



An evaluation of a biopsychosocial framework for health-related quality of life and disability in rheumatoid arthritis

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ABSTRACT

Objective: To examine the relationships between physical, psychological, and social factors and health-related quality of life (HRQOL) and disability in rheumatoid arthritis (RA).

Methods: A sample of 106 patients with rheumatoid arthritis (RA) completed measures of self-reported disease activity and psychosocial functioning, including coping, personal mastery, social network, perceived stress, illness beliefs, the SF-36 and Health Assessment Questionnaire Disability Index (HAQ-DI). In addition, physician-based assessment of disease activity using the Disease Activity Scale (DAS-28) was obtained. Hierarchical multiple regression analyses were used to evaluate the relationships between psychosocial factors and scores on the SF-36 and HAQ-DI.

Results: Lower self-reported disease activity was associated with higher SF-36 physical functioning scores, while the contribution of active coping, passive coping, and helplessness was significant only as a block. Lower self-reported disease activity, higher personal mastery, and lower perceived stress contributed to higher SF-36 mental health functioning, and higher self-reported disease activity and lower helplessness were associated with greater disability, as indexed by the HAQ-DI. The DAS-28, an objective measure of disease activity, was unrelated to any of these outcomes.

Conclusions: The findings highlight the importance of targeting psychological factors to enhance HRQOL and disability in the clinical management of RA patients.

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Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory disease that can lead to disability and significantly interfere with functional adaptation [1,2]. Symptoms such as joint pain, swelling, and fatigue are disease-specific stressors that tax the adaptive resources of patients and heighten the risk for patient reported declines in function (i.e., difficulties in carrying out activities of daily living) as well as reports of emotional disturbance [3] which together create enormous psychological and financial loss for those afflicted [4].

Given the salience of such subjective reports of declines in patients' physical, social, and psychological functioning, there is growing interest in using patient-reported outcomes (PROs) to assess treatment effectiveness [5]. PROs represent a patient's evaluation of his/her unique health status distinct from the evaluations of physicians and laboratory findings, and have a long history of use in

the measurement of outcomes such as psychological distress, pain, and depression in patients with RA. Increasingly, PROs are being adopted as a mechanism for evaluating clinical efficacy in randomized clinical trials [6,7] to allow for an analysis of whether treatments that are designed to reduce disease activity, for example, will also improve clinical functioning from the patient's perspective.

An important measure of PROs is health-related quality of life (HRQOL). While various definitions have been proposed, HRQOL generally refers to the ways in which a given health condition affects a patient's physical ability and capacity to function in a variety of social and emotional roles. HRQOL, which may be generic or disease-specific, is generally divided into measures of physical functioning and emotional well-being [8]. In contrast to disability measures, which assess how health limits a patient's ability to perform specific tasks, HRQOL is a more global construct that indicates how well a patient is doing given the totality of his/her medical condition. Hence, the determinants of disability and HRQOL are likely to differ, as they are distinct constructs tapping different facets of functioning.

A key issue in HRQOL research in RA concerns the identification of variables, along with disease activity, that play prominent roles in

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explaining physical and mental health functioning. A common observation among rheumatologists is that significant variability in health functioning exists among RA patients who have similar levels of disease activity and joint damage [1,9], raising the question of what factors are responsible for these functional differences. In fact, research has demonstrated that disease activity and inflammation in RA correlate only modestly with HRQOL and other psychosocial measures [10,11]. The same pattern has been found in other rheumatic diseases such as systemic lupus erythematosus [12].

At this juncture, research has not adequately addressed the variables contributing to HRQOL in RA. Indeed, while studies have demonstrated that variables such as illness beliefs, coping, and social support are correlated with pain and psychosocial adjustment in RA patients [13–15], the contribution of such factors to HRQOL has not been adequately determined. This research adopted a biopsychosocial framework [16] to evaluate the role of psychosocial and biomedical factors, in understanding patient variability in functional outcomes. Previous research has not explicitly adopted this approach in conceptualizing the variables affecting HRQOL in RA. This study evaluated this framework for HRQOL and disability in a sample of patients with RA in the greater metropolitan Los Angeles area.

Materials and methods

Patient recruitment

Patients were recruited through advertisements in local newspapers and flyers posted in clinic offices in the Departments of Rheumatology at UCLA and Cedars Sinai Medical Center (CSMC), Los Angeles to participate in a treatment outcome study that would help them manage their RA. Recruitment for the study started in spring 2004 and ended in winter 2008. After a brief telephone screening conducted by the project coordinator at UCLA, patients were referred to CSMC to determine medical eligibility. The study rheumatologist (MW) conducted a diagnostic evaluation that included assessments of tender and swollen joints and disease activity using the DAS-28 to confirm a diagnosis of RA. Eligible participants were required to: (1) be 18 years of age or older, (2) meet American College of Rheumatology (ACR) revised criteria for RA, (3) be on a stable disease-modifying drug regimen for three months prior to study entry, with no change in drug dosage for at least three months prior to study entry, (4) have a stable disease course for three months (no major changes requiring medication changes or administration of injected or pulse corticosteroids), (5) be free of serious co-morbid medical conditions such as diabetes, congestive heart failure, renal failure, or cancer that would confound interpretations of health status, and (6) not pregnant. Patients meeting these eligibility criteria were referred to UCLA for an evaluation of psychiatric status, physical functioning, and psychosocial adjustment. The project coordinator administered the Structured Clinical Interview for DSM Disorders (SCID) [17]. SCID diagnoses were made in a consensus meeting with the principal investigator (PN) and project psychiatrist (MI) with attention to criterion validity. Patients who had a serious psychiatric condition such as bipolar disorder, psychosis, or post-traumatic stress disorder, or who were at risk for suicide, were ineligible to participate in the study.

Data collection

Baseline data were collected from all eligible participants who qualified for the treatment outcome study. However, some of these participants, for various reasons, did not enter the clinical trial after they participated in the baseline phase of the study. We report findings from all eligible participants at baseline in this paper. At baseline, the psychosocial functioning and disease activity of participants were evaluated. The psychosocial component of the

evaluation consisted of paper and pencil assessments of: illness beliefs, pain coping, perceived stress, personal mastery, and social network/support. Participants also completed self-report measures of disease activity, health-related quality of life, and disability.

Medication use

Reports of current medication use were collected for each of the following categories: analgesics/nonsteroidal anti-inflammatory drugs, biologic agents, disease-modifying anti-rheumatic drugs (DMARDs), and “other” (drugs for other medical conditions, including psychotropic agents).

Psychosocial measures

Illness beliefs

The 5-item Helplessness and 7-item Internality Subscales of the Arthritis Helplessness Index (AHI) [14,18] were used to measure patients' beliefs about their ability to manage RA. The Helplessness subscale reflects a perceived inability to control RA symptomatology (e.g., pain) and disease course (e.g., “arthritis is controlling my life”) while the Internality subscale measures perceived control over RA (e.g., “managing arthritis is my own responsibility”).

Pain coping

The Pain Management Inventory (PMI), developed by Brown and Nicassio [15], was used to measure the degree to which patients reported either active (e.g., distraction, functioning in spite of pain) or passive (e.g., avoiding activity, lying down) coping strategies when pain from RA reached a moderate or greater level of intensity.

Perceived stress

The Perceived Stress Scale (PSS) is a 10-item scale [19] that measures the degree to which participants find their lives to be unpredictable, uncontrollable, and overwhelming. The PSS assesses the cognitive and emotional burden of feeling stressed rather than events that may lead to stress.

Personal resources

Personal mastery

The Personal Mastery Scale (PMS), a 7-item scale developed by Pearlin [20], assessed the personal resources dimension in the model. The PMS assesses the construct of personal mastery – the extent to which individuals believe their life circumstances are under their control as opposed to being fatalistically determined. Theoretically, higher scores reflect greater capacity on the part of the individual to manage the disease process and to be resilient under stress.

Social resources

Patients' social network size assessed the social resources dimension in the model. The Berkman and Syme Social Network Index (SNI) [20] calculates network size based on the interaction one has with a spouse, relatives, close friends, group activities, and participation in religious meetings or services. The method described in Loucks et al. [21] was adopted in which the following categories were scored; married (no=0; yes=1); close friends and relatives (0–2 friends and 0–2 relatives=0; all other scores=1); group participation (no=0; yes=1); participation in religious meetings or services (<every few months=0; once or twice a month=1). Scores in the sample ranged from 0 to 4, indicating increasing network size.

Disease activity

Disease activity was evaluated using two measures, the DAS-28 [22] and the Rapid Assessment of Disease Activity in Rheumatology (RADAR) [23]. The DAS-28 is a physician-based measure composed of the following indices that are aggregated to form a summary score: tender and swollen joint counts (0 to 28), erythrocyte sedimentation rate (ESR), and patient global score (0 to 100). The RADAR was used to measure self-reported measure disease activity. The RADAR consists of questions about past and current disease activity, pain, morning stiffness, and the degree of pain/tenderness in 10 joints on the right and left sides of the body. In previous research, the RADAR has been shown to be an efficient, valid proxy for physician assessments of disease activity and joint pain [24,25].

HRQOL

The SF-36 [8] evaluated generic HRQOL. The measure consists of 36 items tapping eight components of well-being: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, energy/vitality, social functioning, role limitations due to emotional problems, and emotional well-being. A scoring algorithm was used to aggregate the eight components into physical and mental health summary scores.

Disability

The Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) [26] was used to evaluate RA disability. The HAQ-DI is a validated self-report instrument that assesses the difficulty of completing tasks in 8 categories – dressing, arising, eating, walking, hygiene, reach, grip, and usual activities. Extensive research on the validity of the HAQ-DI and its use in clinical and research settings has been accumulated over the last 30 years [27].

Statistical approach: tests of the model

We used the conceptual model depicted in Fig. 1 as a framework for analyzing the contribution of disease activity, psychological, and social factors to HRQOL and disability in RA. Key assumptions of the model are the following: (1) disease activity, social resources (e.g., social network), and personal resources (e.g., personal mastery) have independent, additive effects on HRQOL and disability; (2) the coping

process, composed of variables such as helplessness, pain coping, and perceived stress, affects outcomes directly and serves as a mediator of the effects of disease activity on HRQOL and disability; (3) social and personal resources affect HRQOL and disability directly or indirectly by affecting elements of the coping process; (4) the model is dynamic over time in that the coping process, HRQOL, and disability may potentially affect changes in disease activity over time, although this hypothesis was not evaluated in the present cross-sectional analysis. Hence, the contributions of the first three components of the model were primarily tested.

Using hierarchical multiple regression analysis, independent variables were entered sequentially in four blocks into the regression equation. A hierarchical multiple regression approach is recommended when there is a theoretical framework guiding the selection of variables (see Fig. 1) and the goal is to determine the contribution of a variable or set of variables after controlling for others that have previously been tested [28,29]. In the present analyses, for the three criterion variables (HRQOL physical and mental health summary scores and HAQ-DI) predictors were entered into the regression equation in the following order: (1) medication use (four predictors: biologic use, DMARD use, NSAID use, and other medication use), (2) disease activity (two predictors: RADAR, DAS-28), (3) social network size and personal mastery (two predictors: SNI, PMS), and (4) coping process variables (five predictors: AHI-helplessness, AHI-internality, PMI-active coping, PMI-passive coping, and PSS). This process depicts the manner in which patients' perceptions of control over disease (helplessness/internality) can affect mode of coping (active/passive) which, in turn, can result in perceptions of stress. Mean substitution was used to estimate missing data for some variables. To reduce Type I error, a Simes correction was applied to the significance criterion for blocks and for variables within blocks.

Results

Sample characteristics

There were 106 predominantly female (83%) participants with an average age of 56.2 years and an average of 16.0 years of education. The majority of participants (52.8%) were Caucasian, with 10.4% African-American, 14.1% Hispanic, and 22.6% of "other" ethnic descent. Average disease duration was 12.00 years ($sd=11.4$). DAS-28 scores indicated moderate disease activity ($m=4.3$, $sd=.1$), and SF-36 summary scores indicated substantial difficulty with physical functioning ($m=33.2$, $sd=7.9$). Means for helplessness, passive coping, and active coping approximated findings from other RA samples [14,15]. Scores on internality reflected considerable perceived control over RA. In addition, personal mastery scores indicated a high degree of perceived control over

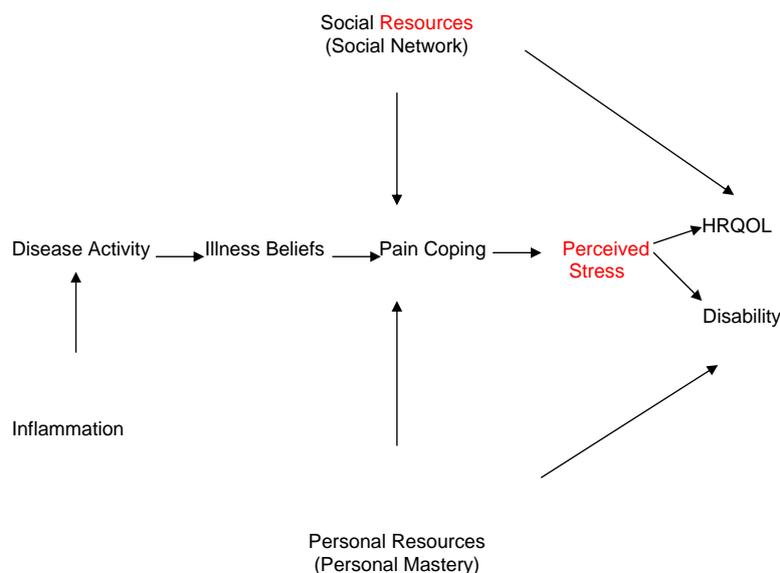


Fig. 1. Conceptual model describing the contribution of biological, psychological, and social factors to HRQOL and disability in RA.

life circumstances in general (see Table 1). Participants reported social networks of modest size ($m=1.8$, $sd=1.1$).

Multiple regression results

Physical functioning

Medication use at step 1 did not contribute to physical functioning; however, at step 2, the entry of disease activity was significant, accounting for 10% of the variance in physical functioning. Higher RADAR scores, reflecting greater disease activity, were associated with poorer physical functioning ($\beta=-.29$, $p<.01$), while the relationship between physical functioning and DAS-28 scores was not significant. At step 3, social network and personal mastery did not contribute variance to physical functioning, but at the final step, coping process variables were significant, uniquely explaining 17% of the variance. After correction for multiple tests, none of the individual variables was statistically significant; however, the variables most likely contributing to the overall effect of the block on physical functioning were active coping (positive effect), passive coping (negative effect), and helplessness (negative effect). Internality and perceived stress appeared not to be related to physical functioning scores. The model as a whole accounted for 29% of the variance in physical functioning (see Table 2).

Mental health functioning

At step 1, medication use did not contribute to mental health functioning scores, but at step 2, disease activity for 6% unique variance in mental health functioning ($p<.05$). Greater self-reported disease activity ($\beta=-.25$) was associated with poorer mental health scores; however, the DAS-28, as in the preceding analysis, was not significant. The entry of personal mastery and social network scores at step 3 proved highly significant, accounting for 22% unique variance; however, personal mastery, itself, accounted for 21% of the variance ($\beta=.49$), while social network was not related to mental health functioning. Coping process variables at step 4 contributed an additional 27% unique variance to mental health functioning scores. Perceived stress alone accounted for 23% of the variance in this step ($\beta=-.69$), while other variables were unrelated to mental health functioning. Overall, the model accounted for 60% of the variance in mental health functioning scores (see Table 3).

Disability (HAQ-DI)

Medication use contributed 10% of the variance at step 1 to disability ($p=.053$); however, this was not statistically significant, especially after Simes correction. Disease activity at step 2 added 26% unique variance to disability. Higher RADAR scores ($\beta=.51$) were associated with greater disability, while DAS scores were not. Personal mastery and social network were not significant at step 3, but coping process variables added 16% unique variance at the final step. Higher helplessness was associated with greater disability ($\beta=.26$), while internality, passive coping, active coping and

perceived stress did not contribute to disability. The model explained 50% of the variance in HAQ-DI scores (see Table 4).

Fig. 2 displays the results by each outcome variable, reflecting the respective contribution of medication use, disease activity (DAS-28; RADAR), and psychosocial variables (social network, personal mastery, helplessness, internality, active coping, passive coping, and perceived stress). The pattern is quite different for mental health functioning compared to the other two outcomes. In particular, psychosocial variables played a greater role, and disease activity played a more limited role, in mental health functioning than in physical functioning and disability.

Discussion

Despite significant improvements in the medical management, treatment, and prognosis of RA, it is common for patients to experience deficits in physical and mental health functioning. This research adopted an integrated, biopsychosocial framework [16] to evaluate the relative contribution of disease activity and psychosocial factors to physical and mental health functioning outcomes in a sample of RA patients living in greater metropolitan Los Angeles. Based on this conceptual framework, hierarchical multiple regression analysis isolated the sequential contribution of variables to physical functioning, mental health functioning, and disability. A major objective of these analyses was to determine the impact of psychosocial factors on physical and mental health and disability after controlling for medication use and disease activity. Analyses provided important, new information on the contribution of psychosocial factors and the overall relevance of this framework to functional outcomes in RA.

In general, psychosocial factors and self-reported disease activity proved influential in explaining variability in all three outcomes. While self-reported RADAR scores were significantly correlated with physical functioning, mental health functioning, and disability scores, physician-assessed DAS-28 scores were not correlated with any outcome, a finding that is consistent with previous research showing that physician-based assessments of RA disease activity may not be associated with functional outcomes or psychological variables [10,11]. Together, these findings underscore the importance of using patient-reported outcomes such as HRQOL and the value of evaluating the clinical status of patients based on their subjective appraisal of their illness experience.

It is noteworthy that the contribution of psychosocial variables in this research varied across HRQOL domains and disability. For physical functioning, some support was found for the roles of active coping, passive coping, and helplessness, but only when these variables were evaluated as a block. Since none of these variables was individually significant, their contribution to physical functioning is largely undetermined in this study. Nonetheless, these findings are consistent with previous research that has shown active coping to correlate modestly with negative outcomes such as pain and psychological distress in RA patients [15] and more strongly with better psychosocial functioning in other populations [30]. In general, active coping has proven to be more closely related to indices of positive adaptation than passive coping and helplessness, which have been shown to predict negative physical and psychological outcomes in arthritis [31], whiplash [32], and fibromyalgia [33]. Further research on the role of pain coping strategies as predictors of HRQOL and other indices of positive adaptation in RA is recommended to clarify the results from this research.

Psychological factors were particularly important in explaining mental health functioning. High personal mastery and low perceived stress accounted for a major proportion of the variance in mental health functioning, although these factors did not predict physical functioning. Other research [11] has shown depression to be a major determinant of SF-36 mental health scores in RA patients. Personal mastery, unlike arthritis internality, is a global measure of perceived control that reflects a general disposition of competence that may serve as a mechanism through which better mental health functioning

Table 1
Participant and variable descriptive statistics.

Variable	Total N=106	(Min–max)
Sociodemographic characteristics		
Age	56.22±12.45	(22–79)
Years of education	15.96±2.39	(12–21)
Yearly median income (\$) by zip	51,142±18,631	(17,644–121,527)
Years with RA	11.97±11.40	(<1–53)
Ethnicity		
Caucasian	56(52.8%)	
African American	11(10.4%)	
Hispanic	15(14.1%)	
Other	24(22.6%)	
Gender		
Female	88 (83%)	
Male	18 (17%)	
Marital status		
Married	47 (44.3%)	
Not married	47 (44.3%)	
Other/unknown	12 (11.4%)	
Model variables		
SF-36 physical functioning composite	33.19±7.92	(15–47)
SF-36 mental health composite	55.21±10.51	(21–70)
Disability (HAQ-DI)	.84±.60	(0–2.38)
Disease activity (RADAR)	11.45±9.34	(0–36)
Disease activity (DAS-28)	4.32±.95	(1.68–7.32)
Personal mastery (PMS)	23.58±3.46	(13–28)
Social network (SNI)	1.75±1.13	(0–4)
Active coping (VPMI)	22.77±4.73	(12–35)
Passive coping (VPMI)	24.84±6.99	(12–43)
Helplessness (AHI)	14.75±3.93	(7–28)
Internality (AHI)	30.25±5.93	(7–42)
Perceived stress (PSS)	11.35±6.90	(0–36)

Table 2
Hierarchical regression model: physical functioning.

Model	Variable	R	R ²	R ² change	F change	df _{1,2}	F change p	β	t	p	sr ²
1		.11	.01	.01	.29	4,98	.88				
	Biologics							.05	.48	.63	.00
	DMARDs							-.10	-.92	.36	.01
	NSAIDs							-.02	-.16	.87	.00
	Other							.05	.50	.62	.00
2		.33	.11	.10	5.28	2,96	<.01				
	Disease activity (RADAR)							-.29	-2.97	.00	.08
	DAS-28							-.09	-.84	.40	.01
3		.34	.12	.01	.42	2,94	.660				
	Personal mastery							.04	.43	.67	.00
	Social network							-.08	-.84	.40	.01
4		.54	.29	.17	4.20	5,89	<.01				
	Active coping							.21	2.06	.04	.03
	Passive coping							-.21	-1.85	.07	.03
	Helplessness							-.19	-1.69	.10	.02
	Internality							.04	.40	.69	.00
	Perceived stress							.15	1.14	.26	.01

β Standardized regression coefficient.

sr²: unique variance.

Note. All statistical values reflect the contribution of variables at the respective step of the regression equation.

is achieved. Perceived stress, on the other hand, is a general indicator of burden that may be the result of numerous life stressors, including those connected with having a chronic disease. Acting influentially but in opposite directions, these factors were far more important in explaining mental health functioning than self-reported disease activity.

The findings on disability illustrated the contribution of helplessness. Helplessness independently accounted for variability in disability, over and above the effects of self-reported disease activity. Similar results have been reported elsewhere [18] and indicate that perceptions of helplessness are key to understanding deficits in functioning, but not quality of life. Specific functional problems in RA reflect idiosyncratic beliefs about the uncontrollability of pain and other aspects of the disease course but, as this research has shown, are independent of both general beliefs of mastery or specific expectancies of control over RA. The finding that different psychological processes may be involved in quality of life and disability is not surprising in view of the disparate nature of these outcomes, including their level of specificity or generality, and their differential sensitivity to the disease process.

Importantly, while this study has demonstrated the applicability of a comprehensive framework for understanding HRQOL and disability in RA, its findings should be interpreted cautiously for several reasons, and warrant replication in future research. We proposed a conceptual model that allowed for variable selection and statistical tests, but it is possible that other models may be used to generate research on these important outcomes. Importantly, the findings in this study may lead to alternate frameworks that can be developed and tested. In addition, the study itself possessed some methodological limitations. One drawback was its cross-sectional design, which precluded interpretations of directionality among model variables. Future research evaluating this model longitudinally would shed light on whether psychosocial factors predict functional outcomes over time while controlling for prior levels of disease activity. Longitudinal research could also address whether such variables as coping and perceived stress mediate the effects of disease activity on these outcomes. Another limitation of the study was that participants were volunteers recruited from the community. Volunteers tend to be more mobile and possess fewer of the medical co-morbidities associated with more advanced RA and may thus not be adequately representative of RA

Table 3
Hierarchical regression model: mental health functioning.

Model	Variable	R	R ²	R ² change	F change	df _{1,2}	F change p	β	t	p	sr ²
1		.19	.04	.04	.96	4,98	.43				
	Biologics							-.01	-.11	.92	.00
	DMARDs							.08	.74	.46	.01
	NSAIDs							-.09	-.84	.41	.01
	Other							.14	1.34	.18	.01
2		.32	.10	.06	3.28	2,96	.04				
	Disease activity (RADAR)							-.25	-2.55	.01	.06
	DAS-28							.02	.19	.85	.00
3		.57	.32	.22	15.39	2,94	<.001				
	Personal mastery							.49	5.42	<.001	.21
	Social network							.06	.72	.47	.00
4		.77	.60	.27	12.08	5,89	<.001				
	Active coping							.03	.36	.72	.00
	Passive coping							-.02	-.17	.86	.00
	Helplessness							-.07	-.87	.39	.00
	Internality							-.02	-.19	.85	.00
	Perceived stress							-.69	-7.10	<.001	.23

β Standardized regression coefficient.

sr²: unique variance.

Note. All statistical values reflect the contribution of variables at the respective step of the regression equation.

Table 4
Hierarchical regression model: disability.

Model	Variable	R	R ²	R ² change	F change	df _{1,2}	F change p	β	t	p	sr ²
1	Biologics	.31	.10	.10	2.43	4,98	.06	-.05	-.47	.64	.00
	DMARDs							.28	2.66	.01	.07
	NSAIDs							.03	.26	.80	.00
	Other							-.23	-2.22	.03	.05
2	Disease activity (RADAR)	.60	.36	.26	18.55	2,96	<.001	.51	5.98	<.001	.25
	DAS-28							.02	.21	.83	.00
3	Personal mastery	.60	.36	.01	.46	2,94	.63	-.06	-.72	.48	.00
	Social network							.06	.70	.49	.00
4	Active coping	.71	.50	.13	4.49	5,89	<.001	-.03	-.32	.75	.00
	Passive coping							.17	1.72	.09	.02
	Helplessness							.26	2.73	<.01	.04
	Internality							-.08	-.81	.42	.00
	Perceived stress							.06	.57	.57	.00

β Standardized regression coefficient.

sr²: unique variance.

Note. All statistical values reflect the contribution of variables at the respective step of the regression equation.

patients with more severe disease. A larger sample of patients with varying stages of disease progression would enable tests of the generalizability of the model, including the importance of the specific variables that were identified in this research as critical to understanding functional outcomes. Such improvements would provide a more definitive test of the model proposed in this research.

In spite of these limitations, the data suggest that the evaluation of patients with RA in clinical settings should address psychosocial functioning using PROs and psychological measurements. The identification of psychosocial factors that interfere with HRQOL and lead to disability would set the stage for behavioral interventions that could facilitate management and contribute to more positive functional adaptations [34,35].

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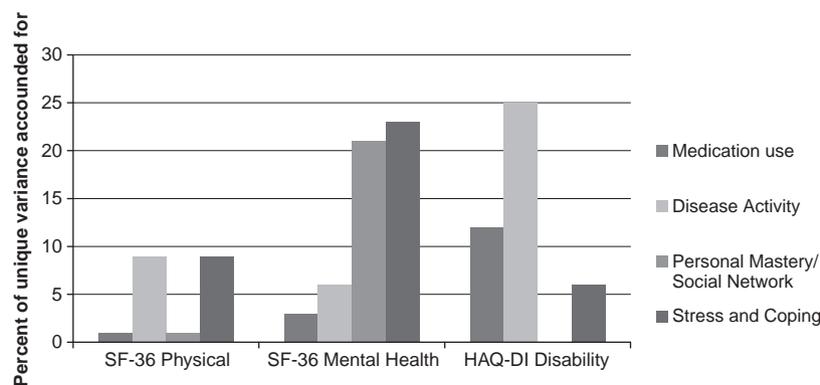


Fig. 2. Variance explained by variable domains.

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