deal of social support may also be a source of significant social stress, for example, a devoted spouse who has serious medical illnesses. In addition, social stress is different from problematic social support, in which the provider's actions may be well intentioned but are not desired by the recipient, for example a sib-

ling who persistently offers uninformed advice. In a study to more precisely assess different types of social support in relation to RA fatigue, Riemsma, *et al* measured both social support and problematic social support[35]. They found that fatigue was not correlated with social support, but was highly and directly correlated with problematic social support. To date, the contributions of problematic social support and social stress to RA fatigue have not been assessed extensively, and it is not known what interventions might help modify these factors in this population.

It was also interesting to find that psychosocial variables explained more of the variance in fatigue in the RA group compared to controls. This was the case for both the cross-sectional and longitudinal analyses. One possible explanation for this may be that these variables were more likely to be abnormal in the RA group, and therefore more likely to contribute to fatigue. Another possible explanation is that the interaction of these variables is more complex in RA, perhaps somehow due to the underlying disease mechanism of RA. Currently, there are no other studies comparing multivariate analyses for similar variables between an RA group and controls.

Several large studies have assessed fatigue in RA without comparison to control groups and have collectively considered a wide spectrum of variables. In general, most studies found that psychosocial and lifestyle variables, especially pain, sleep disturbance, less physical activity, disability, comorbidity, anxiety, and depressive symptoms were related to RA fatigue, but there were inconsistent findings for other variables, such as age, sex, erythrocyte sedimentation rate, and joint count[1,2,4-6,9,10,35]. Because of variations in study design and variations in the types of variables considered, it is difficult to compare findings from these studies and to determine a conclusive picture of RA fatigue. For example, most studies reported many bivariate correlates of fatigue, but just a few reported multivariate comparisons. When covariability was accounted for, then fewer variables emerged as independently correlated with fatigue. For example, in one large study, Wolfe, *et al* found in bivariate analysis that age, education, pain, sleep disturbance, anxiety, depressive symptoms, and disability were associated with fatigue; however, only pain, sleep disturbance, depressive symptoms, and disability remained significant in multivariate analysis[1]. Similarly, we found many bivariate relationships with fatigue, but only several emerged as critical in multivariate analysis. This issue has practical relevance, because identifying modifiable independent variables will help direct the development of new interventions to ameliorate this symptom.

Regarding fatigue in controls, we found that all but one control at enrollment and all but 2 at the followup reported some fatigue during the preceding week. Several studies have shown that fatigue is relatively common in the general population, with about 20% of healthy subjects reporting substantial fatigue some of the time[11-14]. Despite its prevalence, fatigue as a normal phenomenon is poorly understood, and

possible relationships with biological markers are currently being sought[16,36]. Fatigue has been reported in most studies to be more common in women, but not consistently related to any other demographic characteristic, including age[4,11,12,14,36]. However, fatigue in healthy individuals has been attributed to psychosocial and lifestyle characteristics, particularly depressive symptoms, anxiety, role stress, and less physical activity[11,12,14-16,36,37]. In one study, anxiety, depressive symptoms, and sleep disturbance were significant in bivariate analysis, and anxiety and depressive symptoms remained significant in multivariate analysis[16].

In our longitudinal analysis we found little difference in fatigue scores measured one year apart for both the RA group and controls. This may mean that fatigue was relatively stable during the one-year period of our study, or alternatively it may mean that fatigue varied during this time, but happened to be similar at the 2 timepoints when we measured it. There are few longitudinal studies addressing the temporal pattern of fatigue. In one study, Belza reported little change in fatigue in individuals with RA and controls when measured 3 times during a 6 to 8-week interval[4]. Interestingly, Stone, *et al* measured diurnal fatigue patterns in RA using an electronic wristwatch device that prompted participants to record fatigue levels 7 times a day over 7 consecutive days[38]. Although, on average, fatigue varied from 1 to 2.25 on a 6-point scale during each day, it had a consistent pattern across the 7 days. In another recent study, Wolfe, *et al* found that change in fatigue, measure at 2 timepoints 6 months apart, was weakly correlated with change in health status, possibly because fatigue varied little during this period[9]. Thus, these studies provide some evidence that fatigue may be relatively stable over days to months, and therefore may have more characteristics of a trait, in contrast to a state[4].

Our study has several limitations. First, all participants were employed individuals, thus the severity and characteristics of their fatigue may differ from other populations. Second, we did not include biological markers of RA, and thus did not comprehensively report disease activity and its relationship to fatigue. Third, our controls were healthy employed urban dwellers having routine primary care visits in a tertiary care medical center, and may not be completely representative of other healthy individuals in other settings. Fourth, the Fatigue Severity Scale is a brief generic measure and may not record possible domains and unique features of fatigue in RA.

This longitudinal study found that highly functional individuals with RA had worse fatigue compared to healthy controls, and that fatigue measured after about one year was relatively unchanged. Also, we found that psychosocial variables, such as anxiety, disability, and social stress, were independently correlated with fatigue in the RA group. Additional studies are needed to confirm the role of these variables and to elucidate how they may cause fatigue. Future studies also should explore the impact of these variables in a broader spectrum of

patients, for example, those who are not employed or in urban settings. In addition, studies are needed to determine whether these factors vary in importance during quiescent versus more active disease periods. Finally, a new critical area of investigation will be to determine whether novel disease-altering drugs influence the relationship between fatigue and psychosocial variables.

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