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# Psychological stress in rheumatoid arthritis: a systematic scoping review

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## ABSTRACT

**Background:** Rheumatoid arthritis (RA) considerably impacts patients' mental health. However, it is largely unclear how people suffering from RA experience psychological stress beyond depression or anxiety, and what drives stress in these patients.

**Objective:** To examine the impact of RA on psychological stress, as follows: 1) How is stress defined and described in studies on RA? 2) Do patients with RA experience more stress than the general population or people suffering from other chronic conditions? 3) What are risk factors for developing stress in this context?

**Methods:** We systematically searched EMBASE, PubMed, Web of Science Core Collection and Cochrane Library for English language peer-reviewed reports published up to 19 April 2020. Eligible studies included any measure or definition of psychological stress as an outcome in patients with RA. Data were extracted on patient and study characteristics, instruments used to measure stress and predictors of stress, and were summarized descriptively. Study quality was assessed with the MINORS or AXIS-tool for longitudinal and cross-sectional studies, respectively.

**Results:** Among 11.115 potentially relevant studies, 16 studies were included. Remarkably, 13 different instruments to measure stress were reported in these studies. Different types of stress experienced by patients with RA included role stress, social stress, and work stress. Work stress and social stress, particularly resulting from interpersonal stressors, were reported as more prevalent in patients with RA compared to healthy controls. Stress at disease onset appeared more pronounced in patients with RA compared to people suffering from osteoarthritis, while psychological stress was reported as higher in patients with chronic pain syndromes compared to patients with RA. More disability, more pain, less social support, lower income, younger age and personality traits like excessive worrying, pessimism, and sensitivity to anxiety, seemed to increase the risk for higher stress levels.

**Conclusions:** This scoping review is, to our knowledge, the first to address the important heterogeneity of the measurement tools and definitions of psychological stress in RA research. This review could provide a basis to standardize the concept of stress in people suffering from RA, with a view to proposing tailored stress-reducing interventions.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that often has a significant long-term impact on patients' physical and psychological wellbeing (1). Although much progress has been made in the treatment of RA, the condition's incurable nature and its often-unpredictable course can be demanding for patients on a psychosocial level (2). This is reflected in the considerable number of patients who report unmet needs despite good clinical responses to therapy (3,4). Therefore, it is crucial to adopt a biopsychosocial approach to treatment to provide the best possible patient-centered care.

The biopsychosocial approach is based on the observation that the course of RA is not only affected by biological factors, but also by psychological and social factors (5). For instance, increasing pain and fatigue can diminish one's capacity to work or to function socially, which might in turn induce feelings of psychological stress. However, stress remains a challenging concept to define and should not be limited to feelings of depression or anxiety. The *Transactional Model of Stress and Coping* by Lazarus and Folkman (6) defines stress as a perceived imbalance between demands encountered in daily living and a person's capability to respond to or cope with these demands. In addition to coping, resources such as social support and professional counseling could help tip the scales by buffering stressful feelings, although this is specific to each person's individual needs (7). This dynamic interplay between stressors and buffers and the effect of coping mechanisms, personality traits and social support, implies that stress as a concept is often a very personal experience.

In RA research, it has long been recognized that there is a complex and bidirectional relationship between psychological factors and the impact of the disease. For instance, illness perceptions evolve over time and influence pain and functioning in patients with RA (8,9), depression and anxiety are prevalent in RA and negatively impact clinical outcomes (10–12), and certain personality characteristics and psychological stressors during the early course of the disease have been associated with long-term anxiety and depression (13). However, although chronic stress can undoubtedly contribute to the development of psychiatric conditions such as clinical depression and anxiety disorder, people suffering from RA might experience more general forms of psychological stress that are not solely related to such psychopathology. Moreover, previous research has suggested that general indicators of psychosocial wellbeing are independently and bidirectionally related to disease activity in RA

(14). On the other hand, psychological factors do not necessarily align with the clinical disease state, which could contribute to patient-physician discordance (15). This growing recognition of the importance of patients' psychosocial wellbeing has prompted some investigators to propose a dual-target approach to RA management, separating the patient's perspective from the clinical treatment target (16). Consequently, a better understanding of the relationship between RA and different forms of psychological stress could provide more insight into possible psychosocial interventions that could improve the management of RA (17,18).

Therefore, we aimed to systematically review the literature assessing the impact of RA on psychological stress. Since, to our knowledge, no comprehensive framework to define stress in the context of RA is available, we adopted the approach of a scoping review aiming to answer the following research questions:

- 1) How is stress defined and described in studies on RA?
- 2) Do patients with RA experience more stress than the general population or than people suffering from other chronic conditions?
- 3) What are the risk factors for developing stress in the context of RA?

## **METHODS**

This systematic scoping review was conducted in accordance with PRISMA guidelines (19).

### **Search strategy and inclusion procedure**

We performed a systematic literature search in EMBASE, PubMed (including MEDLINE), Web of Science Core Collection and The Cochrane Library. The search strategy was developed in collaboration with biomedical reference librarians of the KU Leuven Libraries and was based on combining the concepts of "rheumatoid arthritis" AND "psychological stress" or "psychological interventions" (Supplement 1). We included studies published from inception up to April 19, 2020. Endnote X9 3.2 was used to remove duplicates. All studies were screened by two independent reviewers (CV and AVB) by title and abstract, using Rayyan QRCI. A third reviewer (DDC) was consulted to resolve conflicts. Finally, the full texts were screened for all remaining articles, and additional records were identified by screening the references of included articles.

## **Selection criteria**

Only articles published in English language peer-reviewed journals and relating to at least one of the three research questions were included. Articles were thus eligible for inclusion if they 1) included patients with RA aged  $\geq 18$  years, 2) reported any definition or measure of psychological “stress” or “distress”, either descriptively or as the outcome of an intervention. No formal classification criteria for RA were required for eligibility, as long as a diagnosis of RA was explicitly mentioned. However, studies were excluded if they reported on psychological wellbeing only in terms of psychiatric disorders, including depression and anxiety, unless they additionally mentioned the terms “stress” or “distress”. In addition, qualitative studies were not considered in order to maximize comparability between studies (research question 1) and because they were deemed less suitable to answer research questions 2 and 3. Animal studies, case reports, and conference proceedings were excluded. There was no limit on the number of patients per study, disease duration or the duration of follow-up.

## **Quality assessment**

Study quality was assessed by the Methodological Index for Non-Randomized Studies (MINORS-tool)(20) for longitudinal studies and by the Appraisal Tool for Cross-Sectional studies (AXIS-tool)(21) for cross-sectional studies. The MINORS-tool provides a global score of 0-16 for non-comparative studies and 0-24 for comparative studies. The AXIS-tool consists of 20 yes/no-items and was scored on a numeric 0-20 scale for the purposes of this review. For both tools, higher scores represent lower risk of bias.

## **Data extraction and analysis**

The following data were manually extracted by two independent reviewers (CV and MD) for all included records: study characteristics (including first author, publication year, country, and study design); number and characteristics of study participants (including age, sex, and disease duration); the definition and, when applicable, subtypes used to define stress; the psychometric instrument to assess or measure stress; the specific time frame stress was assessed in; and, when available, the reported levels and predictors of stress. When predictors of stress were described, we additionally extracted details on the statistical analyses that were used to study these predictors. All extracted data were summarized descriptively. Due to the heterogeneity of the stress concept, no meta-analysis was performed.

## **RESULTS**

### **Search results**

The systematic database search in EMBASE, PubMed, Web of Science Core Collection and Cochrane Library identified 5644, 3044, 6354 and 293 references, respectively, resulting in a total of 15335 references. After removing duplicates, 11115 studies were screened by title and abstract, of which 543 articles were eligible for full-text screening. A total of 15 studies met the inclusion criteria for the final review. After searching the reference lists of the included articles, only one additional study meeting the selection criteria was identified. In total, 16 studies were included in this scoping review (Figure 1).

### **Study characteristics and methodological quality (risk of bias)**

Table 1 presents characteristics on study design, study population, the reported measuring instrument for stress and the study quality assessment based on MINORS or AXIS. Of the 16 included studies, 8 were longitudinal and 8 used a cross-sectional design. Publication dates ranged from 1997 to 2017, with most studies (9/16) published since 2010. Where disease duration was reported, most studies included a population with established RA. Only one study (22) included an early RA subgroup (disease duration <6 months). Finally, although methodological quality was variable, most included studies were considered to have a moderate to low risk of bias (Table 1, Supplement 2).

### **Stress assessment: psychometric instruments**

Among the 16 included studies, a total of 13 different instruments to measure stress were reported (Table 1). These psychometric instruments varied considerably both in complexity, ranging from single questions or Visual Analog Scales (VAS) to multiple-item questionnaires, and in the way they conceptualized stress. For instance, while most of the reported instruments measure the level of stress as perceived by the patient, some psychometric tools attempt to measure stress by quantifying the occurrence of stressful events. Examples of the latter include the Social Readjustment Rating Scale (SRRS), the Life Event Inventory (LEI), the Inventory of Small Life Events (ISLE), and the Hassles and Uplifts Scale (HUS), all of which are based on a list of potential stressors with varying degrees of severity (23–26). Even other

psychometric instruments focus on a specific context where stress might occur, including social (Duke Social Support and Stress Scale; DUSOCS) and work-related contexts (Effort-Reward Imbalance questionnaire; ERI) (27,28).

Furthermore, only 3 of the reported measures of stress were used in more than a single study, further underlining the heterogeneity of these measures. First, the most used psychometric instrument was the 21-item version of the Depression Anxiety and Stress Scale (DASS-21), which contains a distinct 7-item subscale for stress assessment that registers a state of nervousness, irritability and agitation during the previous week (29). Second, two studies used the Perceived Stress Scale (PSS), a 14-item scale that measures how uncontrollable, unpredictable and overloaded one's life was during the previous month (30). Finally, two studies used the Symptom-Checklist-90 (SCL-90), a multidimensional scale based on psychopathological symptoms in 9 dimensions. The SCL-90's Global Severity Index (GSI) summarizes the results of all dimensions as a global distress score (31).

#### **A. How is stress defined and described in studies on RA?**

In parallel with the considerable variation in psychometric instruments, the outcome of stress was defined in various ways across the included studies, both in terms of stressor severity, stress content and the types of stressors that might provoke it. Figure 2 presents a descriptive framework summarizing these concepts.

First, stressor severity was defined in several studies as either *major life events* or *minor life events/day-to-day hassles* (26), scored with instruments like the SRRS, LEI, HUS, and ISLE.

Second, three types of stress content were described in the included studies, namely role stress, social stress and work stress. Coty et al. (32) examined the impact of *role stress* on other psychological outcomes, and described this as a product of three types of stressors. First, "role conflict" was defined as difficulties to accomplish the role-expectations, for example in terms of household management. Second, "role overload" was described as feeling overwhelmed by role-related responsibilities. Third, "role balance" was interpreted as the product of an imbalance between different roles.

*Social stress* was defined by Mancuso et al. (33) as stress caused by the circumstances and actions of others, while such stressful events induced by interaction with other people were described as interpersonal stressors in two other studies (34,35).



Finally, only one study (36) examined *work stress*, defined through the ERI instrument as the product of effort, overcommitment and reward (subdivided in esteem, job promotion and job security).

#### **B. Do patients with RA experience more stress than the general population or than people suffering from other chronic conditions?**

Six of the 16 included studies compared patients with RA to a control group consisting of either healthy controls (HC), patients with a different musculoskeletal condition such as osteoarthritis (OA) or patients with chronic pain syndromes (Table 2).

*RA versus healthy controls.* Four studies compared stress in patients with RA to a HC-group. Mancuso et al. (33) found no significant difference in social stress between both groups. However, in the study by Smith et al. (34), more exposure to interpersonal stressors was found in patients with RA or OA than in a HC-group, and also in arthritis or control participants with higher scores on personality traits such as neuroticism and interpersonal sensitivity. Interestingly, individuals who scored higher on both neuroticism and interpersonal sensitivity also reported more disease activity during periods of increased interpersonal stress. Third, Richter et al. (36) found significantly more work stress in patients with RA compared to the control group, with higher ERI-scores for efforts, effort/reward-ratio, and overcommitment; and lower scores for rewards. Finally, Turner Cobb et al. (37) found no significant differences between patients with RA and healthy control adults in frequency or impact of either major or minor life events. However, the authors did conclude that children of parents with RA reported significantly more minor life events than children of control families did.

*RA versus other chronic conditions.* One study found significantly more recalled major life event stress at disease onset in patients with RA compared to an OA group (38). For instance, only 26% of the patients with RA reported no recalled stress at disease onset, compared to 47% in the OA group. However, the long interval since disease onset, with a mean disease duration of 13.5 years in the RA group and 17.5 years in the OA group, means that this comparison is inevitably at risk of recall bias.

Finally, a more recent study (39) reported significantly higher levels of stress, measured using the DASS-21 stress subscale, in patients with chronic pain syndromes compared to an RA

sample, with almost 50% of chronic pain patients experiencing at least mild stress compared to only 10% in the RA group.

### **C. What are the risk factors for developing stress in the context of RA?**

Nine studies examined predictors of stress in patients with RA (Table 3). Although outcome measures and instruments varied considerably across these studies, predictors of stress included demographic characteristics such as younger age, socioeconomic factors such as lower income and education, and disease-related aspects like functional disability, more pain, and higher disease activity.

Furthermore, social support and fewer concerns about social recognition were associated with reduced stress in numerous studies (22,40–42). Additionally, one study reported more stress in patients who were divorced, widowed or separated (43), and Zautra et al. identified a patient's relationship with their spouse as the most important determinant of exposure to interpersonal stressors (35).

Some studies found additional associations between psychological factors and stress in patients with RA. For instance, trait-like factors such as excessive worrying and anxiety sensitivity were associated with increased stress in one study (44), while Treharne et al. (22) found an association between a more pessimistic mindset and increased stress levels. In addition, a one-year follow-up study of Dutch patients with RA found a stronger state of mindfulness to protect against psychological distress (40).

Conversely, the relationship between gender and stress remains somewhat unclear, with one study reporting a stronger sense of social isolation in Polish men with RA (42), while women with RA tended to experience more psychological distress in a Swedish study (41).

### **DISCUSSION:**

This scoping review investigated how people suffering from RA experience psychological stress and what drives stress in these patients. First, we found that stress content was described as either role stress, social stress, or work stress, while a distinction can also be made depending on the severity of the stressor, defined as either major or minor life events. Although no clear differences were shown in terms of the occurrence or impact of both major

and minor life events, our results suggest that patients with RA experience more work stress and are exposed to more interpersonal stressors than the general population. Moreover, when compared to patients with a different chronic condition, our review found more recalled stress at disease onset in patients with RA than in patients with OA, although even higher stress levels were reported in people suffering from chronic pain. Finally, reported risk factors to develop stress in patients with RA included functional disability, more pain, higher disease activity, younger age, lower income, lower education, insufficient social support and psychological traits such as excessive worrying, anxiety sensitivity and pessimism.

One of the most crucial goals when caring for people suffering from any medical condition is to improve their quality of life, or ultimately, to promote happiness. A recent study on the determinants of happiness in patients with RA exemplified the importance of psychological factors for this concept, with more 'positive' personality traits contributing to happiness both directly and by mitigating the negative impact of disease activity (45). On the other hand, various studies have shown that rheumatoid arthritis has a considerable impact on patients' mental health (46). Furthermore, psychological comorbidities such as depression and anxiety are not only associated with a reduced probability of achieving disease remission (12,47–49), but it has also been shown that patients in remission often still report unmet needs in terms of mental health (3,50,51). However, the concept of psychological stress refers to more than mood disturbances or psychiatric conditions. Only one review has to date investigated the relationship between stress and arthritis, but this review focused on chronic stressors as risk factors for the development of self-reported arthritis and did not use rigorous arthritis definitions (52). By contrast, our scoping review included only studies reporting a confirmed RA population. Moreover, we focused in particular on the impact of RA on psychological stress, rather than the inverse.

An important finding of our review is that patients with RA seem to experience more work stress than the general population. Work stress can arise when there is an imbalance between efforts, rewards and overcommitment in a professional context. When these imbalances occur in a personal context, this is more commonly referred to as role stress, which is influenced by role overload, role balance and role conflict. Role stress has been described as an important contributor to impaired psychological wellbeing in patients with RA (32). Moreover, a study by Gignac et al. concluded that suffering from inflammatory arthritis

conflicted with both work and personal roles, leading to role overload and role conflict (53). Living with RA can be challenging, and experiencing disease-related symptoms of RA combined with the responsibilities of everyday life can result in both role stress and work stress for many patients. In addition, one study found higher levels of exposure to interpersonal stressors in patients with RA compared to healthy controls (34). Intriguingly though, the level of social stress, which could be interpreted as the result of coping with such interpersonal stressors, was not found to differ between patients with RA and healthy controls in a different study (33). Clearly, psychological stress is a complex and heterogeneous concept, and considering sources of stress as part of a holistic approach to RA management remains therefore challenging.

To help mitigate this challenge, our review also identified several predictors and protective factors for psychological stress in patients with RA. In general, a more physically impactful disease, as reflected by higher joint counts, higher disease activity, more pain and functional disability, appears to be associated with higher levels of stress. Although these associations appear logical, the finding that younger age is related to more stress is intriguing. Persson et al. (41) attributed this to the fact that younger patients with RA on average have more work demands or marital expectations and more demanding household roles. Being aware of such risk factors and their role in the development of stress, could be an important step towards predicting different stress trajectories among people suffering from RA. The trait-like risk factors for experiencing stress, such as excessive worrying, a more pessimistic mindset and anxiety sensitivity, could particularly help to identify the optimal target population for psychological interventions to prevent stress development, such as cognitive behavioral therapy, supportive counselling and mindfulness-based cognitive therapy (17).

Finally, our review illustrates several issues in the current stress-related literature on RA. First, there is no consensus on how to define stress, and terms such as stress, stressor and distress are often used interchangeably. On a physiological level, stress is a vitally important state of neuro-endocrinal activation, centered around the hypothalamic-pituitary-adrenal (HPA) axis, in response to threats (54). However, this crucial physiological response can become pathological when chronic stressors with a strong perceived impact give rise to a dysfunctional stress response. Folkman et al. (6) define stress as the experience of an imbalance between the demands of life and one's capacity to meet these demands, and indirectly refer to a

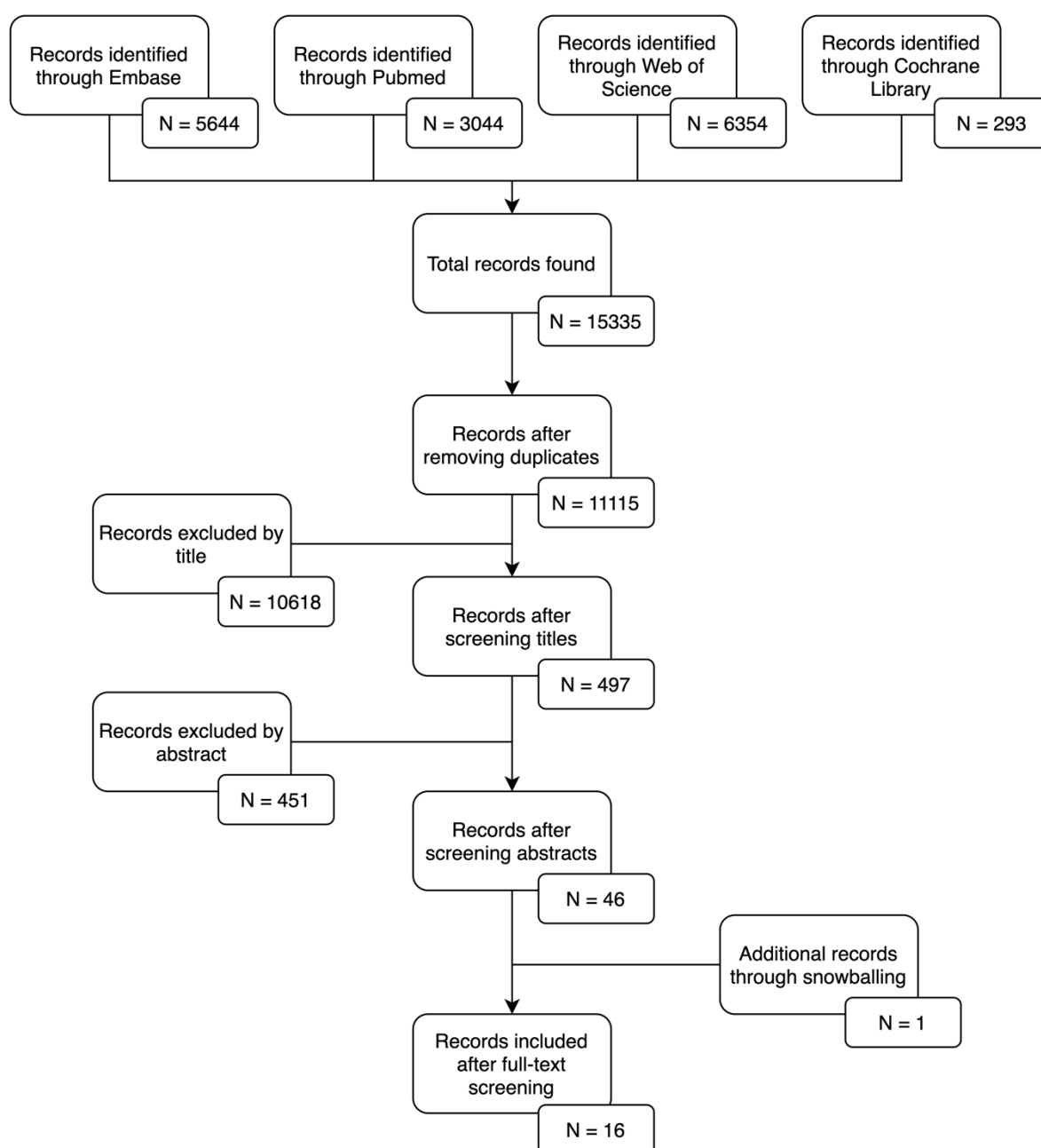
threshold above which stress becomes pathological. Nonetheless, this threshold and the perceived impact of stressors are person-dependent and difficult to generalize. Therefore, many studies discuss psychological stress in the context of anxiety or depressed mood (55–58), while even others refer to stress as a feeling of social isolation or being a burden (42). Second, there is no standardized method to measure stress in patients with RA. For instance, 13 different instruments to measure stress were reported in our included studies, of which only 3 tools were used in more than one study, and many other studies were excluded because they measured psychological stress solely by a range of anxiety/depression-scales. Moreover, none of the psychometric instruments were specifically designed for patients with RA, and the time interval for stress evaluation by recall varied among scales. Finally, a considerable heterogeneity exists in the types of stress and the severity of stressful events measured by specific scales. Therefore, the varied conceptualization and measurement of stress often impair the generalizability of conclusions made by individual studies on this topic. These inconsistencies in stress-related research also represent an inherent limitation of our scoping review. For instance, some records were excluded because they defined psychological stress as either depression or anxiety, while qualitative studies were not considered. However, since no coherent definition of stress currently exists, these decisions might have excluded valuable conceptual information. Secondly, no single definition of stress, stress content or stressors specific for the context of RA could be identified. Consequently, although it was based solely on studies in RA populations, our literature-derived framework to describe psychological stress should not be interpreted as a representation of uniquely RA-related stress. Future research on stress in patients with RA should clearly define its concept and attempt to measure this with validated instruments that minimize recall bias and are optimally adjusted for disease-specific factors.

## **Conclusion**

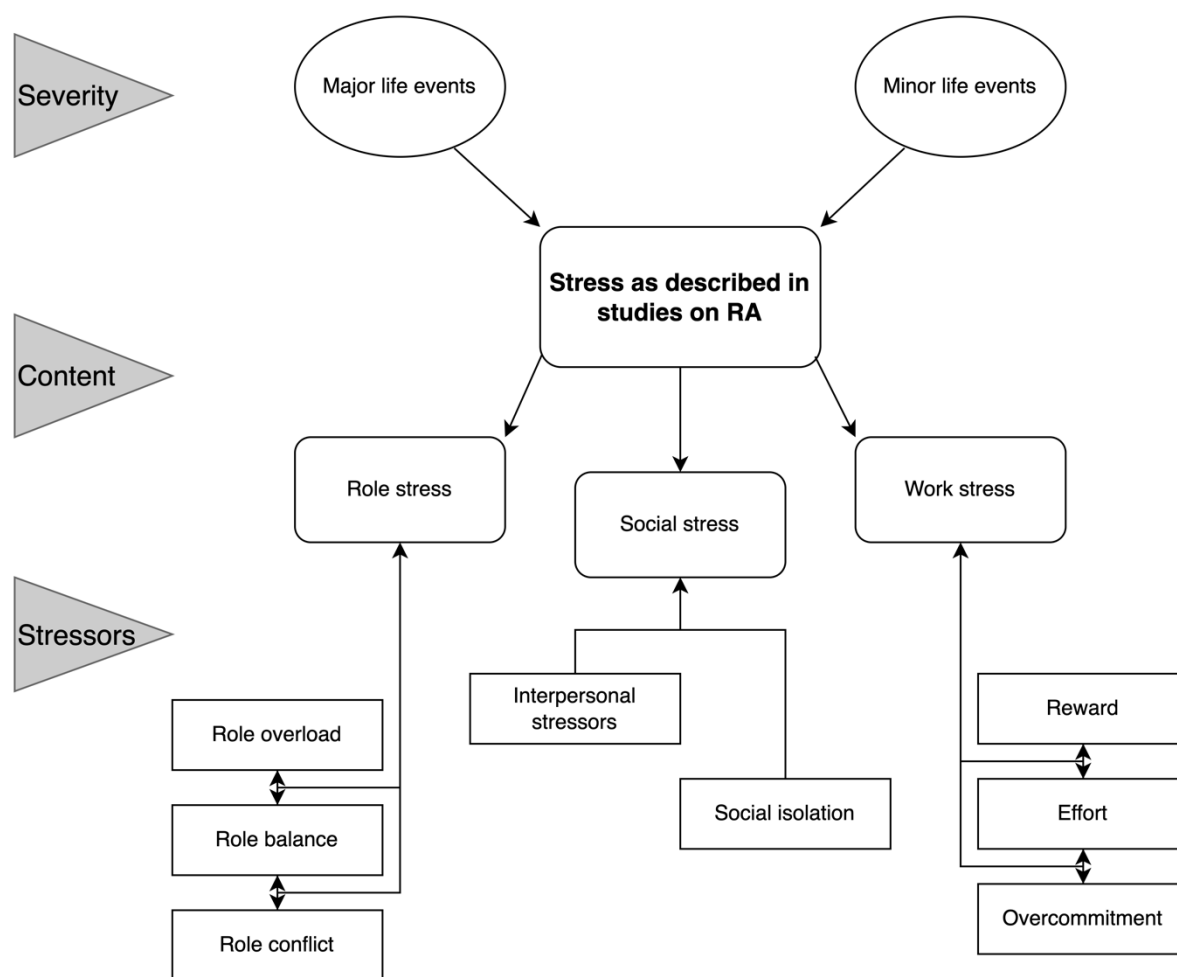
This scoping review suggests that patients with RA tend to experience more work stress and interpersonal stressors than the general population, and that risk factors for the development of stress include more pain, functional disability, higher disease activity, younger age, lower socioeconomic status, certain psychological traits, and insufficient social support. However, the evidence considering the impact of RA on psychological stress is hampered by considerable heterogeneity in the conceptualization and measurement of stress. In this

scoping review, we proposed a literature-based framework for how psychological stress can be described in studies on RA. This way, we hope to provide a foundation for future research aiming to assess the burden of psychological stress in patients with RA, with a view to meeting these needs with person-centered interventions.

**Figure 1.** PRISMA flowchart for the systematic review process.



**Figure 2.** Descriptive summary of stress definitions reported in studies on rheumatoid arthritis (RA).





**Table 1.** Characteristics of the included studies.

Reference	Country	Design	Number (n)	Study population			Stress instrument	Timeframe	Study quality
				Age (mean $\pm$ SD)	Disease duration (mean $\pm$ SD)	Female (%)			
<b>Latman (1996)</b>	USA	Cross-sectional	207 (RA: n = 128, OA: n = 79)	RA: 56y $\pm$ - OA: 63y $\pm$ -	RA: 13.5y $\pm$ - OA: 17.5y $\pm$ -	RA: 74% OA: 71%	SRRS	Previous year	AXIS 20/20
<b>Zautra (1997)</b>	USA	Longitudinal	41	55 $\pm$ 10y	-	100%	ISLE	Previous week	MINORS 12/16
<b>Turner Cobb (1998)</b>	UK	Longitudinal	38 individuals (RA: n = 14, HC: n = 24) and their children	RA: 42 $\pm$ 8y HC: 39 $\pm$ 4y	9.6 $\pm$ 14y	RA: 93% HC: 55%	LEI	Previous 6m	MINORS 17/24
							HUS	Day of inquiry	
<b>Smith (2002)</b>	USA	Longitudinal	255 (RA: n = 93, OA: n = 82, HC: n = 80)	RA: 62y $\pm$ 7y OA: 65y $\pm$ 7y HC: 62y $\pm$ 7y	-	100%	Single question*	Previous week	MINORS 17/24
<b>Persson (2005)</b>	Sweden	Longitudinal	158	51y $\pm$ 13y	10 $\pm$ 4y**	64%	SCL-90 R	Previous week	MINORS 12/16
<b>Mancuso (2006)</b>	USA	Longitudinal	244 (RA: n = 122, HC: n = 122)	RA: 49 $\pm$ 12y HC: 49 $\pm$ 10y	14 $\pm$ 10y	RA: 84% HC: 91%	DUSOCS	Day of inquiry	MINORS 20/24
<b>Treharne (2007)</b>	UK	Longitudinal	134	55y $\pm$ 14y	Varying***	75%	PSS	Previous month	MINORS 11/16
<b>Bugajska (2010)</b>	Poland/Germany	Cross-sectional	437 (Poland: n = 300, Germany: n = 137)	Age categories (Poland/Germany): $\leq$ 30y: 5%/1% 31-40y: 8%/16% 41-50y: 16%/37% >50y: 71%/38%	Poland: 9 $\pm$ 8y Germany: 13 $\pm$ 10y	Poland: 79% Germany: 83%	- Social isolation: questions 6 + 10 of SF-36 - "Being a burden": two individual questions <sup>†</sup>	Previous 4 weeks	AXIS: 16/20
<b>Goulia (2015)</b>	Greece	Longitudinal	168	55 $\pm$ 13y	14 $\pm$ 9y	83%	SCL-90 R	Previous week	MINORS 11/16
<b>Nyklicek (2015)</b>	The Netherlands	Longitudinal	201	57 $\pm$ 12y	5 $\pm$ 9y	55%	PSS	Previous month	MINORS 13/16
<b>Cunha (2016)</b>	Portugal	Cross-sectional	80	58y $\pm$ -	-	83%	DASS-21	Previous week	AXIS 10/20
<b>Rice (2016)</b>	Canada	Cross-sectional	330 (RA: n = 163, CP: n = 167)	RA: 56 $\pm$ 13y CP: 45 $\pm$ 11y	-	RA: 76% CP: 64%	DASS-21	Previous week	AXIS 18/20
<b>Coty (2017)</b>	USA	Cross-sectional	80	54 $\pm$ 12y	2 $\pm$ 1y	74%	- Role conflict: (gender-modified) RCQW - Role overload: 8 items of Reilly's Overload Scale	In general	AXIS 17/20

							- Role balance: VAS		
<b>Rice (2017)</b>	Canada	Cross-sectional	445 (RA: n = 226, CP: n = 229)	RA: 58 ± 15y CP: 45 ± 12y	RA: 13 ± 11y CP: 6 ± 7y	RA: 76% CP: 64%	DASS-21	Previous week	AXIS 17/20
<b>Rahim (2018)</b>	Malaysia	Cross-sectional	189	52 ± 11y	5 ± 9y	88%	DASS-21	Previous week	AXIS 17/20
<b>Richter (2018)</b>	Germany	Cross-sectional	695 (RA: n = 270, HC: n = 178)	RA: 48 ± 10y HC: 43 ± 10y	9 ± 8y	RA: 85% HC: 90%	ERI	During current or last occupation	AXIS 17/20

\* "Overall, how stressful were your relations with your spouse (or significant other), with your family members, with your friends this past week?"

\*\* Median (IQR)

\*\*\* Early RA (<6 months): n = 44 (33%); intermediate duration (1-7 years): n = 48 (36%); long-standing RA (>7 years): n = 42 (31%)

<sup>⊥</sup> "Do you require help of other persons in everyday life? Who provides help?"; "How much of daily time do other persons use for helping you?"

- = missing or not applicable

USA = United States of America, UK = United Kingdom, RA = rheumatoid arthritis, OA = osteoarthritis, HC = healthy controls, CP = chronic pain, SF-36 = 36-Item Short Form Survey, RCQW = Role Conflict Questionnaire for Women, VAS = visual analog scale, DASS-21 = 21-item Depression Anxiety and Stress Scale, SCL-90-R = Symptom Checklist-90-Revised, SRRS = Social Readjustment Rating Scale of Holmes and Rahe, DUSOCS = Duke Social Support and Stress Scale, PSS = Perceived Stress Scale, ERI = Effort-Reward Imbalance questionnaire, LEI = Life Event Inventory, HUS = Hassles and Uplifts Scale, ISLE = Inventory of Small Life Events

**Table 2.** Overview of psychological stress severity, stress content, or exposure to stressors, in people suffering from RA compared to control groups.

Control group	Main conclusion		Stress instrument	Reference
Healthy controls	Social stress	RA = HC	DUSOCS	Mancuso (2006)
	Work stress	RA > HC	ERI	Richter (2018)
	Interpersonal stressors	OA – RA > HC	Individual questions*	Smith (2002)
	Major life events	RA = HC	LEI	Turner Cobb (1998)
Osteoarthritis	Minor life events	RA = HC**	HUS	
	Major life events at disease onset	RA > OA	SRRS	Latman (1996)
Chronic pain	Psychological stress***	CP > RA	DASS-21	Rice (2016)

\* “Overall, how stressful were your relations with your spouse (or significant other), with your family members, with your friends this past week?”

\*\* However, patients with RA experienced fewer positive events than healthy controls did, and their children reported significantly more minor life events than children from control families.

\*\*\* Not further specified.

OA = osteoarthritis, CP = chronic pain, HC = healthy control, RA = rheumatoid arthritis, DUSOCS = Duke Social Support and Stress Scale, ERI = Effort-Reward Imbalance questionnaire, LEI = Life Event Inventory, HUS = Hassles and Uplifts Scale, SRRS = Social Readjustment Rating Scale of Holmes and Rahe, DASS-21 = 21-item Depression Anxiety and Stress Scale

**Table 3.** Predictors of psychological stress reported as significant in studies on RA.

Reference	Predictor	$\beta$	r	OR	p-value	Outcome
<b>Zautra (1997)</b>	Pain (VAS)	-0.13			<0.01	Interpersonal stress (ISLE) – 1 week later
<b>Persson (2005)</b>	Functional disability (HAQ)		0.35		<0.01	Psychological distress (SCL-90 R) - during early disease
	Pain (VAS)		0.20		<0.05	
	Social support		-0.40		<0.01	
	Age		-0.21		<0.05	
	Gender (female)				<0.01*	
	Marital status (single living)				<0.05*	
<b>Treharne (2007)</b>	Optimism		-0.37		<0.01	Stress (PSS) - at baseline
	Social support		-0.38		<0.01	
	Pessimism		0.36		<0.01	
<b>Bugajska (2010)</b>	Gender (male)	0.17			0.003	Social isolation
	Education (tertiary bachelor's degree)	-0.08			<0.01	
	Functional disability (categorical)	0.23			0.002	
				0.17	<0.001	Feeling of 'being a burden'
<b>Goulia (2015)</b>	Education (mean years)		-0.27		<0.01	Psychological distress (SCL-90 R)
	Marital status (divorced/widowed/separated)	-0.23**			<0.01	
	Functional disability (HAQ-DI)		0.36		<0.001	
	Improvement in HAQ-DI		0.25		0.045	
	Pain (VAS)		0.38		<0.001	
	Improvement in pain (VAS)		0.25		<0.05	
	Sense of coherence		-0.55		<0.001	
			0.34 <sup>⊥</sup>		<0.001	
<b>Nyklicek (2015)</b>	Disease duration (months)	-0.002			0.016	Psychological distress as a composite of PSS, SAD-4, GMS and SWLS
	Functional disability (HAQ)	0.77			<0.001	
	Social desirability (MCSDS)	-0.039			0.029	
	Mindfulness (FMI-s)	-0.098			0.010	
	Mindfulness (moderator of time-disability)	-0.036			0.022	
<b>Cunha (2016)</b>	Low household income				0.019***	Stress (DASS-21)
	Patient global assessment (VAS)	0.31			0.005	
<b>Rice (2017)</b>	Pain (VAS)	0.31			0.001	Stress (DASS-21)
	Excessive worrying	0.23			0.001	
	Anxiety sensitivity	0.02			0.001	
<b>Rahim (2018)</b>	Age		-0.24		0.001	Stress (DASS-21)
	Education (categorical)				0.039****	
	Pain (VAS)		0.41		<0.001	
	Pain (VAS)			1.04 (1.0-1.1)	NA	
	Tender joint count		0.26		<0.001	
	Swollen joint count		0.15		0.043	
	Disability (HAQ)		0.32		<0.001	
	DAS28-ESR		0.27		<0.001	

Only predictors reported as significant in the included articles are presented. Predictors were studied with the following statistical methods, unless otherwise specified: 1) when a regression coefficient  $\beta$  is presented, the predictor was studied with multivariable linear regression; 2) when a correlation coefficient r is presented, the correlation between the predictor and the stress outcome was studied univariately; and 3) when an odds ratio is presented, the predictor was studied with multivariable logistic regression.

\* Resulting from an unpaired t-test; \*\* Resulting from univariate linear regression with improvement in psychological distress over time as the outcome; \*\*\* Resulting from Kruskal-Wallis test; \*\*\*\* Resulting from Chi-square test with higher education levels associated with more stress; <sup>⊥</sup> Resulting from correlation between sense of coherence and improvement in psychological distress over time. OR = odds ratio, VAS = visual analog scale, HAQ = Health Assessment Questionnaire, ISLE = Inventory of Small Life Events, SCL-90 R = Symptom Checklist-90-Revised, PSS = Perceived Stress Scale, DASS-21 = 21-item Depression Anxiety and Stress Scale, MCSDS = Marlowe–Crowne Social Desirability Scale, FMI-s = Freiburg Mindfulness Inventory-short-form, SAD-4 = Symptoms of Anxiety and Depression scale, GMS = General Mood Scale, SWLS = Satisfaction With Life Scale, DAS28-ESR = Disease Activity Score in 28 joints using erythrocyte-sedimentation rate

## **DISCLOSURE STATEMENT**

The authors declare no conflicts of interest in relation to this publication (see attached ICJME standardized disclosure forms).

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