Multifactorial explanatory model of depression in patients with rheumatoid arthritis: a structural equation approach

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Abstract

Objective

Depressive symptoms are common among patients with rheumatoid arthritis (RA). This study was aimed at developing a multifactorial explanatory model that evaluated the influence of personality traits, disease activity, perceived disease impact, and comorbidities.

Methods

This cross-sectional study used structural equation modelling estimation to analyse the associations between these dimensions, pursuing three hypotheses. Depressive symptoms were assessed using the Hospital Anxiety and Depression Scale, disease impact by the Rheumatoid Arthritis Impact of Disease score, personality by the Ten Item Personality Inventory and the disease activity through the Disease Activity Score 28 joints. The influence of comorbidities was investigated by multigroup analysis.

Results

The final model derived from data of 254 patients presented a good fit. Disease activity had an indirect relation with depressive symptoms mediated by disease impact (β=0.17, p<0.001), but the direct relationship between disease activity and depressive symptoms was not significant (β=0.09; p=0.07). "Positive" personality had a strong negative direct relation with depressive symptoms as well as an indirect relationship mediated by disease impact (total effect β=-0.61, p<0.001). The final proposed model explained 58% of the variance of depressive symptoms. Multigroup analysis showed an invariant model when comparing patients with and without comorbidities ($d\chi^2$=9.03; df=12; p=0.70).

Conclusion

Personality characteristics seem to have a major influence upon the impact of disease and the patient's adjustment to RA, including the vulnerability or resilience to depression. Individual personality traits deserve attention in tailored assessment and treatment of patients with RA, in order to optimise outcomes.

Key words

rheumatoid arthritis, depression, outcome assessment (health care)

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Introduction

Rheumatoid arthritis (RA) can severely disturb all aspects of patients' lives, including social relationships, family life and psychological well-being (1). The body of evidence confirms that depressive symptoms and major depression disorder are common in patients with RA, with a prevalence of 10–20% (2-6). Depression is a mood disorder characterised by sustained sadness and/or a loss of interest or pleasure in daily activities, along with a set of cognitive symptoms such as feelings of self-worthlessness, guilt, and hopelessness as well as somatic symptoms such as fatigue, sleep and appetite dysregulation (7). It has been shown that depression is associated with increased worry about illnesses and negative illness perceptions related with the consequences, controllability and emotional impact of the disease, which add to the disease burden (8-10).

Patients with RA and comorbid depression also have worse health outcomes including higher levels of pain (2) and increased functional disability (11). These associations persist even when the disease activity is under control or remission (8-11). Patients with comorbid depression at the onset of treatment, with or without biological agents, have been shown to have a lower rate of remission or low disease activity (up to 30% less) as a result of smaller effects upon not only pain and patient-reported outcomes but also on swollen joint counts and acute phase reactants (12-14). This suggests that depression influences the disease process itself and not simply the self-rated impact of disease. In fact, these interactions should not come as a surprise given the known influences of depression and its treatments upon the immune system (15-17). These observations underline that depression in patients with RA deserves a lot more attention than it usually receives by health professionals (18-21), not only because it affects the patient's lives beyond disease control (22), but also because it hinders the efficacy of the immunosuppressive therapy.

Studies that investigated the nature of the relationship between depression and RA suggest that it is multifactorial (8, 23, 24). Factors that may contribute to depression in RA patients include the direct effect of pro-inflammatory cytokines on the central nervous system as well as indirect effects of disease activity such as pain, disability, loss of social life and fear of disease's progression (8, 23). Moreover, psychological variables may affect both depression and the experienced impact of the disease. In the current study, personality is assumed to be an overarching psychological variable that should be considered next to disease activity because it predisposes to the experience of more or less impact of the disease (25) and depression (26, 27). Finally, comorbidities are assumed to have an impact on depression because they add to the impact of the disease. Sociodemographic variables, such as female gender, younger age, less formal education and socioeconomic disadvantage were also observed to be risk factors for depression among RA patients (23, 28).

Most studies examined relationships between these variables using linear regression models, while mutual interactive relationships likely give a better reflection of the complex interrelations between disease activity and impact, depression and personality traits. Taking this into consideration, this study aims to test an integrative model where the interconnections between variables are highlighted. A better understanding of these interactions can inform current approaches to RA and improve health outcomes by optimising the design of holistic interventions. Our study is based on three main hypotheses:

H_1 – Disease activity is associated with depressive symptoms, both directly and indirectly through impact of disease;

H_2 – "Positive" personality traits are negatively related with depressive symptoms, both directly and indirectly through perceived impact of disease;

H_3 – The hypothesised model varies as a function of the presence of comorbidities.

Materials and methods

Study design

This is a secondary analysis of an observational, cross-sectional study, performed in a single rheumatology

outpatient department (22), designed to explore the determinants of patient global assessment of disease activity in RA. The study included consecutive adult patients who had the ability to interpret the applied questionnaires and who agreed to participate through written informed consent. Ethical approval was granted by the Ethics Committee of the Faculty of Medicine of the University of Coimbra (CEU 037/2015).

Measures/ Instruments

Depressive symptoms were assessed using the Hospital Anxiety and Depression Scale (HADS) (29), a 14-item (rated on a 4-point Likert) scale. In this analysis we only used the depression subscale, for which scores ≥11 correspond to probable depression (29).

Disease impact was assessed with the Rheumatoid Arthritis Impact of Disease (RAID) score (30, 31), which is composed of 7 items scored on a 10-point numeric rating scale. A higher score indicates greater impact of the disease. The domains fatigue, sleep and emotional well-being were excluded due to the potential overlap with the emotional and somatic aspects of depressive symptoms.

Personality was assessed by the Ten Item Personality Inventory (TIPI) (32), a brief measure of the Big-Five personality dimensions (*i.e.* extraversion, agreeableness, conscientiousness, emotional stability and openness to experience), each being scored as the mean of 2 items (rated on a 7-point Likert scale). Higher scores indicate a stronger expression of the respective trait. We designated the latent higher order factor derived from TIPI as "Positive" personality, to denote the predominantly adaptive nature of the represented dimensions.

Disease activity was measured with the Disease Activity Score 28 joints (DAS28), in its three variables (3v) and C-reactive protein (CRP) variant – DAS28CRP3v (33). We excluded the Patient Global Assessment, considered in the 4v models of DAS28, due to its close relationship with depression and RAID (22). Patients were categorised according to DAS28CRP3v into four levels of disease activity: remission <2.40, low ≤2.90, moderate ≤4.60 and high >4.60 (34).

Demographic data, disease characteristics, presence/absence of comorbidities (fibromyalgia, low back pain, fracture, osteoporosis and stroke) and current treatment were collected from medical records.

Data analysis

The software SPSS®, v. 23 (IBM, Armonk NY, USA) was used to perform descriptive and correlational analyses. The assumptions of normality and multicollinearity were confirmed (35). The skewness of score distributions ranged from -1.00 to 1.00 and kurtosis from -0.91 to 1.15. Variance Inflation Factor (VIF) showed values below 4.80 for all variables included in the model, excluding multicollinearity as an issue. Pearson correlation analyses were conducted to examine the associations between disease activity, disease impact, personality traits and depressive symptoms and interpreted according to Cohen's benchmark values (36) as low (<0.30), moderate (0.30 to 0.50) or high (>0.50).

Structural equation modelling (SEM, Latent variable structural model) was used to estimate the association between these variables and performed with AMOS® 24.0 (IBM® SPSS® Inc, Chicago IL, USA), using a maximum likelihood estimation (MLE). A set of goodness of fit indices were used to test the plausibility of the model: (i) the chi-square (χ^2), (ii) the Comparative-of-Fit-Index (CFI), (iii) the Goodness-of-Fit Index (GFI), (iv) the Tucker-Lewis Index (TLI), and (v) the Root Mean Square Error of Approximation (RMSEA). A good fit of the models was assumed when: the ratio of χ^2 to its degrees of freedom was less than 3.0; CFI, GFI, TLI were larger than 0.90 (37); RMSEA values <0.06, were considered ideal and values between 0.08 and 0.10 were considered acceptable (35). When paths were not significant they were excluded, leading to the readjustment of the initially hypothesised model (such as DAS283v -> depressive symptoms). Two variables identified in the literature as risk factors for depression (age and formal education) were also excluded from the model because they were also not statistically significant and conditioned the fit of the model.

Furthermore, the bootstrap resampling method, with 1000 bootstrap samples and 95% bias-corrected CIs around the standardised estimates of total, direct and indirect effects, was used to test the significance of the mediational path (38). Statistically significant effects were assumed for $p<0.05$.

In order to analyse whether the existence of comorbidities (having at least one comorbidity versus not having any) influenced the proposed model, we performed a multigroup analysis through a critical ratios and chi-square differences procedure. Critical ratio values higher than 1.96 were indicative of significant difference between groups.

Results

Patient characteristics

A total of 254 patients with RA were included in this analysis. Their demographic and clinical characteristics are presented in Table I. Participants were aged between 27 and 88 (M=59.1; SD=12.7) years, had a mean disease duration of 11.8 (SD=8.8) years and an average of 7.6 years of school education. The majority of patients (n=179, 70.5%) had at least one identified comorbidity. The mean DAS28CRP3v was 2.47, with 53.2% (n=135) of patients being in remission according to this index (<2.40). Around 22% of patients (n=57) were "probably depressed" according to HADS scores.

Correlation coefficients

Pearson correlation coefficients are presented in Table II. Extraversion, emotional stability and openness to experience were negatively associated, with low to moderate correlations coefficients, with all dimensions of impact of disease; agreeableness and conscientiousness were not associated with any of the dimensions of impact of disease. Depressive symptoms correlated high and positively with all dimensions of impact of disease, low and positively with disease activity [DAS28CRP3v], and low to moderate and negatively with all "positive" personality traits.

Table I. Sociodemographic and clinical characteristics of the sample (n=254).

Variables	Scores[#]
Age, years	59.1 (12.7)
Female gender, n (%)	206 (81.1)
School education, years	7.6 (4.7)
Disease duration, years	11.8 (8.8)
Rheumatoid factor positive, n (%)*	180 (72.6)
Anti-citrullinated antibody positive, n (%)*	118 (68.2)
Presence of comorbidities (at least one), n *(%)*	179 (70.5)
Fibromyalgia	42 (16.5)
Low Back Pain	64 (25.2)
Osteoporotic fractures	23 (9.1)
Osteoporosis	76 (29.9)
Stroke	6 (2.4)
Current treatment with Biologic Agents, n (%)	77 (30.4)
Tender 28-joint counts, (0–28)	1.37 (2.9)
Swollen 28-joint counts, (0–28)	1.43 (2.6)
C-reactive protein (mg/dl)	0.88 (1.4)
DAS28CRP3v (0–9.4)	2.47 (.92)
Remission (<2.4), n (%)	135 (53.2)
Low (≤2.9), n (%)	53 (20.9)
Moderate (≤4.6), n (%)	57 (22.4)
High (>4.6), n (%)	9 (3.5)
Physician global assessment (VAS, 0–100)	13.8 (15. 5)
Patient global assessment (VAS, 0–100)	48 (28.6)
Rheumatoid Arthritis Impact of Disease (0–10)	
Pain	4.9 (2.5)
Functional disability	4.9 (2.5)
Fatigue	5.1 (2.7)
Emotional well-being	4.6 (2.6)
Sleep	4.4 (2.9)
Coping	4.2 (2.7)
Physical well-being	4.9 (2.5)
Hospital Anxiety and Depression Scale (0–21)	7.2 (4.2)
Not depressed (≤7), n (%)	135 (53.1)
Possibly depressed (8-10), n (%)	62 (24.4)
Probably depressed (≥11), n (%)	57 (22.5)
Ten Item Personality Inventory (1–7)	
Extraversion	4.2 (1.5)
Agreeableness	5.7 (1.2)
Conscientiousness	5.7 (1.2)
Emotional Stability	3.6 (1.5)
Openness to Experience	4.4 (1.5)

[#]Values are mean (Standard deviation) unless stated in contrary. *Percentages of patients with missing data for Rheumatoid Factor were 2.3% and for Anti-citrullinated antibody 31.8%.

Finally, disease activity showed moderate positive associations with impact of disease and a small negative association with emotional stability.

Structural equation modelling

The results obtained in the structural equation measurement model indicated a good fit to the data [$\chi^2_{(42)}$=100.04, χ^2/df=2.38, p<0.005; CFI=0.95; GFI=0.93; TLI=0.94; RMSEA=0.07, p=0.02, 95% CI=0.06 to 0.09]. The direct path coefficients for the model are shown in Table III and Figure 1. The total model explained 58% of the variance of the depressive symptoms (R^2=0.58). "Positive" personality and disease activity explained 23% of the variance of impact of disease (R^2=0.23) (Fig. 1).

H_1 – *Disease activity is associated with depressive symptoms, both directly and indirectly through perceived impact of disease*

The results did not corroborate a direct association between disease activity [DAS28CRP3v] and depressive symptoms (β=0.09; p=0.07), and confirmed an indirect association (β=0.17, 95% CI= 0.10 to 0.23, p=0.001) with depressive symptoms through the perception of impact of disease (Table III, Fig. 1). Disease activity showed a significant positive direct relation with impact of disease (β=0.36; p<0.001) which, in turn, showed a significant positive direct relation with depressive symptoms (β=0.48; p<0.001).

H_2 – *"Positive" personality traits are negatively related with depressive symptoms, both directly and indirectly through perceived impact of disease*

"Positive" personality traits had a total effect of β=-0.61 on depressive symptoms, including a direct effect of β=-0.46 (p<0.001) and an indirect effect of β=-0.15 (95% CI= -0.23 to -0.08, p=0.001) through impact of disease, indicating a mediating influence in this relationship (Table III, Fig. 1). The model also showed a direct negative relation between "Positive" personality traits and impact of disease (β=-0.31; p<0.001).

H_3 – *The hypothesised model varies as a function of the presence of comorbidities*

The multigroup analysis revealed that the global model was invariant (dχ^2=9.03; df=12; p=0.70) between patients with RA with and without comorbidities. However, analysis of the critical ratio differences between parameters indicated only one difference that did not influence the overall model. The groups differed significantly (z=-1.96; p=0.05) in the individual path from pain to disease impact, with the group with comorbidities showing a greater standardised weight (β=0.91) than the group without comorbidities (β=0.77). This indicates that pain contributed more to disease impact in the group with than without comorbidities (Table IV).

Discussion

This study addressed in a single model the relationships between disease activity, impact of disease, personality traits and depression. Among the strengths of our work we would underline the combination of objective and subjective evaluations of disease within the same model, and the inclusion of adjustments for multiple relevant variables, such as comorbidities. This provides

Table II. Pearson correlation coefficients among all variables of interest.

	1	2	3	4	5	6	7	8	9	10	11
Rheumatoid Arthritis Impact of Disease											
Pain (1)	1.0										
Functional disability (2)	0.83**	1.0									
Physical well-being (3)	0.76**	0.83**	1.0								
Coping (4)	0.74**	0.75**	0.78**	1.0							
Positive Personality											
Extraversion (5)	-0.16**	-0.20**	-0.17**	-0.22**	1.0						
Agreeableness (6)	-0.01	-0.01	-0.04	-0.11	0.06	1.0					
Conscientiousness (7)	0.02	-0.06	-0.06	-0.09	0.29**	0.40**	1.0				
Emotional stability (8)	-0.24**	-0.29**	-0.32**	-0.27**	0.25**	0.20**	0.18**	1.0			
Openness to experience (9)	-0.15*	-0.18**	-0.18**	-0.22**	0.32**	0.18**	0.27**	0.20**	1.0		
Depressive symptoms (10)	0.52**	0.57**	0.56**	0.59**	-0.39**	-0.19**	-0.26**	-0.38**	-0.28**	1.0	
DAS28CRP3v (11)	0.34*	0.40**	0.34**	0.30**	0.02	-0.06	0.01	-0.14*	0.01	0.27**	1.0

DAS28CRP3v: Disease Activity Score using 28 joints and C-reactive protein and 3 variables. * $p<0.05$; ** $p<0.001$

Table III. Regression weights between structural parameters.

	Unstandardised direct effects	Standardised direct effects	Standard Error	Critical Ratio	Significance level
Impact of disease ← Positive personality	-0.79	-0.31	0.22	-3.7	<0.001
Impact of disease ← DAS28CRP3v	0.88	0.36	0.15	6.0	<0.001
Extraversion ← Positive personality	1.00	0.57	#	#	#
Agreeableness ← Positive personality	0.51	0.37	0.12	4.3	<0.001
Conscientiousness ← Positive personality	0.73	0.52	0.13	5.6	<0.001
Emotional stability ← Positive personality	0.78	0.46	0.15	5.2	<0.001
Openness to experience ← Positive personality	0.83	0.49	0.15	5.4	<0.001
Coping ← Impact of disease	1.00	0.84	#	#	#
Physical wellbeing ← Impact of disease	0.98	0.89	0.05	18.6	<0.001
Function disability ← Impact of disease	1.04	0.92	0.05	19.6	<0.001
Pain ← Impact of disease	0.96	0.87	0.05	17.8	<0.001
Depressive symptoms ← Positive personality	-2.19	-0.46	0.40	-5.5	<0.001
Depressive symptoms ← Impact of disease	0.88	0.48	0.10	8.5	<0.001

#Constrained paths. DAS28CRP3v: Disease Activity Score using 28 joints and C-reactive protein 3 variables. Unstandardised direct effects come directly out of the estimation procedure. Due to the metric differences of the instruments, in this case, standardised direct effects should be preferred to indicate the strength of the associations (magnitude between -1.0 and +1.0). Higher absolute values indicate a stronger (positive or negative) association. An absolute critical ratio >1.96 reflects that path coefficients are significant at the 0.05 level.

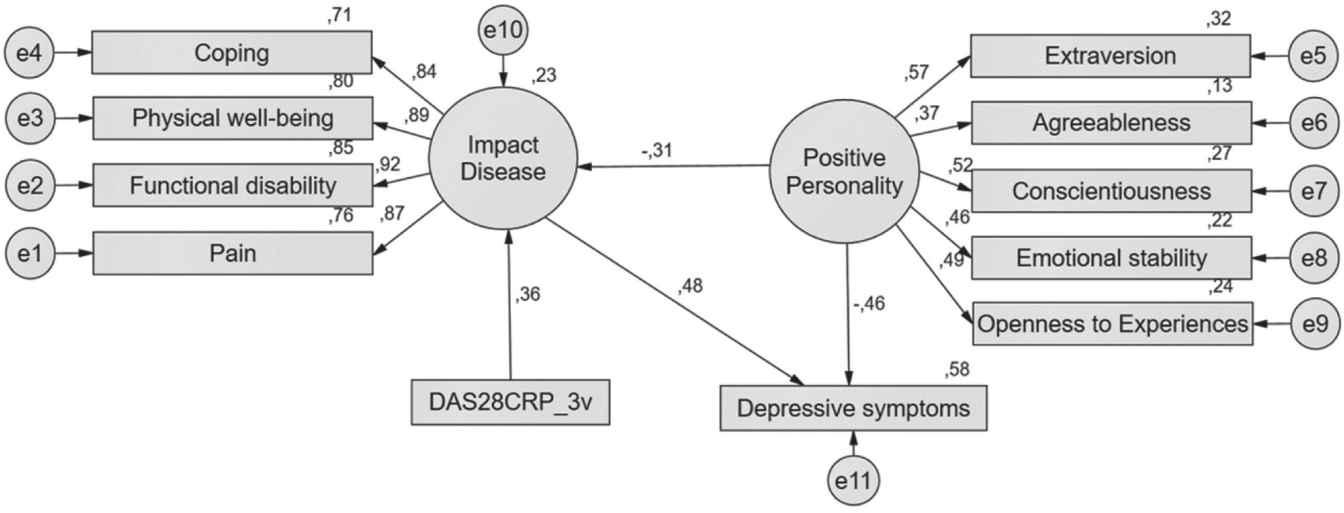

Fig. 1. Estimated standardised direct effects for the proposed model.
DAS28CRP3v: Disease Activity Score using 28 joints and C-reactive protein 3 variables. Circles represent latent factors. Squares represent measured variables (the scale scores). Arrows connecting circles and rectangles in one direction show a hypothesised direct relationship between the two variables. Circles with the letter "e" written in it represent the associated error.

Table IV. Multigroup differences for the influence of comorbidities using critical ratios.

	Comorbidities			No comorbidities			z-score
	Unstandardised direct effects	Standardised direct effects	Significance level	Unstandardised direct effects	Standardised direct effects	Significance level	
Impact of disease ← Positive personality	-0.64	-0.27	0.009	-0.80	-0.30	0.04	-0.33
Impact of disease ← DAS28CRP3v	0.80	0.36	<0.001	0.72	0.31	0.007	-0.26
Extraversion ← Positive personality	1.00	0.56	#	1.00	0.55	#	#
Agreeableness ← Positive personality	0.45	0.30	0.003	0.69	0.55	0.001	0.94
Conscientiousness ← Positive personality	0.69	0.47	<0.001	0.97	0.68	<0.001	0.89
Emotional stability ← Positive personality	0.72	0.43	<0.001	0.88	0.49	0.002	0.48
Openness to experience ← Positive personality	0.79	0.46	<0.001	0.85	0.50	0.002	0.18
Coping ← Impact of disease	1.00	0.80	#	1.00	0.87	#	#
Physical wellbeing ← Impact of disease	1.00	0.87	<0.001	0.98	0.91	<0.001	-0.15
Function disability ← Impact of disease	1.11	0.92	<0.001	1.00	0.91	<0.001	-0.99
Pain ← Impact of disease	1.06	0.91	<0.001	0.84	0.77	<0.001	-1.96*
Depressive symptoms ← Impact of disease	0.85	0.42	<0.001	0.90	0.51	<0.001	0.23
Depressive symptoms ← Positive personality	-2.43	-0.51	<0.001	-1.89	-0.41	0.003	0.65

DAS28CRP3v: Disease Activity Score using 28 joints and C-reactive protein 3 variables. #Constrained paths. *Path coefficients are significant at 0.05 level.

a robust network model with multiple relations reflecting the spectrum of mutually interacting variables.

Overall, the results confirm that disease activity, disease impact and depressive symptoms are mutually associated. They do not allow conclusions regarding causal relationships, given that systemic inflammation may cause or contribute to depressive symptoms (8, 12, 39), and that the inverse relationship, depression increasing inflammation, is also supported by evidence. Depression may negatively affect the disease course, its impact and the treatment outcome due to its influence on the experience of symptoms, health behaviour and the actual response to medication (40). Our model supported an indirect relationship between disease activity and depression mediated by impact of disease, but not a direct relationship between these two dimensions.

The path testing the association between personality and depression is strongly significant. The model indicates that positive personality traits are directly and indirectly associated with depressive symptoms. This underlines that psychological vulnerability and resilience factors associated with personality should be taken into consideration while trying to understand the consequences of disease and in designing strategies to improve both disease and depression. The association between personality and depression is not surprising as a wealth of literature already suggests that depression is linked to traits such as neuroticism and (low) extraversion and conscientiousness (26, 27, 41, 42). Our results emphasise the importance of personality in the appraisal of and coping with the impact of disease and as a protective factor against depression in the context of a chronic, painful, and potentially disabling condition.

The mutual associations between disease activity, disease impact and depression are of major importance to practising health professionals, such as rheumatologists, focused on achieving the best possible outcome for patients, including but going beyond disease control. Depressive symptoms and helplessness have been shown to lead people towards a higher impact of disease (2, 11), lower quality of life and happiness. They have also been associated with lower adherence to both pharmacological and non-pharmacological interventions (*e.g.* physical exercise or strength training) (43), and to reduce the effectiveness of treatments (44). Conversely, disease activity, through inflammatory cytokines, pain and disability, increases the prevalence and severity of depressive symptoms (2, 4, 45) while effective treatment of RA improves the rate of depression (46). Thus, a wise management plan should try to reduce both disease activity and depression (23, 47, 48), while taking account of their relations and the decisive contextual role of personality.

Additionally, our results show that the contribution of pain to disease impact is greater in patients with than in patients without comorbidities. One possible explanation for this finding may be the fact that the most prevalent comorbidities in our sample, fibromyalgia, low back pain, have pain as the cardinal symptom.

Despite the rigour that we imposed to our analyses, our results are subject to some limitations. First, as the recruitment was carried out in a single center, caution is needed in the generalisation of these results, despite the size and diversity of the studied sample. Second, these are cross-sectional data, which do not allow establishing causal relationships. However, the between-subjects analyses allowed us to show which persons are more vulnerable or resilient to depression, which is useful to tailor interventions. Third, depressive symptoms were assessed through HADS, which does not allow a formal diagnosis of depression. However, this "screening" tool has shown high reliability as well as sensitivity and specificity to predict the diagnosis of depression (49). Fourth, the relatively small sample size forced us to lump different comorbidities into a single group. A more detailed analysis of the specific influence of different types of comorbidities upon the model could constitute a relevant target for future studies. Finally, since the vast majority of the sample is female, we opted not to

perform gender analysis, although we recognise its potential importance.

In conclusion, personality characteristics seem to have a major influence upon the impact of RA in patients' lives and the patients's adjustment, including the vulnerability to or resilience against depression. Depression is, conversely, associated with disease activity and impact. Individual personality traits deserve attention in tailoring approaches to optimise outcomes in the management of RA. A multidisciplinary and multimodal approach will probably be required to fully accomplish this potential.

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