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Multifactorial explanatory model of fatigue in patients with Rheumatoid Arthritis: a path analysis

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MULTIFACTORIAL EXPLANATORY MODEL OF FATIGUE IN PATIENTS WITH RHEUMATOID ARTHRITIS: A PATH ANALYSIS

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RESUMO

Introdução: A fadiga é um dos sintomas mais prevalentes e impactantes entre os doentes com Artrite Reumatóide (AR). Contudo, é também um dos sintomas mais negligenciados pelos profissionais de saúde. A etiologia da fadiga permanece incerta, particularmente o papel da atividade da doença. O presente estudo tem por intuito desenvolver um modelo explicativo multidimensional da fadiga nos doentes com AR.

Métodos: Foi realizada uma análise secundária de um estudo observacional, transversal, num serviço de Reumatologia. Foi aplicado um questionário com informação sobre os dados sociodemográficos, sono, dor, incapacidade funcional, ansiedade, depressão e personalidade. A fadiga foi avaliada através da escala *Functional Assessment of Chronic Illness Therapy – Fatigue*. Os valores de atividade da doença e de hemoglobina foram cedidos pelo médico. Foi efetuada uma análise de trajetórias para desenvolver um modelo hipotético de fadiga.

Resultados: Foram incluídos 142 doentes, predominantemente do sexo feminino (83,1%), com uma média de idades de 61,1 anos. O modelo final apresentava bom ajustamento ($\chi 2_{(16)}$=50,674, p<0,001), explicando 60,0% da variância da fadiga. Os fatores explicativos dominantes foram a depressão (61.2 %) e a incapacidade funcional (46,5%). A idade (-16,2%) e os distúrbios do sono (15,7%) também apresentaram uma ligação direta com a fadiga. O traço de personalidade, extroversão (-22,4%), a dor (20.0%) e a atividade da doença (14,9%) apenas exerceram uma influência indireta.

Conclusão: Os fatores que melhor explicaram a fadiga nos doentes com AR foram a depressão, a incapacidade e os distúrbios do sono. A atividade da doença e a dor pareceram ter um papel secundário. Estes resultados podem ser cruciais na mudança do paradigma dos cuidados, na direção de uma abordagem holística, integrando modalidades terapêuticas coadjuvantes àquelas com enfoque na remissão da doença.

Palavras-chave: Artrite Reumatóide, Fadiga, Análise de trajetórias.

ABSTRACT

Background: Fatigue is one of the most prevalent and disabling symptoms among patients with Rheumatoid Arthritis (RA), however it is also one of the most neglected by the health professionals. Its aetiology remains unclear, namely the role of disease activity. The present study aimed at developing a multidimensional explanatory model of fatigue in patients with RA.

Methods: This was an ancillary analysis of an observational, cross-sectional, single centre study. Patients completed a questionnaire that included demographic data and measures of sleep, pain, disability, anxiety, depression and personality. Fatigue was assessed by the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F). Disease activity (DAS28) and haemoglobin levels were provided by the physician. Path analysis was performed to develop a hypothesised model for fatigue.

Results: A total of 142 patients were included, mostly females (83.1%), with a mean age of 61.1 years. The final path analysis model presented good fit ($\chi 2_{(16)}$=50.674, p<0.001), and explained 60.0% of the variance of fatigue. The dominant explanatory factors were depression (61.2%) and disability (46.5%). Age (-16.2%) and sleep disturbance (15.7%) also had a direct link to fatigue. Personality trait extroversion (-22.4%), pain (20.0%), and disease activity (14.9%) only exerted indirect influence on fatigue.

Conclusion: Depression, disability and sleep disturbance were the factors that better explained fatigue in patients with RA. Disease activity and pain seemed to play only a secondary role. These findings may be crucial in shifting the paradigm of patient care towards a more holistic management of fatigue, integrating more adjunctive therapies in association with measures driven towards disease remission.

Keywords: Rheumatoid Arthritis, Fatigue, Path Analysis.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, autoimmune disease characterized by synovial inflammation, leading to pain, stiffness, progressive destruction of the joints and variable degrees of disability.[1,2] It is estimated that RA affects around 0.7% of the adult Portuguese population, being more prevalent in females,[3] which is similar to observations worldwide.[4]

Although joint involvement is the basilar manifestation of RA, systemic manifestations are common.[2] Among these manifestations, fatigue is one of the most commonly referred by patients (up to 40 to 80%)[2,5,6] with 42 to 49% reporting it as severe.[7]

Fatigue can be defined as a chronic feeling of weakness, lack of energy, tiredness or exhaustion.[5] It has an important impact on the quality of life as it affects the activities of daily living and is associated with functional decline, worse mental health status and greater use of health care.[8] Fatigue is consistently prioritized by patients in their top outcome priorities,[7] and its effective treatment clearly remains an 'unmet need'.[9]

These observations led to an authoritative international recommendation, that fatigue should be integrated as an outcome measure in all clinical trials of RA.[10,11] Despite this orientation and the recently increased interest in research focusing fatigue,[7] this symptom is often undervalued by health professionals, inducing in the patients a sense of lack of support and disbelief.[5,12]

Much of this problem results from the lack of knowledge about the aetiology of fatigue and, therefore, lack of effective strategies to prevent or treat it.[9,13] The most complete conceptual model of fatigue in RA was proposed by Hewlett and collaborators,[12] and emphasizes it's multifactorial nature through the interaction of three main factors: (i) disease processes, including disease activity, anaemia, medication, sleep disorders and pain; (ii) cognitive and behavioural factors; and (iii) personal factors, including age, gender, individual responsibilities, social support, and comorbidities.

The influence of disease activity upon fatigue has not been consistently demonstrated.[8] Recent studies have shown that fatigue is prevalent even among patients in remission, which suggest the existence of other explaining factors.[9,14,15] More consistent relationships have been found with pain,[16,17] disability,[8,17] sleep disturbance,[8] depression[17] and anxiety.[18] Younger patients have also shown higher levels of fatigue.[17] There is no direct relationship between haemoglobin levels and fatigue[19] in this context. Currently there is no data regarding the role/relationship between personality and fatigue.[20]

Given the multifactorial nature of fatigue, univariate analysis has proven to be restrictive and only explained a small part of the variance of fatigue. Accordingly, some studies recently emerged analysing possible explanatory models of fatigue.[21,22,23,24] The predominant influence of mood and sleep disturbance on fatigue emerges as consensual among these models. Disability also appears as a relevant factor but with variable contribution, in the different models. Pain was only studied in two models, showing both a direct and indirect (mediated by disability) influence.[22,23] Disease activity has shown the most inconstant role, seeming to play more an indirect rather than a direct role.[8] Less commonly investigated variables include sense of control,[23] gender,[22] obesity, psychical activity, smoking, low fitness, low lean mass and muscle weakness.[24] Age and personality traits have not been studied in these multifactorial models.

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

METHODS

Study design and setting

This was an ancillary analysis of an observational, cross-sectional study, performed in a single Rheumatology outpatient department, in Portugal between September and December 2015.[15]

Participants

The original study included consecutive adult patients diagnosed with RA (ACR 1987 revised criteria or ACR/EULAR 2010 Classification Criteria),[11,25] who had the ability to read and interpret the questions and who agreed to participate. For the present study where included the patients who answered to all measurements required to develop this 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 signed an informed consent according to Declaration of Helsinki. Additional approval for this ancillary study was not required.

Measurements

Fatigue

The validated Portuguese version of the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) scale was used.[26] This is a 13-item tool, measured on a 5-point Likert scale (0 = very much fatigued to 4 = not at all fatigued), with the total score ranging from 0 to 52 points.[27] For a better understanding of the paths analysis model in this study, it was decided to reverse the global score in order to make a higher score correspond to higher level of fatigue.

Explanatory factors of fatigue

Disease activity was evaluated using the Disease Activity Score-28 (DAS28) with three variables (3v), which includes tender and swollen joints count (28 joint count) and C-Reactive Protein (CRP) (mg/dl).[28] The CRP variant was chosen because it is more readily available. The

final score is given by a formula ranging from 0 (remission) to 9.4 (high disease activity).

Disability was measured with the Health Assessment Questionnaire (HAQ) which is a self-reported tool that evaluates the person's functionality over the past week in eight domains: dressing, rising, eating, walking, hygiene, grip, reach objects and other activities. The sum of the scores is divided by 8 and the final score ranges from 0 (no difficulty) to 3 (unable to do).[29]

Sleep and pain were measured using the corresponding two domains of the Rheumatoid Arthritis Impact of Disease (RAID) score, where these dimensions are evaluated by numerical rating scales (NRS), from 0 (no impact) to 10 (high impact).[30]

Depression and anxiety were assessed with the Hospital Anxiety and Depression Scale (HADS). This is a 14-item scale subdivided in two subscales that evaluate anxiety and depression. Each item is scored on a four point Likert scale (0 = almost always to 3 = never).[31] Like fatigue, these scores were inverted for the present study, with higher scores (ranging from 0 to 21, each) corresponding to worse psychological states.

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. Each dimension is scored as the mean of 2 items, through a 7-point Likert scale.[32] With higher scores corresponding to more agreement with the personality trait.

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

Statistical analyses

Descriptive analyses were performed for patient's characterization.

This was a two-fold analysis. In the first step, Pearson's correlation and Student's t-test were

used to evaluate the relationship between the variables described and fatigue and, therefore, to support the selection of explanatory factors for the multivariable model. The variables were selected to integrate the model if $p<0.05$ or if they fit the theoretical framework. IBM® SPSS® Statistics version 20.0 software (IBM, Armonk, NY, USA) was used for this step.

In the second step, based on the correlational structure observed between the variables and theoretical framework, a path analysis was conducted to evaluate hypothetical relationships between variables towards the explanation of fatigue. Path analysis is a form of multiple regression statistical analysis used to evaluate explanatory models by examining the relationships (direct and indirect) between a dependent variable (as known as endogenous variables) and two or more independent variables (as known as exogenous variables).[33]

IBM® SPSS® Amos software, version 22.0, was used to perform the path analysis and to calculate the maximum likelihood estimates for model fit. The presence of outliers was evaluated by the squared Mahalanobis distance and the normality by the coefficients of symmetry and kurtosis uni and multivariable. No variables showed severe violations to the normal distribution ($|Sk|<3$ and $|Ku|<7$-10).[33] There were no observations considered outliers. The variance inflation factor (VIF) was used to assess the presence of multicollinearity: all VIF values were inferior to 5, meaning that there was not significant multicollinearity between the independent variables. Modification indices for regression weights were also used to evaluate linkage between the variables.[33]

The model fit was assessed by different criteria, namely: (i) the Goodness of Fit Index (GFI) (good fit if ≥ 0.9); (ii) the Comparative Fit Index (CFI) (good fit if ≥ 0.9); (iii) the Root Mean Square Error of Approximation (RMSEA) (acceptable fit if ≤ 0.10); Maximum-Likelihood Expected Cross-Validation Index (MECVI) (lowest values meaning better fitting of the model).[33]

The significance of the direct, indirect and total effects were evaluated with the Sobel test.[33] The effects with $p \leq 0.05$ were considered statistically significant.

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 standardized coefficients were used (i.e. means = 0 and standard deviations = 1.0). The path coefficients are equivalent to the standardized regression coefficients (i.e., the β weights), with higher values indicating stronger relationship. The direct effect corresponds to the standardized coefficient (β). The indirect effect (mediation effect) is given by multiplying the two standardized coefficients [β(exogenous → mediator) * β(mediator → outcome]. When a variable has a direct effect and indirect effect (through a mediator), its total effect is given by the sum of its direct and indirect effects.[33]

RESULTS

Patient characteristics

A total of 142 participants were included in this analysis and their demographic and clinical characteristics are presented in Table 1. The majority of patients were female (83.1%), the mean age was 61.1 years (standard deviation, SD=11.7) and the mean duration of disease was 12.0 years (SD=8.9). The mean of disease activity was 2.6 years (SD=0.9) and 16.9% of the patients were being treated with biological disease-modifying anti-rheumatic drugs (bDMARDs). The mean level of fatigue was 21.7 points (SD=9.4).

Table 1 – Demographic and clinical characteristics of the sample (n=142). Values represent mean (SD) otherwise stated in contrary.

Demographic and clinical characteristics	Mean (SD)
Age, years	61.1 (11.7)
Female gender, n (%)	118 (83.1)
Formal Education, years	6.9 (4.4)
Disease duration, years	12.0 (8.9)
DAS28-CRP (3v)	2.6 (0.9)
Haemoglobin (mg/dL)	13.0 (1.3)
Fatigue (0-52)	21.7 (9.4)
Pain (NRS, 0-10)	5.8 (2.1)
Sleep (NRS, 0-10)	5.4 (2.4)
HAQ (0-3)	1.3 (0.7)
HADS-Anxiety (0-21)	9.6 (4.1)
HADS-Depression (0-21)	8.5 (4.0)
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)
Biological agents, n (%)	24 (16.9)

Note: DAS28 = Disease Activity Score using 28 joints; HAQ= Health Assessment Questionnaire; HADS = Hospital Anxiety and Depression Scale; NRS = Numerical Rating Scale; TIPI = Ten Item Personality Inventory.

Univariate Analysis

Prior to designing the model, relationships between the variables that could potentially be on the model were assessed. Correlations between the variables are presented in Table 2.

The variables with stronger statistically significant correlation with fatigue were disability (r_p=0.67), depression (r_p=0.65), anxiety (r_p=0.54) and sleep (r_p=0.51). Pain (r_p=0.43) and disease activity (r_p=0.26) presented weak correlations. Extraversion was the personality dimension with stronger correlation with fatigue (r_p=-0.36). Age and haemoglobin did not correlate significantly with fatigue, but age presented a significant correlation with most variables, being included in the theoretical model to be tested. Anxiety was strongly correlated with depression (r_p=0.59), thus only depression was included in the model. There was no statistically significant difference in fatigue between men and women ($t_{(140)}$=1.415; p=0.159).

Table 2 – Pearson's Correlation between the variables considered for the model (n=142).

	Fatigue	Age	Disease Activity	Hb	Pain	Sleep	Disability	Anxiety	Depression
Age	0.16	-	-	-	-	-	-	-	-
Disease Activity	0.26*	0.08	-	-	-	-	-	-	-
Hb	-0.14	-0.18*	-0.15	-	-	-	-	-	-
Pain	0.43*	0.25*	0.30*	-0.06	-	-	-	-	-
Sleep	0.51*	0.28*	0.32*	-0.04	0.46*	-	-	-	-
Disability	0.67*	0.36*	0.35*	-0.27*	0.47*	0.44*	-	-	-
Anxiety	0.54*	0.04	0.07	-0.05	0.17	0.32*	0.25*	-	-
Depression	0.65*	0.24*	0.26*	-0.10	0.30*	0.46*	0.46*	0.59*	-
Extraversion	-0.36*	0.02	-0.06	-0.05	-0.11	-0.11	-0.20*	-0.31*	-0.37*
Agreeableness	0.08	-0.01	-0.14	0.04	0.06	-0.01	0.06	-0.02	-0.11
Conscientiousness	-0.24*	0.02	-0.14	0.08	0.02	-0.18*	-0.16	-0.26*	-0.29
Emotional Stability	-0.18*	0.00	-0.16	-0.06	-0.12	-0.16	-0.05	-0.46*	-0.32*
Openness to experience	-0.10	-0.19*	0.01	0.19*	-0.01	0.01	-0.07	-0.01	-0.16

Note: *p<0.05. Hb = haemoglobin.

Development of the model

Based on the univariate analysis and theoretical framework a model was hypothesized (Figure 1). Age influenced directly and indirectly (through disability) fatigue. Depression influenced disability, sleep and fatigue directly. Disease activity influenced fatigue both directly and indirectly (through disability, pain and sleep disturbance). Disability, pain and sleep disturbance where considered mediators between fatigue and other factors, influencing directly fatigue. Pain also influenced disability and sleep disturbance. Furthermore, the extraversion personality trait influenced directly fatigue.

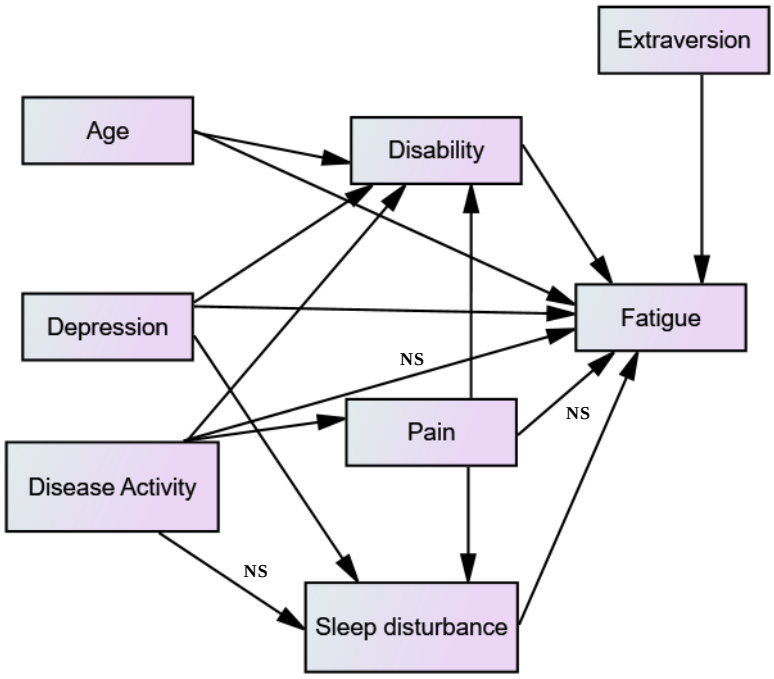

Figure 1 – Initial explanatory model of fatigue in RA. $\chi^2_{(13)}$=60.840, p<0.001; GFI=0.90, CFI=0.85; RMSEA=0.16; MECVI=0.78.

Notes: GFI = Goodness of Fit Index; CFI = Comparative Fit Index; RMSEA = Root Mean Square Error of Approximation; MECVI = Maximum-Likelihood Expected Cross-Validation Index. NS = Not Statistically Significant (p>0.05).

Although this initial model provided a good fit to the data ($\chi 2_{(13)}$= 60.840, p<0.001; GFI=0.90, CFI=0.85; RMSEA=0.16; MECVI=0.78), some of the paths were not statistically significant to the model (represented in Figure 1). Therefore, were removed one by one in an effort to simplify the model and improve its fit. Also, the modification indices for regression weights suggested linkage between extraversion and depression, underlying a path from extraversion to depression, a change performed in the following tested model.

Best Fitted model

The final model (Figure 2) was well-fitted ($\chi 2_{(16)}$=50.674, p<0.001; GFI=0.92; CFI=0.89; RMSEA=0.12; MECVI=0.66) 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.

Depression was the variable with highest percentage of explanatory effect with 61.2% of standardized total effect: 41.2% as direct effects (β = 0.412); and 20.0% indirectly, through disability and sleep disturbance (β = 0.141 and β = 0.059, respectively).

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

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

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

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

Path age to fatigue was negative (β= - 0.162), meaning that younger patients had higher levels

of fatigue. Age also exerted indirect influence on fatigue through its influence on disability (β = 0.103).

Extraversion exerted only indirect influence on fatigue (-22.4%), as patients with more extraversion were less depressed (β = - 0.368).

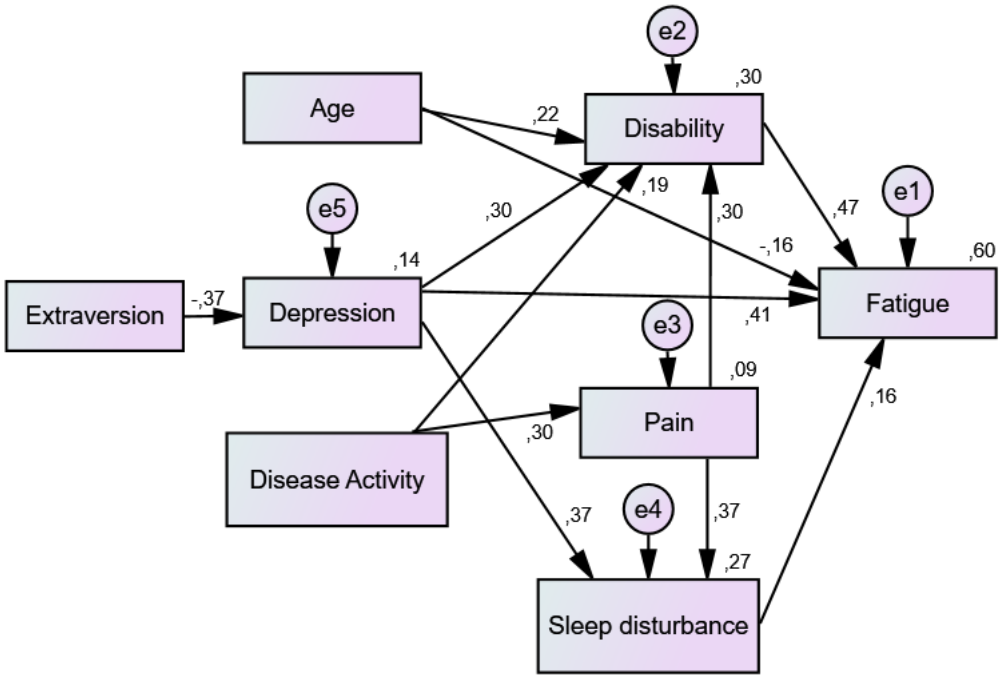

Figure 2 – Final path analysis model with standardized coefficients. $\chi 2_{(16)}=50.674$, $p<0.001$; GFI=0.92; CFI=0.89; RMSEA=0.12; MECVI=0.66.

Notes: GFI = Goodness of Fit Index; CFI = Comparative Fit Index; RMSEA = Root Mean Square Error of Approximation; MECVI = Maximum-Likelihood Expected Cross-Validation Index.

DISCUSSION AND CONCLUSION

The present study aimed to fill some of the knowledge gaps regarding the aetiology of fatigue in patients with RA. According to the path analysis model, depression and disability where the major explanatory factors of fatigue, exerting a direct influence. Sleep disturbance also influenced directly fatigue but at a lower intensity. Disease activity and pain, both related to disease processes, had only an indirectly influence on fatigue through disability and sleep disturbance, staying in the background as explanatory factors. Surprisingly, age had a negative correlation with fatigue: elderly people perceive less fatigue than younger people, in the context of similar clinical and psychological background. Furthermore, extroverts presented less depressive symptoms and, consecutively, less fatigue.

The final model presented a good fit and explained 60.0% of the variance of fatigue, a percentage that falls within the range of variance explained in other models, which vary between 40.0% and 72.0%. [21, 22, 23, 24]

Similar to previous studies,[21, 22, 24] depression played a prominent role in this 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%).[21] In one study, depression was described as a primary predictor of fatigue, together with poor sleep quality, obesity and disease activity.[24] 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 was also described in other studies with a similar explained variance.[21,23] Impaired sleep is often observed in depression and confers additional effects of depression on fatigue.[8] Although the mediation effect through disability had not been studied yet, it is known that depression is associated with increased disability.[34] It is also known the high prevalence of depression in patients with RA and its association with poorer health outcomes.[21,23,34] This underlines the

importance of including psychological evaluation and interventions in the care plan management of RA.[34]

Disability has been referred as one of the main contributors to fatigue,[23,24] probably due to the higher energy required to perform simple tasks in disabled patients.[8] In our study, disability was the second major explanatory factor of fatigue, explaining 46.5% of the variance, directly. In the study reported by Dartel and collaborators,[23] 65.0% of the variance of fatigue was directly explained by disability, while Druce et al[22] reported only 16.0%. This difference could be related to the longitudinal design of the latter study, which included patients starting anti-Tumour Necrosis Factor (anti-TNF) bDMARDs.[22]

According to our model, pain only affects fatigue through disability and sleep disturbance (20.0%), but, contrary to our expectations, does not have a direct effect. Our results are similar to those of a former study.[23] In another study, pain was found to directly explain 31.0% of the variance in fatigue.[22] Altogether, pain has been one of the most consistently associated factors to fatigue.[8] However, some researchers believe that causality is difficult to interpret: pain and fatigue seem to fluctuate synchronously but there is no evidence that pain precedes fatigue or vice-versa.[16]

Importantly, disease activity only explained 14.9% of the variance of fatigue, through indirect effect upon pain and disability. There were no significant direct effects. Our results are strongly discordant from previous studies in which disease activity was directly accountable for 25.0% to 29.0% [21,24] and indirectly for 82.0% (mediated by pain, mental health and disability)[22] of the change in fatigue. Only one precedent study[23] showed no statistically significant influence on fatigue. These data underline that the role of disease activity as an etiological factor of fatigue is very controversial.[8,21,22,23,24] It is interesting to note that studies using DAS28-3vCRP, tend to find more prominent indirect effects,[22] whereas studies with self-reported disease activity

instruments tend to find more direct effects.[21,24] This may suggest commonalities in the perception of fatigue and disease activity which may overemphasise correlation. It is imperative to standardize how to this concept is measured to resolve this crucial issue. Meanwhile, it is important to notice that improvement in disease activity, as assessed by the currently recommended instruments, may not have a decisive impact upon fatigue.[15]

When both disease activity and pain are considered, the first one seems to assume just a secondary role. Pain appears to be the predominant aspect among those related to the disease processes. This may suggest that an efficient treatment of pain could be important to diminish fatigue in patients with RA.[35]

Sleep disturbance directly explained 15.7% of fatigue, a percentage lower than what was observed in previous studies, in which sleep disturbance was estimated to explain between 40.8% and 42.0% of the variance.[21,23] This is also a highly prevalent problem in patients with RA, associated to many health outcomes, such as fatigue, pain and depression.[8,36] Sleep disturbance could also be involved in a vicious cycle whereby sleep problems could aggravate pain thresholds and increase inflammation, which can in turn worsen sleep problems and indirectly worsen fatigue.[8]

This study introduced age as an explanatory factor, despite not being correlated with fatigue in univariate analysis, because it was highly correlated with the majority of other variables was included in the model. In fact, age proved to be relevant to the multidimensional model, both directly and indirectly (trough disability influence). Contrary to a more 'naive' hypothesis, elderly patients seem to experience less fatigue than younger patients when other factors remain the same, namely disability, depression, sleep disturbance and pain. This was a rather surprising finding, although could be explained by a stronger resilience to the fatigue by the elderly, as

suggested by a large longitudinal study where younger patients with RA remained more fatigued over time than elderly patients.[9]

Personality, for the first time considered in these models, played an indirect influence upon fatigue, through its relation with depression. Patients more extraverted seemed to be less prone to depression and, in turn, to fatigue.

Even though the model presented a good fit, the authors recognize some limitations in the study which should be taken into account while interpreting the results. This was a single centre study with consecutive patients, thus caution should be taken when generalizing the results to other populations. However, the study integrated a satisfactory number of patients with a wide range of clinical characteristics. A single-item was used to evaluate sleep instead of a multidimensional scale which may have hampered the evaluation, even though the single-item measures have been shown to be valid and reliable to evaluate sleep quality.[37]

Moreover, this was a cross-sectional study, which means that the causal relations are merely hypothetical, as they were inferred on the basis of a theoretical model derived from published evidence and univariate analysis. For some of the relationships the direction of the influence is even more difficult to understand as the literature is not congruent. These limitations could only be overcome by longitudinal studies or randomised controlled trials.

The present study has also some strengths. The inclusion of personality and age in the model differentiates it from others and, although they are non-modifiable factors, knowledge about their protective influence increases our understanding of the phenomenon and to 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 which is considered useful to explore causality.[27] Disease activity was evaluated with a validated composite score, which included a laboratorial inflammatory parameter (DAS28-3vCRP). This

fact stands out from other studies, since most of them used self-reported questionnaires for disease activity evaluation,[21,24] which is exposed to bias.

Overall, the model constructed suggests that factors related to disease processes, like disease activity, play a secondary role when compared to other factors such mood disturbance, sleep disturbance and disability. This results align with the predominant view of current evidence in suggesting that the management of fatigue in patients with RA requires a multidimensional approach, beyond disease control, as demonstrated by the insufficient effect of biological agents and even disease remission.[15,38] Non-pharmacological interventions such as physical exercise and psychosocial interventions have shown to be effective in reducing fatigue.[39] The health domains tested as main predictors in the present and previous models are likely to be improved by combining these different kinds of interventions.

These findings may be crucial in shifting the paradigm of patient care towards a more holistic view with the active integration of adjunctive therapies in association with measures driven towards disease remission. In the future, it would be important to validate the present model, testing it in another sample of RA patients, and evaluate the impact of multidimensional therapeutic approaches through randomized controlled trials.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Cristiana Silva had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Cristiana Silva, José Pereira da Silva, Cátia Duarte, Ricardo Ferreira.

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