Depression, disability and sleep disturbance are the main explanatory factors of fatigue in rheumatoid arthritis: a path analysis model

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Abstract

Objective

Fatigue is one of the most prevalent and disabling symptoms among patients with rheumatoid arthritis (RA), however, it is frequently neglected by health professionals. This study aimed to develop a multidimensional explanatory model of fatigue in patients with RA as a basis for better understanding and intervention.

Methods

This was an ancillary analysis of an observational, cross-sectional, single centre study. Patients completed a questionnaire including demographic data and measures of pain, sleep, disability, anxiety, depression, and personality. Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F). Disease activity and haemoglobin levels were assessed. Path analysis was performed to test and improve a hypothesised model for fatigue.

Results

This analysis included 142 patients, with a mean (SD) age of 61.1 (11.7) years. The final path analysis model presented acceptable fit and explained 60.0% of the variance of fatigue. The predominant direct explanatory factors identified were disability (46.5%) and depression (41.2%), the latter having an additional indirect influence of 19% through disability. Age (-16.2%) and sleep disturbance (15.7%) were also directly linked to fatigue. Personality trait extroversion (-22.4%), pain (20.0%), and disease activity (14.9%) are only indirectly related to fatigue.

Conclusion

Depression, disability and sleep disturbance appear to be the main factors explaining fatigue in patients with RA. Disease activity, pain, and personality seem to play only a secondary role, extroversion being the only personality trait associated with fatigue. These findings foster a shift in the paradigm of care towards a more holistic management of fatigue, integrating adjunctive therapies beyond measures targeted solely at disease remission.

Key words

rheumatoid arthritis, fatigue, depression, sleep, path analysis, non-pharmacological treatments

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Introduction

Although joint involvement is the nuclear manifestation of RA, systemic manifestations are common and contribute significantly to disease burden (1, 2). Fatigue, defined as a chronic feeling of weakness, lack of energy, tiredness or exhaustion (3), is one of the most frequent complaints, referred by up to 80% of the patients (2-4), 42 to 49% reporting it as severe (5). It has an important impact upon quality of life, and is associated with worse self-rated health, functional decline and mental health status, as well as greater use of health care (6). Patients consistently place fatigue among their top outcome priorities (5) and its effective treatment remains an 'unmet need' (7).

These observations led to an authoritative international recommendation that fatigue should be integrated as an outcome measure in all clinical trials of RA (8, 9). Despite this orientation and the recent increase in research focusing fatigue (5), this symptom is often undervalued by health professionals, inducing, in patients, a sense of lack of support and disbelief (3, 10). Much of this problem is due to health professionals' poor understanding of the aetiology of fatigue and, also, the absence of effective strategies to prevent or treat it (7, 11).

The influence of disease activity upon fatigue has not been consistently demonstrated (6). Recent studies have shown that fatigue is prevalent even among patients in remission, underlining the importance of other explanatory factors (7, 12, 13). Anaemia does not seem to explain fatigue in this setting (14). More consistent relationships have been found with pain, disability, sleep disturbance, depression, anxiety and younger age (6, 15-17). Currently there is no data regarding the relationship between personality and fatigue (18). The most comprehensive conceptual model of fatigue in RA, proposed by Hewlett and collaborators (10), emphasises its multifactorial nature, rooted in the interaction between: (i) disease factors, (ii) cognitive and behavioural factors, and (iii) personal factors. Given this multifactorial nature of fatigue, some recent studies explore direct and indirect relationships (2, 19-21). The predominant influence of mood and sleep disturbance on fatigue emerges as consensual among these models. The role of disability, pain and disease activity is more controversial.

This study aimed to develop a multidimensional explanatory model of fatigue, testing the direct and indirect effects of disease activity, haemoglobin, pain, disability, mood disturbance, sleep disturbance, personality, gender and age.

Patients and methods

Study design and setting

This was an ancillary analysis of an observational, cross-sectional study, performed in a single rheumatology outpatient department (22).

Participants

The original study included consecutive adult patients diagnosed with RA (ACR 1987 revised criteria or ACR/EULAR 2010 Classification Criteria) (9, 23), who had the ability to read and interpret the questions and who agreed to participate. For the present study, we included all patients who answered all measurements required to develop the model.

Ethical approval was granted by the Ethics Committee of the Faculty of Medicine of the University of Coimbra (CEU 037/2015) and all patients provided signed informed consent form, according to Declaration of Helsinki. Additional approval for this ancillary study was not required.

Fatigue

The Portuguese version of the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) was used (24). This tool has 13 items, measured on a 5-point Likert scale from 0 (very much fatigued) to 4 (not at all fatigued), the total score ranging from 0 to 52 points (25). To facilitate understanding of the path analysis model in this study, it was decided to reverse the global score of FACIT-F in order to make a higher number correspond to a higher level of fatigue. For descriptive statistics the non-inverted values are presented.

Explanatory factors of fatigue

Disease activity was evaluated using

the Disease Activity Score with 28-joint counts (DAS28) with three variables (3v), which includes tender and swollen 28-joint counts and C-reactive protein (CRP, mg/dl). Patients were categorised according to DAS28CRP3v into four levels of disease activity: remission ≤2.4, low ≤2.9, moderate ≤4.6 and high >4.6 (26). The CRP variant was chosen because it is more readily available. Higher values correspond to higher disease activity.

Disability was measured with the Health Assessment Questionnaire Disability Index (HAQ-DI), a self-reported tool that evaluates the person's functionality over the past week in eight domains: dressing, rising, eating, walking, hygiene, grip, reach of objects and other activities. Its score ranges from 0 (no difficulty) to 3 (unable to do) (27).

Sleep disturbance and pain were measured using numerical rating scales (NRS), from 0 (no impact) to 10 (high impact) (28).

Depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS) (29). This is a 14-item scale subdivided in two subscales dedicated to anxiety and depression. Each item is scored on a four point Likert scale, with higher scores (ranging from 0 to 21, each subscale) corresponding to a worse psychological state. Scores ≥11 on either scale indicate a probable clinical condition.

Personality was assessed with the Ten-Item Personality Inventory (TIPI), which evaluates five personality dimensions, namely extraversion, agreeableness, conscientiousness, emotional stability and openness to experience (30). Each dimension is scored as the mean of 2 items, through a 7-point Likert scale with higher scores reflecting a stronger expression of the corresponding personality trait.

Demographic data (sex, age, years of formal educational), clinical data (disease duration, haemoglobin level) and current medication were collected from medical records.

Statistical methods

Descriptive analyses were used for patients' characterisation. A path analysis (a form of multiple regression statistical analysis) was conducted to evaluate hypothetical relationships between variables towards the explanation of fatigue, using the IBM® SPSS® Amos software, v. 22.0 (31). The selection of explanatory factors included in the model was based on published literature.

Several steps were taken to test the assumptions of the model. No outliers were observed through the squared Mahalanobis distance. No severe violations of the normal distribution (|Skewness| <3 and |Kurtosis| <7-10) were observed, both in uni and multivariable analyses (31). No significant multicollinearity between the independent variables were observed [variance inflation factor (VIF) <5]. Modification indices for regression weights were also used to evaluate linkage between variables (31). The model fit was assessed by different criteria, namely: (i) the Goodness of Fit Index (GFI) (good if ≥0.9), (ii) the Comparative Fit Index (CFI) (good if ≥0.9), and (iii) the Root Mean Square Error of Approximation (RMSEA) (acceptable if ≤0.10) (31). The significances of the direct, indirect and total effects were evaluated with the bootstrap resampling method, with 200 bootstrap samples and 95% bias-corrected CIs around the standardised estimates. Effects with $p<0.05$ were considered statistically significant (32).

A path diagram was used to represent the model: the direct effect is the pathway from an exogenous variable to fatigue, while the indirect effect has a mediator variable in between. To estimate the strength of the relationships, standardised coefficients were used (*i.e.* means = 0 and standard deviations = 1.0). The direct path coefficients are equivalent to the standardised regression coefficients (*i.e.* β weights), while the indirect effect (mediation effect) is given by multiplying the two standardised coefficients [(β exogenous → mediator) * (β mediator → outcome]. When a variable has both a direct effect and indirect effect its total effect is given by their sum (31). Higher β values indicate stronger relationships.

Results

Patient characteristics

This study included 142 patients with RA (83% female) whose demographic and clinical characteristics are summarised in Table I. Patients presented, on average, low number of formal years of education, long disease duration, and low disease activity levels. Patients included in the ancillary study were similar to the original study regarding socio-demographic characteristic, disease duration and disease activity (DAS28-PCR3v). The mean score of FACIT-F was 30.3 points (SD=9.4).

Table I. Demographic and clinical characteristics of the sample (n=142). Values represent mean (SD) unless stated otherwise.

Demographic and clinical characteristics	
Age, years	61.1 (11.7)
Gender (Female), n (%)	118 (83.1)
Educational background, years	6.9 (4.4)
Disease duration, years	12.0 (8.9)
DAS28-CRP(3v)	2.6 (0.9)
Remission (≤2.6) n (%)	80 (56.3)
Low activity (≤2.9) n (%)	36 (25.4)
Moderate activity (≤4.6) n (%)	21 (14.8)
High activity (≥4.6) n (%)	5 (3.5)
Haemoglobin (mg/dL)	13.0 (1.3)
FACIT-F (0-52)	30.3 (9.4)
Pain (NRS, 0-10)	5.8 (2.1)
Sleep disturbance (NRS, 0-10)	5.4 (2.4)
HAQ-DI (0-3)	1.3 (0.7)
HADS-Anxiety (0-21)	9.6 (4.1)
Not Anxious (≤7) n (%)	44 (31)
Possibly Anxious (8-10) n (%)	44 (31)
Probably Anxious (≥11) n (%)	54 (38)
HADS-Depression (0-21)	8.5 (4.0)
Not Depressive (≤7) n (%)	55 (38.7)
Possibly Depressive (8-10) n (%)	45 (31.7)
Probably Depressive (≥11) n (%)	42 (29.6)
TIPI (1-7)	
Extraversion	3.9 (0.7)
Agreeableness	5.7 (1.2)
Conscientiousness	5.6 (1.3)
Emotional stability	3.6 (1.4)
Openness to experience	4.3 (1.4)
Current treatment with glucocorticoids, n (%)	93 (65.5)
Current treatment with DMARDs, n (%)	124 (87.3)
Current treatment with biological agents, n (%)	24 (16.9)

DAS28CRP3v: Disease Activity Score using 28-joint counts, with C-reactive protein and 3 variables; DMARDs: disease-modifying anti-rheumatic drugs; FACIT-F: Functional Assessment of Chronic Illness Therapy - Fatigue; HADS: Hospital Anxiety and Depression Scale; HAQ-DI: Health Assessment Questionnaire - Disability Index; NRS: Numerical Rating Scale; TIPI: Ten Item Personality Inventory.

Univariable analysis

Disability (r_p=0.67), depression (r_p=0.65), anxiety (r_p=0.654) and sleep disturbance (r_p=0.61) showed the

Table II. Pearson's Correlation Coefficients between the variables considered for the model

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Fatigue	1.00	-	-	-	-	-	-	-	-	-	-	-	-	-
2. Age	0.16	1.00	-	-	-	-	-	-	-	-	-	-	-	-
3. Disease Activity	0.26*	0.08	1.00	-	-	-	-	-	-	-	-	-	-	-
4. Haemoglobin	-0.14	-0.18*	-0.15	1.00	-	-	-	-	-	-	-	-	-	-
5. Pain	0.43*	0.25*	0.30**	-0.06	1.00	-	-	-	-	-	-	-	-	-
6. Sleep Disturbance	0.51**	0.28*	0.32**	-0.04	0.46**	1.00	-	-	-	-	-	-	-	-
7. Disability	0.67**	0.36**	0.35**	-0.27*	0.47**	0.44**	1.00	-	-	-	-	-	-	-
8. Anxiety	0.54**	0.04	0.07	-0.05	0.17	0.32**	0.25*	1.00	-	-	-	-	-	-
9. Depression	0.65**	0.24*	0.26*	-0.10	0.30**	0.46**	0.46**	0.59**	1.00	-	-	-	-	-
10. Extraversion	-0.36**	0.02	-0.06	-0.05	-0.11	-0.11	-0.20*	-0.31**	-0.37**	1.00	-	-	-	-
11. Agreeableness	0.08	-0.01	-0.14	0.04	0.06	-0.01	0.06	-0.02	-0.11	-0.26	1.00	-	-	-
12. Conscientiousness	-0.24*	0.02	-0.14	0.08	0.02	-0.18*	-0.16	-0.26*	-0.29**	0.27*	0.45**	1.00	-	-
13. Emotional Stability	-0.18*	0.00	-0.16	-0.06	-0.12	-0.16	-0.05	-0.46**	-0.32**	0.17*	0.13	0.10	1.00	-
14. Openness to Experience	-0.10	-0.19*	0.01	0.19*	-0.01	0.01	-0.07	-0.01	-0.16	0.23*	0.24*	0.15	0.17*	1.00

*p<0.05; **p<0.001.

stronger correlations with fatigue (all p<0.001) (Table II). Pain and disease activity presented weak correlations (r_p=0.43 and 0.26, respectively). Extraversion showed, among personality dimensions, the strongest correlation with fatigue (r_p=-0.36). Age and haemoglobin did not correlate significantly with fatigue (p>0.05). Anxiety and depression were strongly correlated among themselves (r_p=0.59). There was no statistically significant difference in fatigue levels between men and women ($t_{(140)}$=1.415; p=0.159), neither between current medication, namely glucocorticoids ($t_{(142)}$=-1.043; p=0.299), DMARDs ($t_{(142)}$=1.393; p=0.166) and biological agents ($t_{(142)}$=1.203; p=0.231).

Development of the model

Based on the theoretical framework, a model was hypothesised (Fig. 1). In this initial model (GFI=0.90; CFI=0.85; RMSEA=0.16) some of the paths were not statistically significant (represented by "ns" in Fig. 1). These were removed one by one, in an effort to simplify the model and improve its fit. Also, the modification indices for regression weights suggested a linkage between extraversion and depression, and the model was changed accordingly.

The final model (Fig. 2) had an acceptable fit (GFI=0.92; CFI=0.89; RMSEA=0.10) and explained 60.0% of the variance of fatigue. All the paths were statistically significant and all, except the path age-fatigue and the path extraversion-depression, were positive.

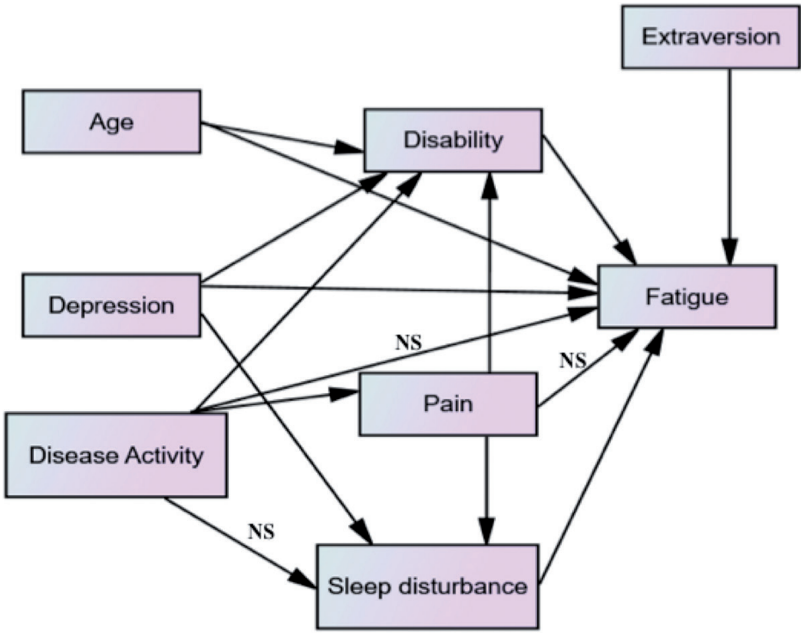

Fig. 1. Initial explanatory model of fatigue in RA.
GFI: 0.90; CFI: 0.85; RMSEA: 0.16.
GFI: Goodness of Fit Index; CFI: Comparative Fit Index: RMSEA: Root Mean Square Error of Approximation; NS: not statistically significant.

Depression had the highest percentage of explanatory effect (61.2%): 41.2% as direct effect (β=0.412; p<0.001) and 20.0% as indirect (β=0.200; p=0.008), through disability and sleep disturbance (β=0.141 and β=0.059, respectively).

Disability was associated with increased fatigue (β=0.465; p<0.001), being directly accountable for 46.5% of the variance of fatigue.

Pain did not have a statistically significant direct effect upon fatigue. However, it exerted influence on disability (β=0.141) and on sleep disturbance (β=0.059), explaining, indirectly, 20.0% (β=0.199; p=0.005) of the variance of fatigue.

Sleep disturbance directly explained 15.7% of the variance of fatigue (β=0.157; p=0.007).

Disease activity only exerted an indirect influence on fatigue (14.9%) (β=0.149; p=0.005), through its connection with disability (β=0.089) and pain (β=0.060).

The path age-fatigue was negative (β=-0.162; p=0.003), meaning that younger patients tend to report higher levels of

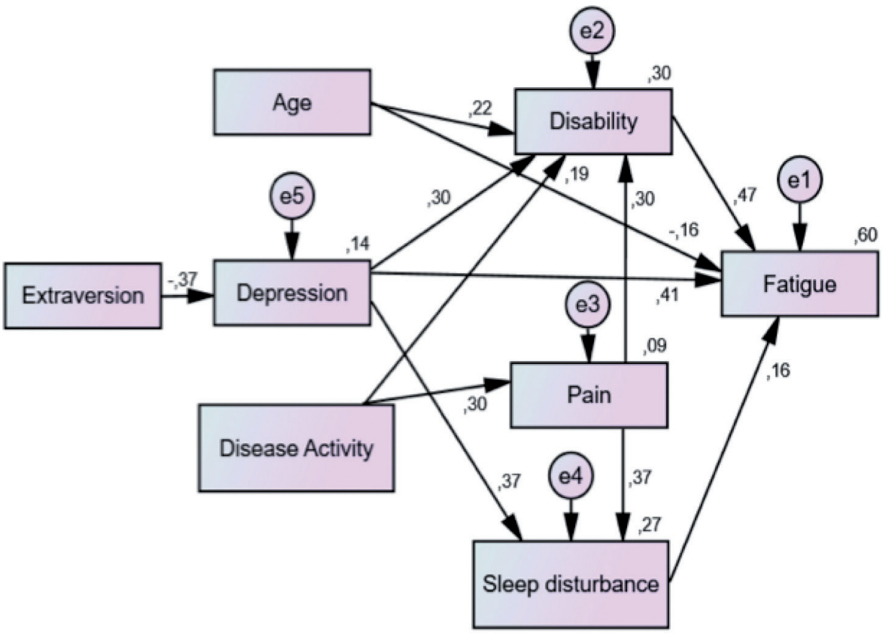

Fig. 2. Final pathway analysis model with standardised coefficients.
GFI: 0.92; CFI: 0.89; RMSEA: 0.10.
GFI: Goodness of Fit Index; CFI: Comparative Fit Index: RMSEA: Root Mean Square Error of Approximation.

fatigue under similar circumstances. Age also exerted an indirect influence on fatigue through its relationship with disability (β=0.104; p=0.04). Extraversion only had indirect connections with fatigue through depression (-22.4%) (β=-0.224; p=0.002), as patients with more extraversion were less depressed (β=-0.368; p<0.001).

Discussion

This study addressed some evidence gaps regarding the aetiology of fatigue in patients with RA. To the best of our knowledge, this is the first study to analyse the relationship between personality traits and fatigue in RA patients. In our study, depression and disability where the major correlates of fatigue, with both direct and indirect connections. Sleep disturbance also influenced directly fatigue but at a lower intensity. Disease activity and pain, both related to the disease process, had only minor and indirec correlations with fatigue, mediated by disability and sleep disturbance, staying in the background as explanatory factors. Surprisingly, age had a negative correlation with fatigue: older people perceive less fatigue, in the context of similar clinical and psychological background, than younger people. Furthermore, extroverted people presented fewer depressive symptoms and, consecutively, less fatigue. These findings are of utmost importance to the practicing rheumatologist, helping to define strategies to address fatigue beyond disease control in patients with RA.

The final model presented an acceptable fit and explained 60.0% of the variance of fatigue, a percentage that falls within the range of variance explained by other proposed models, which varied between 40.0% and 72.0% (2, 19-21). A summary of the published multifactorial explanatory models of fatigue with structural equation modelling analysis is provided in Table III.

Similar to previous studies (2, 19, 21), depression played a prominent role in the present model, explaining 61.2% of fatigue on its own. The direct impact we observed, 41.2%, is somewhat higher than observed by other authors (34.0%) (2). In our study, depression was also indirectly accountable for 20.0% of fatigue, through its influence on disability and sleep disturbance. The mediation effect through sleep disturbance has also been described in other studies with a similar explained variance (2, 20). Although the mediation effect through disability had not been studied yet, it is known that depression is associated with increased disability and poorer health outcomes in RA, making this interaction plausible (2, 20, 33). This underlines the importance of including psychological evaluation and interventions in the management plan for these patients (33).

In our study, disability explained directly 46.5% of the variance of fatigue, which lies within the range presented by Druce *et al*. (19) (16.0%) and Dartel *et al*. (20) (65.0%) and confirms its important role as a determinant of fatigue in RA (20, 21).

According to our model, pain affects fatigue through disability and sleep disturbance (20.0%), but, contrary to our expectations, does not have a direct effect. The literature is contradictory in this respect with one study reporting a direct effect of 31.0% (19) and another one denying such an influence (20). Although pain has been consistently associated with fatigue (6), some researchers stress that both symptoms seem to fluctuate synchronously but there is no evidence that pain causes fatigue or *vice versa* (15).

In our study, disease activity only explained 14.9% of the variance of fatigue, through indirect effects upon pain and disability, there being no significant direct effects. These results are strongly discordant from previous studies, in which disease activity has been considered directly accountable for 25.0% and 29.0% (2, 21) and indirectly for as much as 82.0% (mediated by pain, mental health and disability) of fatigue's variance (19). One study (20) showed no statistically significant influence of disease activity upon fatigue. The reasons underlying this discrepancy are not obvious. It is interesting to note, however, that studies using validated composite scores of disease activity, such as DAS28-CRP3v, tend to find less prominent and mostly indirect effects (19), whereas studies using self-reported disease activity tend to find more direct effects (2, 21). Improvements in objectively assessed disease activity showed controversial impact upon fatigue (13, 34, 35), with sustained remission being more associ-

Table III. Summary of published multifactorial explanatory models of fatigue with structural equation modelling analysis.

Study	Nicassio *et al*., 2012 (2) (n=106)	Druce *et al*., 2015* (19) (n=2652)	Dartel *et al*., 2016 (20) (n=228)	Katz *et al*., 2016 (21) (n=158)	Silva *et al*., 2017 (n=142)
Explained variance	62%	40%	74%	49%	60%
Disease activity	**RADAR**	**DAS28**		**RADAI**	**DAS28**
β direct/ β indirect	0.29 / 0.23	0.05 / 0.82*		0.25 / -	- / 0.15
Mood Disturbance	**CES-ID + PSS**	**SF36**	**SCL-90**		**HADS**
β direct/ β indirect	0.34 / 0.19	0.28 / -	- / 0.32		0.41 / 0.20
Poor Sleep Quality	**PSQI**		**SCL 90**	**PSQI**	**NRS**
β direct/ β indirect	0.41 / -		0.42 / -	0.13 / -	0.16 / -
Pain		**SF36**	**SF 36 + VAS**		**NRS**
β direct/ β indirect		0.31 / 0.09	- / 0.49		- / 0.20
Disability		**HAQ-DI**	**SF 36**		**HAQ-DI**
β direct/ β indirect		0.16 / 0.22	-0.65 / -		0.47 / -
Extraversion					**TIPI**
β direct/ β indirect					/-0.22
Sense of control			**PCS + SES 28**		
β direct/ β indirect			- / #		
Health				**PHQ**	
β direct/ β indirect				0.10 / -	
Obesity				**BMI**	
β direct/ β indirect				0.85 / -	
Gender (Female)					
β direct/ β indirect		0.06 / 0.03			
Age					
β direct/ β indirect					-0.16 / 0.10
No history of depression					
β direct/ β indirect		0.05/ -			

BMI: Body Mass Index; CESD: Centre for Epidemiological Studies Depression scale; DAS28: Disease Activity Score using 28-joint counts; FCS: Fatigue Catastrophising Scale; HADS: Hospital Anxiety and Depression Scale; HAQ-DI: Health Assessment Questionnaire - Disability Index; NRS: Numerical Rating Scale; PHQ = Patient Health Questionnaire; PSQI: Pittsburgh Sleep Quality Index; PSS: Perceived Stress Scale; RADAI: Rheumatoid Arthritis Disease Activity Index; RADAR: Rapid Assessment of Disease Activity in Rheumatology; SCL-90: Symptom Check List 90; SES: Self Efficacy Scale; SF-36: Short Form Health Survey 36; TIPI: Ten Item Personality Inventory; VAS: visual analogue scale.
Only statistically significant values ($p<0.05$) are presented.
*This study comprised subjects starting anti-TNF therapy with evaluation at baseline and 6-month follow-up. The path analysis model evaluated the change in the variables over time.
#The β Indirect between sense of control and fatigue was not possible to determinate in this study, without the primary data, due to multiple mediation variables.

ated with lower levels of fatigue when compared to intermittent remission or low disease activity (35). These results are also corroborated by the insufficient effect of biological agents or the mismatch between disease remission and fatigue resolution (13, 36). On the other hand, non-pharmacological interventions, such as physical exercise and psychosocial interventions have been shown to ameliorate fatigue (37). Taken together, these observations may suggest, in agreement with other lines of evidence (22), that patients incorporate fatigue into their self-assessment of disease activity, which may artificially emphasise the correlation between the two.

When both disease activity and pain are considered in the models, the first one seems to assume just a secondary role, *i.e*. pain appears to be the predominant aspect among those related to the disease processes, as we observed. This suggests that an effective treatment of pain may be important to diminish fatigue in these patients (38), which can be a difficult approach. Pain is a major component of RA flares but its aetiology goes beyond inflammatory factors, in fact, changes in inflammation only explain approximately 40% of the pain variation (39). Factors such genetic background, premorbid characteristics, comorbidities, psychological status and personality can play a major role and, therefore, should be considered in the care managment plan (39, 40).

Sleep disturbance directly explained 15.7% of the variance in fatigue, a percentage lower than observed in previous studies, (around 40%) (2, 20). This may be due to the use of a single item scale rather than a multidimensional scale to assess sleep difficulties. The duration of night sleep and daily naps was associated with higher severity of symptoms in patients with fibromyalgia or chronic fatigue (41) whereas naps at an appropriate time and duration might relieve fatigue (42). Therefore, the role of sleep could have been underestimated in the present study.

Age proved to be relevant to the multidimensional model, both directly and indirectly (through disability influence). Contrary to a more 'naive' hypothesis, elderly patients seem to experience less fatigue than younger patients when other factors remain similar, namely disability, depression, sleep disturbance and pain. Similar observations have been made in a longitudinal study (7).

Personality, for the first time considered in these models, played an indirect influence upon fatigue, through its

relationship with depression. Out of the five personality traits studied, extraversion was the only one having significant influence on fatigue. Extroversion has been related to subjective well-being and positive emotionality (43). A different personality trait, neuroticism, has also been associated with fatigue (44) and negatively linked to subjective well-being (43). Another study has demonstrated a link between genetic factors and fatigue, highlighting that neuroticism has an independent impact particularly in fatigue associated with depression (44). This study showed that extroversion plays a protective role. This means that although personality is a non-modifiable factor, it must be taken into account in clinical practice, as the vulnerability for mental and somatic disorders inherent to different traits of personality might be prevented or modulated with specific intervention strategies (44).

Even though the model presented a good fit, the authors recognise some limitations in the study. This was a single centre study, with consecutive patients presenting an average low disease activity, which limits its generalisability. Other comorbidities beyond depression and anxiety, as cardiovascular diseases, infection or cancer or its correlation with multi-morbidity indexes, which have been associated with fatigue, (45) were not considered in the model. Pharmacological and non-pharmacological adjunctive therapies as painkillers, anti-depressants, coping, exercise which can influence factors associated with fatigue were not considered. The evaluation of some variable may have been affected by the relatively simple instruments used herein, namely for sleep and personality. Another limitation is the absence of information regarding specific sleep-related characteristics that can underestimated the impact of sleep in fatigue. Also, this was a cross-sectional study, which means that the causal nature of relationships is merely hypothetical. Although depression, disability and sleep disturbance seem to be the main factors explaining fatigue, we recognise that these correlations do not imply causality and that there are several external factors, such as metabolic polymorphisms, smouldering inflammation, enteric dysbiosis, among others (44, 46), that could contribute to fatigue. Nevertheless, the present study highlights the importance of addressing both physical and psychological symptoms, a common aspect to other studies (44) .

The present study has also some strengths. We included a satisfactory number of patients, with a wide range of clinical characteristics, and with fatigue levels similar to other studies (47, 48). The inclusion of personality and age in the model differentiates it from others and, although they are non-modifiable factors, recognising their protective influence informs the design of strategies for intervention. The mediation effect between mood disturbance and disability was also innovative. The instrument used to evaluate fatigue was a multidimensional measure that is considered useful to explore causality (25), although other instruments exist to evaluate fatigue in patients with RA (49). Disease activity was evaluated by physicians with a validated composite score, which included a laboratorial inflammatory parameter (DAS28-CRP3v). This fact stands out from most other studies that used self-reported evaluation of disease activity (2, 21) which is exposed to bias as discussed above.

These findings foster the proposal to shift the paradigm of patient care towards a more holistic view with the active integration of adjunctive therapies, designed to assist patients in achieving lower levels of fatigue and higher quality of life, beyond what can be obtained with strategies targeted solely on disease activity remission.

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