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Mediation effect of emotional health on pain in RA

Title:

Effect of physical state on pain mediated through emotional health in rheumatoid arthritis

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Objective:

Pain is one of the main complaints of patients with rheumatoid arthritis (RA). Pain in RA is caused by specific physical changes, such as joint destruction, and is therefore used as a disease activity marker. Although pain can also be influenced by emotional factors, neither the effect of emotional health nor the indirect effect of physical state mediated by emotional health on pain has been quantified.

Methods:

A total of 548 patients with RA participated. Emotional health was assessed using the Hospital Anxiety and Depression Scale (HADS). Measures routinely used in practice were used to evaluate physical state and pain. To quantify 1) the effects of physical state on emotional health, and 2) the effects of both physical and emotional health on pain, we used structural equation modelling with emotional health, physical state, and pain as latent variables.

Results:

The prevalence of anxiety and depression (HADS score ≥ 8 for each) among RA patients was 18.7% and 29.4%, respectively. Emotional health was significantly influenced by physical state ($\beta = 0.21$). Pain was affected by physical ($\beta = 0.54$) and emotional health ($\beta = 0.29$). The effect of physical state on pain was mediated by emotional health, with this mediation effect ($\beta = 0.06$) accounting for 10.2% of the total effect.

Conclusion:

The magnitude of pain in RA is determined by the mediation effect of emotional health as well as the direct physical state. Our findings suggest that emotional factors should

be taken into account when assessing RA disease activity.

Significance and Innovations.

- Patients with RA have a high incidence of anxiety and depression.
- Pain among RA is influenced by both physical state and emotional health and, in addition, this effect of physical state on pain is mediated through emotional health.
- Improvement of emotional health in RA may partially alleviate the level of pain.
- RA disease activity in patients with anxiety and/or depressive symptoms may be overestimated, because disease activity measures include pain components.

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease with a prevalence of 0.5–1% (1, 2). RA is characterized by persistent synovitis, which leads to joint destruction and pain (1). Patients with RA experience various problems, which have been classified as physical dimensions (mobility level, walking and bending, hand and finger function, arm function, self-care tasks and household tasks), social interaction (social activity and support from family and friends), symptoms (pain), role (work) and affect (tension and mood) (3). Approximately 70% of patients with RA report pain among the top three priorities for improvement (3). Furthermore, when patients evaluate their own RA disease activity, pain is considered the most clinically important component (4). Consistent with this patient perspective, physicians regard pain as an important aspect of RA disease activity measurement and a pivotal treatment target (1, 5).

Pain experienced by patients with RA is a subjective measure of disease activity that may be affected by emotional factors. For example, pain sometimes persists despite RA remission, especially when patients have emotional problems such as anxiety (6, 7).

Interestingly, a recent report showed a link between anxiety and/or depression in patients with RA and increased pain 1 year later (8). Based on this finding, a concept of

‘non-inflammatory pain’ in RA has been proposed (8). This suggests that emotional factors have a substantial influence on pain in RA.

Evidence shows that physical state affects emotional health (9-14). Several hypotheses concerning the mechanisms whereby inflammation potentially influences emotional health have been put forward, including dysregulation of the hypothalamic pituitary adrenal axis, changes in glial function and glutamate release in the brain, and activation of the tryptophan metabolising enzyme (9, 11, 13, 15). Of particular interest are findings of clinical studies showing that anti-inflammatory drugs are effective in treating patients with depression (16). In addition, a meta-analysis reported a prevalence of major depressive disorder among those with RA of approximately 17%, a rate much higher than in the general population (17). This suggests that having an inflammatory condition such as RA confers risks for emotional health.

Considering the above information, pain in RA may be related to both physical state and emotional health, and that emotional health may be affected by physical state.

It follows that in addition to the direct effect of physical condition (RA) on pain, the effect of RA on pain may be mediated by emotional health. This led us to construct a

model of relationships among physical state, emotional health and pain, as shown in Fig. 1A. In this study, we evaluated this model using structural equation modeling (SEM), by quantifying the direct (physical state) and indirect effects (physical state → emotional health) on pain in patients with RA.

To evaluate the effect of physical state on pain through emotional health, variables that reflect purely physical and objective components to define physical state. To our knowledge, this is the first study to investigate the effects of physical state in a comprehensive and quantitative manner. Previous studies evaluated physical state using disease activity composite indices (8, 18) or a single item such as the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level or tender joint counts (TJC) (10, 18-20). These evaluations may be problematic because disease activity composite indices generally include subjective components and therefore may be influenced by emotional factors, and single items may be insufficient to assess multifaceted aspects of physical state.

Patients and Methods

Patients

This study included 548 participants from the 2014 Kyoto University Rheumatoid Arthritis Management Alliance (KURAMA) cohort (21). The KURAMA cohort study started in 2011 at the Center for Rheumatic Diseases, Kyoto University Hospital, and aimed to investigate RA in clinical practice. Approximately 500 consecutive patients with RA were enrolled annually. Because we included evaluation of anxiety and depression in 2014, we used data assembled in 2014 to investigate the effect of mental and physical state on pain. All participants met the American College of Rheumatology (ACR) revised criteria for RA 1987, or ACR and European League Against Rheumatism classification criteria for RA 2010 (1). The study was conducted according to the Declaration of Helsinki. Ethics approval was obtained from the Medical Ethics Committee of Kyoto University Graduate School and Faculty of Medicine. All participants were aged over 18 years and provided written informed consent.

Measures

To ascertain the direct effect of physical state and the mediating effect of emotional health on pain, we developed a conceptual model representing relationships among

physical state, emotional health and pain (Fig. 1A). Physical state, emotional health and pain were evaluated with separate sets of indicators (symptoms and laboratory findings); that is, each concept was regarded as having a unique latent trait measured by several observed variables. Observed indicators for the three latent traits are described in the following paragraph. In addition, demographic (age, gender, employment status) and medical information were included in the analysis. Medical information included current psychiatric treatment, physical complications and RA treatments such as methotrexate (MTX), disease-modifying antirheumatic drugs (DMARDs) other than MTX and biological drugs.

Physical state

The activity of RA cannot be examined by a single clinical or laboratory test, and composite indices using several clinical and laboratory variables have been proposed. Three widely used composite indices are the Disease Activity Score 28 joints (DAS28), Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI), all of which are considered valid tools for evaluating RA disease activity (1, 21). However, these composite indices include subjective items, which may obscure accurate measurement of disease activity due to modification by emotional factors (4). In this

study, we aimed to extract purely physical aspects of RA and evaluate physical state independently of emotional factors and pain. Therefore, we eliminated subjective components and items associated with pain from the latent structure for RA physical state. We selected observed variables for RA physical state through a 3-step process. 1) All seven components of the three validated RA disease activity measurements (DAS28, SDAI and CDAI) were extracted: ESR 1h level; serum CRP level; swollen joint count (SJC); TJC; patient's global assessment of disease activity (PtGA); evaluator's global assessment of disease activity (EGA); and patient's assessment of general health (GH). 2) Next, we excluded TJC, PtGA, EGA and GH because TJC is a pain indicator (see Pain below), PtGA and GH are both subjective patient self-evaluations and influenced by emotional health (e.g. depression) (4, 8) and EGA is a subjective evaluator assessment and is not sensitive to objective RA disease outcome or radiographic progression (4). 3) Lastly, we added matrix metalloproteinase-3 (MMP-3) to the remaining three components (i.e., ESR, CRP and SJC) to form a 'physical state' set, because MMP-3 has been reported to directly reflect joint inflammation and destruction (22-24). In effect, in our data, the MMP-3 level was correlated with the yearly radiologic progression (change in van der Heijde-modified total Sharp score per year) (Spearman's, $r=0.12$, $P<0.05$, $n=344$). We used MMP-3 in our analysis because of

the relatively limited data available on radiologic progression. Finally, physical state comprised four variables: ESR, CRP, MMP-3 and SJC. For SJC, we incorporated 68 joints rather than the 28 joints used in the DAS28, SDAI, and CDAI to make our evaluation as thorough as possible.

Pain

We evaluated pain using three aspects: distribution and intensity. We used TJC (68 joints) as an indicator of pain distribution, which the ACR recommends to measure disease activity in clinical trials (25). Pain intensity was ascertained using a visual analogue scale (VAS) anchored by “no pain” (a score of 0) and “the worst pain” (a score of 100) as a continuous variable. Thus, we used two indicators to structure the latent variable of pain: TJC68 and pain VAS.

Emotional health

We used the Hospital Anxiety and Depression Scale (HADS) to assess anxiety and depression (2, 8, 17, 26). The latent trait for emotional health comprised the HADS anxiety and depression subscales. The HADS comprises 14 items (seven items each for anxiety and depression), scored on a four-point Likert scale (0–3); total subscale scores

range from 0–21. We chose the most commonly used cut-offs, with a total subscale score of 0–7 indicating no anxiety/depression, 8–10 possible anxiety/depression, and 11–21 probable anxiety/depression (2, 17). The validity of the HADS has been established with a sensitivity and specificity of approximately 0.80, and internal consistency more than 0.85 (2).

Statistical analysis

We examined the conceptual model (Fig. 1A) using SEM, a powerful tool that is widely used in sociology, psychology and other social sciences to analyze complex modeling with latent factors. SEM techniques have also been used in research with patients with RA. For example, SEM analysis revealed that disease activity, mood disturbance and sleep quality contributed to fatigue in patients with RA (27). Another SEM analysis involving patients with RA showed that self-efficacy for pain partially mediated the relationship between disease activity and pain (28). However, no previous studies have investigated the mediation effect of emotional health on the relationship between physical state and pain in RA, where physical state is defined by purely physical and objective components.

Before the main SEM analysis, we examined correlations of indicators constituting the three structures (i.e. physical state, emotional health and pain) using Spearman's correlation coefficients because of their non-normal distribution (indicated by the Shapiro–Wilk test). We used robust maximum likelihood estimation in the SEM analysis to allow for non-normality distributions. Age and gender were included as covariates. Unless otherwise indicated, we used the full information maximum likelihood (FIML) procedure to manage missing data. Fit between the conceptual model and the data was examined using several fit indices: root mean square error of approximation (RMSEA), comparative fit index (CFI), Tucker–Lewis fit index (TLI) and standardized root mean square residual (SRMR). Along with model fit procedures, we scrutinized modification indices to reach the optimal final model. To verify the indirect effect of physical state on pain through emotional health, we carried out the Sobel test; the 95% confidence interval (CI) of the effect was obtained from the bias corrected bootstrap estimation using 10,000 samples (29, 30).

The Wald test (31) was used to evaluate any difference of moderated mediation effect in binary factors including employment status, presence/absence of current psychiatric treatment, any physical complications (extra-articular manifestations, connective tissue diseases and respiratory diseases) and RA treatments. SEM analyses were performed

using Mplus version 7.31 for Mac (Muthén & Muthén, Los Angeles, CA, USA). Other statistical analyses were performed using STATA version 14 (StataCorp LP., College Station, TX, USA).

Results

Demographic characteristics

As shown in Table 1, 83.5% (n = 456) of the 548 participants were female, which is consistent with previous studies showing approximately 70–90% of people with RA are female (6, 8, 17). Participants' average age was 62.6 years (standard deviation [SD] = 13.1 years) and average disease duration was 14.8 years (SD = 12.0 years).

Classification by Steinbrocker stage showed that 118 participants (21.6%) were Stage I, 135 (24.7%) were Stage II, 101 (18.4%) were Stage III and 192 (35.1%) were Stage IV.

The stage distribution was similar to that of a survey of prevalent RA cases in Akita prefecture, a northern area of Japan (32), implying that our sample was representative.

The representativeness of the sample was further supported by the fact that complications with RA in the present study were comparable with those in other studies (1, 9). In our study, 27.2% of participants (n = 149) had respiratory diseases, 20.1% (n = 110) extra-articular manifestation and 3.1% (n = 17) connective tissue diseases.

Variables related to physical state and pain were summarized in Table1. For emotional factors, the mean HADS-anxiety score was 4.8 (SD = 3.7; median = 4, IQR = 2–7) and the mean HADS-depression score was 5.8 (SD = 3.7; median = 5, IQR = 3–8). HADS scores indicated that 56 patients (10.4%) had possible anxiety and 45 (8.3%) probable

anxiety, and that 93 (17.3%) had possible depression and 65 (12.1%) probable depression.

Correlation analysis

Spearman's correlation analysis showed significant correlations with a medium effect size ($r > 0.3$) (33) among observed variables representing the same latent factor, except one relationship between SJC68 and ESR 1h ($r = 0.272$) (Table 2).

SEM

Following scrutiny of modification indices during the model fit procedures, the final model included covariance between: 1) ESR and CRP, 2) CRP and MMP3, and 3) SJC and TJC (Fig. 1B). Inclusion of these covariances was clinically justified for three reasons. First, ESR and CRP are markers of inflammation and have a strong correlation among RA patients (1, 22). Second, CRP and MMP3 reflect radiological damage and are related to each other in the course of RA with/ without progression of radiological damage (22). Third, SJC and TJC represent symptomatic (i.e. swollen and tender) joint counts (68 joints), and it is reasonable to assume that they are closely related. Fig.1B shows factor loadings for the three latent factors. The fit between the hypothesized

model and the data was satisfactory (31): RMSEA = 0.069, CFI = 0.917, TLI = 0.847 and SRMR = 0.040.

The path coefficient in Fig. 1B revealed a significant direct effect of physical state on pain ($\beta = 0.54$, $p < 0.001$). Path analyses revealed that physical state exerted a significant effect on emotional health ($\beta = 0.21$, $p < 0.05$). In turn, emotional health had a significant influence on pain ($\beta = 0.29$, $p < 0.01$). These results afforded a premise for proceeding to the next step of mediation analysis, as suggested by Baron and Kenny (34).

The indirect effect was calculated in the SEM framework (Table 3). There was a significant indirect effect from physical state through emotional health to pain (Delta: β indirect = 0.06, $p < 0.05$; bias-corrected bootstrap (29) 95% CI : 0.021–0.374). This indicated that the relationship between physical state and pain was partially but significantly mediated by emotional health (Model 1), with the indirect effect accounting for 10.2% of the total effect of physical state on pain. The model yielded an R^2 value of 0.428 for the dependent variable (pain), indicating that direct and indirect paths accounted for 43% of the variance of pain. However, this value could not be

partitioned. Therefore, we computed R² using estimated parameters for the relevant paths. The results indicated that physical state accounted for 28.9% of the variance of pain, 8.6% of which was attributable to emotional health.

The Wald test (31) was found to be non-significant, indicating that there was no significant difference in the moderated indirect effect between groups created by the binary variables (employment status, current psychiatric treatment, any physical complications or RA treatments such as MTX, DMARDs other than MTX and biological drugs) (see “Supplementary material”).

We used FIML throughout the SEM analyses, meaning that all available information was used to maximize the estimation of model parameters. This approach is appropriate when missing data occur at random or completely at random. However, there is a possibility of missing data not at random (NMAR). In explicating NMAR, we re-examined the data with a listwise deletion method. This approach with complete cases (n = 481) revealed virtually identical path coefficients, indicating that missing data occurred at random, which refuted any involvement of NMAR: physical state to emotional health ($\beta = 0.25$, $p < 0.05$), emotional health to pain ($\beta = 0.26$, $p < 0.01$) and

physical state to pain ($\beta_{\text{direct}} = 0.55$, $p < 0.01$; $\beta_{\text{indirect}} = 0.07$, $p < 0.05$). Good model fit was retained: RMSEA = 0.066, CFI = 0.923, TLI = 0.858 and SRMR = 0.038.

Discussion

The SEM analyses of patients with RA showed that physical state significantly affected emotional health. Furthermore, both physical state and emotional health had significant effects on pain. We found that 10.4% of patients with RA had possible anxiety and 8.3% had probable anxiety. The reported prevalence of anxiety varies across studies.

One study using UK and Australian data showed a prevalence of 16.7% possible and 18.6% probable anxiety (2), while a Japanese study found 7.0% probable anxiety among patients with RA (26). In this study, 17.3% of patients with RA had possible depression and 12.1% had probable depression, which is similar to the results of a recent meta-analysis that used identical cut-offs (19.4/14.8% with possible/probable depression) (17).

The significant effect of emotional health on pain found in this study is consistent with previous reports (8, 10, 35). Longitudinal studies have demonstrated a significant effect of anxiety and depression on TJC (an indicator of pain) (8). Another recent study

reported that depression affects pain severity (10). These studies suggest that emotional factors may exacerbate pain in patients with RA.

Our finding of a significant influence of emotional health on pain may have clinical implications for current RA treatment. According to the ACR guideline (5), treatment choices depend on RA disease activity. For example, for an individual with RA with low disease activity, DMARD monotherapy is strongly recommended if the patient is DMARD-naïve. For patients with moderate or high disease activity receiving DMARD monotherapy, combination therapy or biologic treatment is recommended. Therefore, disease activity plays a key role in RA treatment decision-making. In current clinical settings, RA disease activity is evaluated by composite indices such as DAS28, SDAI and CDAI (1, 21). However, these composite indices include TJC (an indicator of pain), and, thus, are potentially influenced by emotional health, as this study illustrated.

Therefore, assessment of disease activity using these measures may be overestimated if an individual has emotional problems. If some degree of high disease activity is attributable to emotional factors, overtreatment may occur. Consideration of emotional factors in evaluating disease activity may avoid undue RA treatment. This may, in part, lead to a reduction of inflated healthcare expenditure ascribed to the increased use of biological drugs (1). Assessing true disease activity targeting for immunosuppressive

therapy is strongly required (7).

Our findings suggest that RA treatments targeting emotional factors can ameliorate pain. A meta-analysis of randomized controlled trials showed that psychological interventions for RA have positive effects on pain as well as on anxiety and depressive symptoms (36). Furthermore, antidepressants have been shown to relieve pain in people with both RA and anxiety/depression (37). These studies and our findings suggest that interventions for emotional health in individuals with RA may substantively alleviate pain, which in turn results in improvement of quality of life (38). Therefore, emphasis should be placed on detailed assessment of emotional health among people with RA.

This study has several limitations. First, there might be problems related to the construction of hypothetical models in SEM. For example, we did not incorporate the effect of pain on emotional health in our theory-driven model, because we focused on the effects of physical state and emotional health on pain, as well as the effect of physical state on emotional health. Further research using longitudinal data is required to investigate causal relationships between the three factors (i.e. physical state, emotional health and pain). Second, selection of variables in the hypothetical models

had limitations. The estimated effects in this study might be influenced by unknown variables, such as social factors (e.g. socioeconomic factors, lifestyle, degree of social activities, health behaviours and lack of support from others), although basic characteristics such as age and gender were incorporated in the model as covariates. Third, all participants were from the KURAMA cohort (21), which comprised outpatients at Kyoto University Hospital (located in one of the largest cities in Japan). This cohort includes patients with RA in clinical remission, which might have led to underestimation of the relationship between inflammation and pain. Thus, caution is needed in generalising our findings to a broader sample of patients with RA. However, the clinical characteristics of participants in this study were similar to those described in other international reports (1, 6, 8, 9, 17, 32). Finally, psychiatric evaluation was based on self-reported questionnaire responses, which may not objectively reflect psychological state.

In summary, our study indicates that emotional health partially but significantly mediates the relationship between physical state and pain in RA, and emotional suffering exacerbates pain. Although pain is currently included in RA disease activity measurement, physicians need to be aware of the possibility of overestimated disease

activity due to inclusion of pain components. When ascertaining RA disease activity, emotional factors should be considered to circumvent overestimation of disease activity and unnecessary, excessive treatment.

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Figures & Figure legends

Fig. 1A. Hypothesized model of the effects of physical and emotional health on pain.

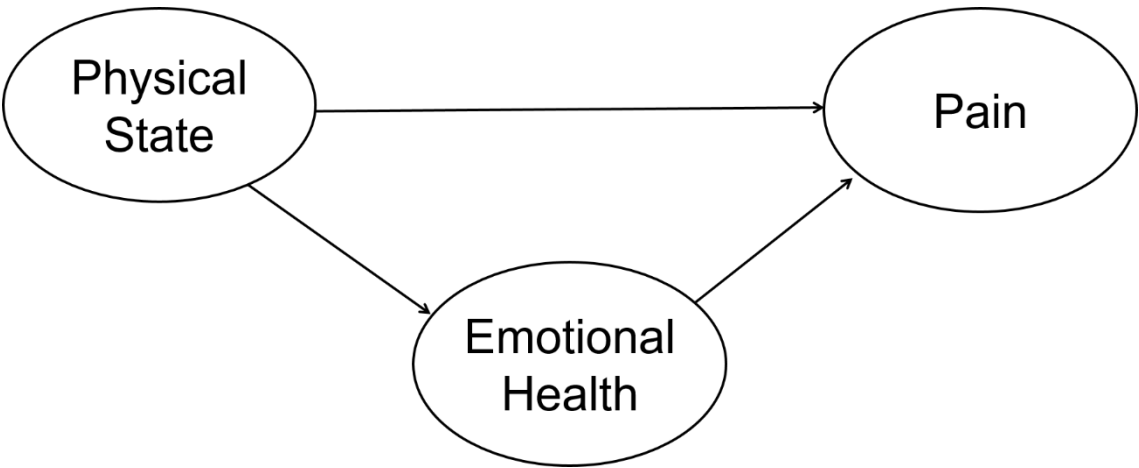
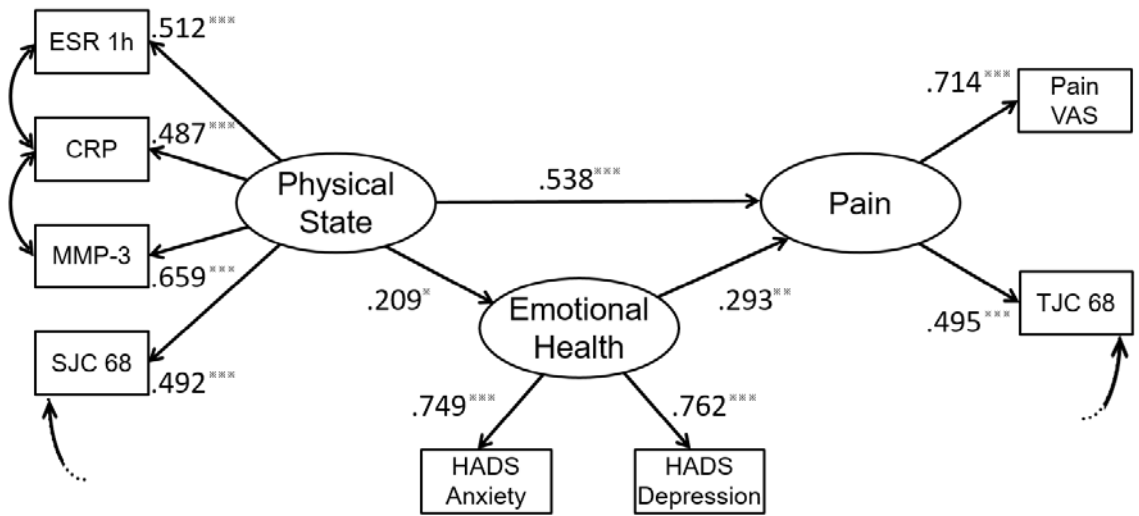


Fig. 1B. Estimated factor loadings and path coefficients for structural equation modeling.

Age and gender adjusted for as covariates in the model



*P < 0.05, **P < 0.01.

ESR 1h, erythrocyte sedimentation rate 1h level (mm/h); CRP, C-reactive protein (mg/dl); MMP3, metalloproteinase-3 (ng/ml); SJC, swollen joint count (68 joints); pain VAS, visual analogue scale for pain; TJC, tender joint count (68 joints); HADS-anxiety, anxiety subscale of the Hospital Anxiety and Depression Scale; HADS-depression, depression subscale of the Hospital Anxiety and Depression Scale.

All paths displayed in the figure are statistically significant. Curved arrows represent covariances. Curved arrows with a dashed line denote omission in the covariance between SJC68 and TJC68. The fit between the hypothesized model and the data was fairly good: root mean square error of approximation = 0.069 (90% confidence intervals 0.054–0.085), comparative fit index = 0.917, Tucker–Lewis fit index = 0.847 and standardized root mean square residual = 0.040.

Table 1. Participants' demographic characteristics

	mean (SD) / n (%)	N
Age (years), mean (SD)	62.6 (13.1)	546
Female, n (%)	456 (83.5)	546
Employed (including housework), n (%)	410 (74.8)	548
Current psychiatric treatment, n (%)	25 (4.6)	540
RA Treatments, n (%)		548
MTX	370 (67.5)	
DMARDs other than MTX	213 (38.9)	
Biological drugs	216 (39.4)	
Stage, n (%)		546
I	118 (21.6)	
II	135 (24.7)	
III	101 (18.4)	
IV	192 (35.1)	
Disease duration from the onset of symptoms (years), mean (SD)	14.8 (12)	443
Physical complications, n (%)		547
Extra-articular manifestations	110 (20.1)	
Connective tissue diseases	17 (3.1)	
Respiratory diseases	149 (27.2)	
EQ5D, mean (SD)	7.5 (2)	548
HADS-anxiety, mean (SD)	4.8 (3.7)	539
Possible anxiety, n (%)	56 (10.4)	

Probable anxiety, n (%)	45 (8.3)	
HADS-depression, mean (SD)	5.8 (3.7)	537
Possible depression, n (%)	93 (17.3)	
Probable depression, n (%)	65 (12.1)	
ESR 1h (mm/h)		527
mean (SD)	22.5 (18.7)	
median (IQR)	16 (9-29)	
CRP (mg/dl)		515
mean (SD)	0.38 (0.73)	
median (IQR)	0.1 (0–0.3)	
MMP3 (ng/ml)		528
mean (SD)	103.5 (110.6)	
median (IQR)	68.05 (44.5–120.9)	
SJC68		529
mean (SD)	1.03 (1.87)	
median (IQR)	0 (0–1)	
TJC68		529
mean (SD)	1.18 (2.08)	
median (IQR)	0 (0–2)	
Pain VAS		547
mean (SD)	27.8 (25.8)	
median (IQR)	18 (5–49)	

RA, Rheumatoid Arthritis; MTX, Methotrexate; DMARDs, disease-modifying

antirheumatic drugs; EQ5D, EuroQol-5D; HADS, Hospital Anxiety and Depression

Scale; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; MMP3, matrix metalloproteinase-3; SJC, swollen joint count; TJC, tender joint count; VAS, visual analogue scale; IQR, interquartile range; SD, standard deviation

Possible anxiety, score of 8–10 on the anxiety subscale of HADS; Probable anxiety, score of 11–21 on the anxiety subscale of HADS

Possible depression, score of 8–10 on the depression subscale of HADS; Probable depression, score of 11–21 on the depression subscale of HADS.

Table 2. Correlations between observed indicator variables

	Physical state				Pain		Emotional health	
	ESR 1h	CRP	MMP3	SJC	TJC	VAS	Anxiety	Depression
ESR 1h	1							
CRP	0.603***	1						
MMP3	0.345***	0.408***	1					
SJC68	0.272***	0.330***	0.325***	1				
TJC68	0.223***	0.291***	0.272***	0.552***	1			
Pain VAS	0.207***	0.244***	0.290***	0.371***	0.443***	1		
Anxiety	0.03	0.061	0.073	0.044	0.112*	0.267***	1	
Depression	0.097*	0.102*	0.166***	0.061	0.130**	0.254***	0.526***	1

*P < 0.05, **P < 0.01, ***P < 0.001. ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; MMP3, matrix metalloproteinase-3; SJC: swollen joint count; TJC, tender joint count; VAS, visual analogue scale.

Table 3. Direct and indirect effects obtained from structural equation modeling

	Std. estimate	SE	P value
Direct effect			
physical state → emotional health	0.209	0.097	0.032
emotional health → pain	0.293	0.088	0.001
physical state → pain	0.538	0.098	<.001
Indirect effect			
physical state → emotional health → pain	0.061	0.028	0.028

Std. estimate, standardized estimate; SE, standard error.

SUPPLEMENTARY TABLE

Moderation analysis of indirect effect by grouping variable

Grouping variable	Wald test value	<i>p</i> -value
Employment status	0.54	0.46
Current psychiatric treatment	0.79	0.37
Any physical complications	1.70	0.19
MTX	0.85	0.35
DMARDs other than MTX	0.27	0.59
Biological drugs	0.01	0.90

MTX, Methotrexate; DMARDs, disease-modifying antirheumatic drugs.