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PSYCHOLOGICAL AND CLINICAL CORRELATES IN PATIENTS WITH RHEUMATIC DISEASES

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Psychological and clinical correlates in patients with rheumatic diseases - Branko Ristić

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LIST OF ABBREVIATIONS

ACR American College of Rheumatology

ACT Acceptance and Commitment Therapy

ANCOVA Analysis of Covariance

anti-TNF Anti–Tumor Necrosis Factor

AS Ankylosing Spondylitis

ASAS Assessment of SpondyloArthritis international Society

ASDAS-CRP Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein

ASQoL Ankylosing Spondylitis Quality of Life

axSpA Axial Spondyloarthritis

BASDAI Bath Ankylosing Spondylitis Disease Activity Index

BASFI Bath Ankylosing Spondylitis Functional Index

bDMARD Biologic Disease-Modifying Antirheumatic Drug

BMI Body Mass Index

BP Bodily Pain

BRAF-MDQ Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire

BREQ-3 Behavioural Regulation in Exercise Questionnaire

CASPAR CLaSsification for Psoriatic Arthritis

CBT Cognitive-Behavioral Therapy

CFQ Chalder Fatigue Questionnaire

COPE-NVI coping orientation to the problems experiences-new Italian version

CRP C-Reactive Protein

csDMARDs Conventional Synthetic Disease-Modifying Antirheumatic Drugs

CTQ-SF Childhood Trauma Questionnaire-Short Form

DAPSA Disease Activity in PSoriatic Arthritis

DAS28-CRP The 28-joint Disease Activity Score and C-Reactive Protein

DMARD Disease-Modifying AntiRheumatic Drug

ESR Erythrocyte Sedimentation Rates

EULAR European Alliance of Associations for Rheumatology

FREE Fatigue reduction in Rheumatic diseases: Efficacy Evaluation

HADS-A Hospital Anxiety and Depression Scale - Anxiety

HADS-D Hospital Anxiety and Depression Scale - Depression

HAQ-DI Health Assessment Questionnaire - Disability Index

Hb Haemoglobin

HLA-B27 Human Leukocyte Antigen B27

HRQoL Health-Related Quality of Life

GAD-7 General Anxiety Disorder scale

GH General Health

GPAQ Global Physical Activity Questionnaire

MCS Mental Component Summary

MH Mental Health

MRI Magnetic Resonance Imaging

NSAID NonSteroidal Anti-Inflammatory Drug

QoL Quality of Life

OR Odds Ratio

PCS Physical Component Summary

PF Physical Functioning

PHQ-9 Patient Health Questionnaire-9

PRO Patient Reported Outcome

PsA Psoriatic Arthritis

PSS Perceived Stress Scale

PSQI Pittsburgh Sleep Quality Index

r-axSpA Radiographic Axial Spondyloarthritis

RA Rheumatoid Arthritis

RDCI Rheumatic Disease Comorbidity Index

PREDIMED PREvencion con DIeta MEDiterranea

RCT Randomized Controlled Trial

RD Rheumatic Disease

RE Role limitations due to Emotional problems

RP Role limitations due to Physical health

rSpA Radiographic Axial Spondyloarthritis

SD Standard Deviation

SF Social Functioning

SF-36 Medical Outcomes Study Short Form-36

SpA Spondyloarthritis

TFEQ-R-18 Three Factor Eating Questionnaire Revised 18

tsDMARDs Targeted Synthetic Disease-Modifying Antirheumatic Drugs

TSH Thyrotropin

VAS Visual Analogue Scale

VT Vitality

WHO World Health Organization

WHOQOL World Health Organization Quality of Life

ABSTRACT

Rheumatic diseases are complex chronic conditions characterized by inflammatory, physical and psychological dimensions that interact to shape the overall disease experience. Beyond joint and tissue pathology, these conditions profoundly affect patients' emotional well-being, coping mechanisms and perceived quality of life. The present thesis sought to examine the dynamic interplay between psychological and clinical variables in rheumatic diseases, adopting a biopsychosocial perspective to better understand the relationship between disease symptoms and outcomes and psychological processes. Specifically, it aimed to investigate how coping strategies are related to fatigue and whether these relationships are mediated or moderated by factors such as depression, anxiety, sex, diagnosis, disease activity and duration. Moreover, the thesis analyzes the determinants of and compares health-related quality of life (HRQoL) among patients with rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. Additionally, it examines the association between disease activity and health-related quality of life, with fatigue as a possible mediator. Furthermore, the thesis examined sex differences in clinical and psychological profiles and developed a non-pharmacological intervention protocol that integrates psychological and physiotherapy-based components. Collectively, the overarching goal was to develop more effective, holistic management strategies for individuals whose symptoms and outcomes remain suboptimal despite standard rheumatological treatment.

The research findings provide a detailed understanding of the interconnections between clinical symptoms and psychological mechanisms in rheumatic diseases. In the first part of the thesis, dysfunctional coping seems to be a significant predictor of fatigue, with depression and anxiety mediating this association. These findings highlight the possible pivotal role of emotional and cognitive processes in maintaining fatigue symptoms, suggesting that how patients interpret and respond to their illness may influence their physical and mental experience of fatigue. Furthermore, diagnosis and sex seem to be significant moderators in the proposed models, while disease activity and duration exerted no significant influence on these pathways. The second segment of the thesis, focused on HRQoL, revealed that while patients with rheumatoid arthritis

reported the lowest quality of life among rheumatic diseases, similar psychosocial mechanisms were related to HRQoL across rheumatic conditions. Common determinants, particularly disease activity, depression, and anxiety, explained a large portion of HRQoL variance. Fatigue partially mediated the relationship between disease activity and physical domains of HRQoL, accounting for up to 40% of this association. Moreover, in psoriatic arthritis, first-line rheumatological treatment was a significant moderator of the direct effect. In contrast, sex and comorbidities did not significantly influence the tested models.

The third section of the thesis examined sex differences in rheumatic diseases, revealing that women consistently scored worse across most clinical and psychological measures. Fatigue, perceived stress, anxiety, and pain were the principal contributors to both physical and mental HRQoL, particularly among female patients, reinforcing the necessity for sex-sensitive clinical and psychological care. Building on these empirical findings, the final phase of the thesis introduced the Fatigue reduction in Rheumatic diseases: Efficacy Evaluation (FREE) trial, a randomized controlled study designed to evaluate two tailored, group-based, non-pharmacological interventions: one psychological and one physiotherapy-oriented. The trial aims to determine and compare whether, and to what extent, each intervention can reduce fatigue, the primary outcome, and improve secondary outcomes such as disease activity, depression, anxiety, pain, physical functioning, sleep quality and overall HRQoL.

Taken together, the results of this thesis highlight the crucial importance of addressing psychological variables alongside clinical factors in rheumatology. By jointly considering sociodemographic, psychological and clinical dimensions, the research provides a comprehensive understanding of the mechanisms linking coping, emotional distress and disease activity, offering a foundation for integrative, patient-centered therapeutic approaches. The exploration of non-pharmacological interventions, such as psychological and physiotherapy-based treatments, represents an essential advancement toward multidisciplinary care models. Ultimately, acknowledging patients' subjective experiences and psychological responses to chronic illness fosters

a holistic, sex-sensitive, and precision-based model of rheumatology care that enhances overall well-being and treatment effectiveness.

Key words: rheumatic disease, coping strategy, fatigue, health-related quality of life, sex difference, non-pharmacological interventions

SUMMARY (ITALIAN)

Le malattie reumatiche sono condizioni croniche complesse caratterizzate da componenti infiammatorie, fisiche e psicologiche che interagiscono nel modellare l’esperienza complessiva della malattia. Oltre alla patologia articolare e tissutale, queste condizioni influenzano profondamente il benessere emotivo dei pazienti, i meccanismi di coping e la qualità della vita percepita. La presente tesi si è proposta di esaminare l’interazione dinamica tra variabili psicologiche e cliniche nelle malattie reumatiche, adottando una prospettiva biopsicosociale al fine di comprendere meglio la relazione tra sintomi della malattia, esiti e processi psicologici. In particolare, l’obiettivo è stato indagare come le strategie di coping siano associate alla fatica e se tali relazioni siano mediate o moderate da fattori quali depressione, ansia, sesso, diagnosi, attività della malattia e durata della malattia. Inoltre, la tesi analizza i determinanti di e confronta la qualità della vita correlata alla salute (HRQoL) tra pazienti con artrite reumatoide, artrite psoriasica e spondiloartrite assiale. Inoltre, viene esaminata la relazione tra attività della malattia e HRQoL, con la fatica come possibile mediatore. La tesi ha anche esplorato le differenze di genere nei profili clinici e psicologici e ha sviluppato un protocollo d’intervento non farmacologico che integra componenti psicologiche e fisioterapiche. Complessivamente, l’obiettivo generale è stato quello di sviluppare strategie di gestione più efficaci e olistiche per individui i cui sintomi ed esiti rimangono subottimali nonostante i trattamenti reumatologici standard.

I risultati della ricerca forniscono una comprensione dettagliata delle interconnessioni tra sintomi clinici e meccanismi psicologici nelle malattie reumatiche. Nella prima parte della tesi, il coping disfunzionale sembra essere un predittore significativo della fatica, con depressione e ansia che mediano tale associazione. Questi risultati evidenziano il possibile ruolo cruciale dei processi emotivi e cognitivi nel mantenimento dei sintomi di fatica, suggerendo che il modo in cui i pazienti interpretano e rispondono alla malattia può influenzare la loro esperienza fisica e mentale della fatica. Inoltre, diagnosi e sesso sembrano essere moderatori significativi nei modelli proposti, mentre attività della malattia e durata della malattia non hanno esercitato un’influenza significativa su questi percorsi. La seconda sezione della tesi,

focalizzata sulla HRQoL, ha mostrato che, sebbene i pazienti con artrite reumatoide riportassero la qualità della vita più bassa tra le malattie reumatiche, meccanismi psicosociali simili sono correlati alla HRQoL attraverso le diverse condizioni reumatiche. Determinanti comuni, in particolare attività della malattia, depressione e ansia, spiegano una larga parte della varianza nella HRQoL. La fatica ha mediato parzialmente la relazione tra attività della malattia e i domini fisici della HRQoL, spiegando fino al 40% di tale associazione. Inoltre, nell'artrite psoriasica, il trattamento reumatologico di prima linea è risultato essere un moderatore significativo dell'effetto diretto. Al contrario, sesso e comorbidità non hanno influenzato in modo significativo i modelli testati.

La terza parte della tesi ha esaminato le differenze di sesso nelle malattie reumatiche, rivelando che le donne hanno ottenuto costantemente punteggi peggiori nella maggior parte delle misure cliniche e psicologiche. Fatica, stress percepito, ansia e dolore sono risultati i principali contributori sia ai domini fisici che mentali della HRQoL, in particolare tra le pazienti di sesso femminile, sottolineando la necessità di un'assistenza clinica e psicologica sensibile al sesso. Sulla base di questi risultati empirici, la fase finale della tesi ha introdotto il Fatigue reduction in Rheumatic diseases: Efficacy Evaluation (FREE) trial, uno studio randomizzato controllato progettato per valutare due interventi personalizzati non farmacologici di gruppo: uno psicologico e l'altro orientato alla fisioterapia. Lo studio mira a determinare e confrontare se, e in quale misura, ciascun intervento possa ridurre la fatica, l'esito primario, e migliorare gli esiti secondari quali attività della malattia, depressione, ansia, dolore, funzionamento fisico, qualità del sonno e HRQoL complessiva.

Complessivamente, i risultati di questa tesi evidenziano l'importanza cruciale di considerare le variabili psicologiche insieme ai fattori clinici in reumatologia. Analizzando congiuntamente le dimensioni sociodemografiche, psicologiche e cliniche, la ricerca fornisce una comprensione completa dei meccanismi che collegano coping, disagio emotivo e attività della malattia, offrendo una base per approcci terapeutici integrati e centrati sul paziente. L'esplorazione degli interventi non farmacologici, come quelli psicologici e fisioterapici, rappresenta un passo essenziale

verso modelli di cura multidisciplinari. Infine, riconoscere le esperienze soggettive e le risposte psicologiche dei pazienti alle malattie croniche promuove un modello di cura reumatologica olistico, sensibile al sesso e basato sulla precisione, in grado di migliorare il benessere complessivo e l’efficacia dei trattamenti.

Parole chiave: malattia reumatica, strategia di coping, fatica, qualità della vita correlata alla salute, differenza di sesso, interventi non farmacologici

CHAPTER 1. INTRODUCTION

1.1 THEORETICAL BACKGROUND

1.1.1 Clinical characteristics of rheumatic diseases

Rheumatic diseases have been recognized in medicine since ancient times. The term *rheumatology* derives from the Ancient Greek verb *ῥέω* (*rhéō*), meaning “to flow” or “to stream,” and the noun *ῥεῦμα* (*rheûma*), meaning “current” or “stream” (Beekes and van Beek, 2010). The term later evolved into *rheumatism*, referring to a disorder characterized by “flux,” in which an excessive flow of rheum into a joint was thought to cause stretching of the ligaments (Beekes and van Beek, 2010; Tsiamis et al., 2006). Rheumatic diseases are defined as diseases affecting the locomotor system, including muscles, bones, joints, tendons, and ligaments, with rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis being among the most common (Sebbag et al., 2019).

Rheumatoid arthritis (RA) is a systemic autoimmune inflammatory disease that primarily affects the joints, leading to cartilage and bone destruction and, ultimately, disability (Di Matteo et al., 2023; Smolen et al., 2016). The prevalence of RA varies considerably worldwide, ranging from 0.25% to 1%, with higher rates generally observed in industrialized nations, likely reflecting, at least in part, differences in risk factors such as environmental exposures (Di Matteo et al., 2023; Finckh et al., 2022). Most epidemiological studies have been conducted in Western countries, reporting prevalence rates between 0.5% and 1.0% among white populations (Smolen et al., 2018). The global incidence of RA is estimated to range between 0.5% and 1% (Smolen et al., 2016). RA can affect individuals at any age, although incidence increases after the age of 40, and women are affected two to three times more frequently than men (Di Matteo et al., 2023).

RA is a heterogeneous and complex disease with variable clinical presentations and pathogenetic mechanisms. Its clinical course typically involves an insidious and gradual onset of joint pain and swelling. RA likely results from multiple factors, including the interplay of environmental and lifestyle influences acting upon genetically predisposed individuals (Smolen et al., 2016; Smolen et al., 2018). The disease imposes a substantial burden on both individuals and society, being associated with high socioeconomic costs, progressive disability, and premature mortality (Smolen et al., 2016; Di Matteo et al., 2023). Current management strategies emphasize early diagnosis and prompt initiation of targeted therapy to prevent joint damage and achieve remission or, at minimum, low disease activity (Smolen et al., 2018).

Spondyloarthritis (SpA) is a multisystem immune-mediated inflammatory disease primarily affecting the axial skeleton, including the sacroiliac joints, spine, and peripheral joints (Bittar and Deodhar, 2025). Although SpA represents a distinct clinical entity, it encompasses several subtypes, including radiographic axial spondyloarthritis (r-axSpA, also known as ankylosing spondylitis [AS]) and psoriatic arthritis (PsA) (Stolwijk et al., 2016). Radiographic axial SpA is characterized by radiographic changes in the sacroiliac joints, although its etiology remains unclear (Yang et al., 2016). Psoriatic arthritis is an immune-mediated inflammatory musculoskeletal disease with a chronic and progressive course that can lead to joint destruction and disability in severe cases (Tarannum et al., 2022). About 15.5-19.7% patients with psoriasis develop PsA (Hernández-Rodríguez et al., 2024).

Variations in the prevalence of SpA, r-axSpA, and PsA are influenced by geographic region, demographic composition, sex distribution and mean age of study populations. The global prevalence of SpA is estimated to range from 0.3% to 1.4%. Much of this heterogeneity can be attributed to geographic variation, with higher prevalence reported in North America (1.35%) and Europe (0.54%) compared with South Asia (0.22%) and Southeast Asia (0.20%). The prevalence of r-axSpA ranges from 0.25% in Europe and 0.20% in North America to 0.02% in Sub-Saharan Africa. Prevalence is higher among males than females and tends to be greater in rural populations. The global prevalence of PsA among adults is approximately 0.11%, with the highest rates observed in Europe (0.19%) and the lowest in the Middle East (0.01%) (Stolwijk et al., 2016).

Diagnosis of axial spondyloarthritis, often delayed by 6 to 8 years after symptom onset, is based on clinical history, laboratory findings such as elevated C-reactive protein levels, and imaging evidence of sacroiliitis on plain radiography or magnetic resonance imaging. The hallmark symptom of axial spondyloarthritis is inflammatory back pain

- characterized by gradual onset before the age of 45, prolonged morning stiffness, improvement with exercise, and lack of relief with rest, affecting more than 80% of patients (Bittar and Deodhar, 2025). PsA occurs exclusively in individuals with psoriasis and can be distinguished from other forms of spondyloarthritis by the presence of peripheral arthritis and asymmetrical spinal involvement. Severe PsA may cause deformities resulting in digital shortening due to extensive joint or bone lysis. The disease burden is evident both in the progression of clinical and radiological damage and in its adverse effects on patients' quality of life and functional status (Gladman et al., 2005).

Comorbidities are highly prevalent among patients with rheumatic diseases. In RA, several comorbidities, such as lung cancer, lymphoma, infections, cardiovascular disease, osteoporosis and depression, occur at higher rates than in the general population. This increased incidence and prevalence may be attributable to underlying inflammatory mechanisms and/or the effects of antirheumatic treatment regimens (Dougados, 2016). Depression is one of the most common comorbidities associated with RA, occurring approximately twice as frequently in women as in men (Krasselt and Baerwald, 2019). Comorbidities are also prevalent among patients with axSpA, who have approximately 80% higher odds of developing heart failure and depression compared with the general population. The presence of comorbidities in axSpA has been linked to increased disease activity, greater functional impairment, reduced quality of life, lower work productivity and higher mortality (Zhao et al., 2020). The most frequent comorbidities in PsA include metabolic syndrome, cardiovascular disease, and inflammatory bowel disease (Hernández-Rodríguez et al., 2024). One study reported that individuals with PsA had an average of 2.0 ± 1.3 comorbid conditions, but the specific type of comorbidity appears to exert a greater influence than the overall number of comorbid conditions (Bavière et al., 2020).

1.1.2 Overview of psychosomatic

Since ancient times, medical illness has been understood as the result of the interplay between the body, the psyche, and even the spirit. Over centuries and even millennia, this perspective has evolved from cultural and spiritual interpretations to a scientific, evidence-based approach in psychosomatic medicine. Historically, ancient medical systems such as the Mesopotamian, Tibetan, and Indian traditions emphasized psychosomatic perspectives in all their aspects. These systems, developed thousands of years ago, highlighted the importance of focusing first on the person and only subsequently on their disease, with particular attention to the emotional states accompanying somatic illnesses (Rees, 1983; Kakar, 1991; Burang, 1974). Similarly, the principal sources of European culture, Greek and Roman traditions, also integrated psychosomatic concepts. Hippocrates advocated for a holistic view, teaching that knowledge of the whole was essential for curing the body, while Galen proposed a psychosomatic system of classification (Rees, 1983). Furthermore, within Judeo-Christian tradition, health was understood as a harmonious state of spirit, psyche, and body (e.g. 1 Thessalonians 5:23, New Revised Standard Version, 1989/2021). Despite this, a materialistic orientation persisted in Greek and Roman medicine, where aspects of mental life, “ideas” and “nous” as described by Plato and Aristotle, were increasingly excluded from medical thought (Alexander, 1962).

During the Enlightenment, philosophical perspectives deepened this separation. Descartes explicitly divided body and soul, while Spinoza, in contrast, proposed the fundamental unity of body and mind. Physicians such as Thomas Sydenham stressed close clinical observation and introduced psychogenic explanations for disease. Johann Christian Heinroth later defined the concept of personality as the indivisible unity of body and psyche, and, notably, he first introduced the term “psychosomatic” in 1818. In the early 20th century, Freud’s psychoanalytic methods enabled systematic study of psychological causal sequences in illness (Alexander, 1962).

A modern revival of interest in psychosomatic medicine emerged in the 1930s and 1940s, driven by pioneers who raised hopes for scientific advances in understanding and treating psychosomatic conditions. However, the dominance of psychoanalytic theory and the methodological limitations of early studies slowed the development of a robust scientific foundation (Rees, 1983). Franz Alexander, often considered a pioneer in the field, identified characteristic emotional patterns consistently associated with particular organic diseases, such as duodenal ulcers, ulcerative colitis, asthma, hypertension, rheumatoid arthritis, thyrotoxicosis, and neurodermatitis. He proposed that patients with chronic organic disease possess dual vulnerabilities: specific emotional predispositions to interpersonal stress and corresponding organic susceptibilities (Alexander, 1962).

By the 1960s, Alexander emphasized the necessity of integrating physiological, psychological and sociological perspectives into a comprehensive understanding of human beings. He warned that neglecting any of these domains would lead to distorted theories and unsatisfactory therapeutic approaches (Alexander, 1962). Building on these foundations, George Engel (1977) formulated the biopsychosocial model, which provided a framework for incorporating social, psychological and behavioral dimensions into medical research, education, and practice. This model requires collaboration between medical specialists and mental health professionals, grounded in mutual respect for their respective contributions (Alexander, 1962).

Although the biopsychosocial model remains influential and continues to gain prominence (Zipfel et al., 2023), its full integration into clinical practice has not yet been achieved globally. The need persists for genuinely comprehensive, interdisciplinary care within medical departments (Adler, 2009). Against this background, the present thesis focuses on observational analysis and subsequent trials within the field of rheumatology. Its aim is to approach this primarily somatic discipline (rheumatology) not only from a biological perspective but also through psychosocial dimensions, in pursuit of more holistic patient care.

1.1.3 Psychological characteristics of rheumatic diseases

Considering rheumatic disease solely as a somatic condition that emphasizes localized physical symptoms risks neglecting the broader significance of its psychosomatic dimensions and its characterization as a psycho-neuro-endocrine disease (Halliday, 1941). Nearly a century ago, Halliday (1941) emphasized that rheumatological practice must "always include a psychological approach as a supplement to routine medical examination." Franz Alexander later identified arthritis as one of the major psychosomatic disorders (Alexander, 1950). Drawing on a psychodynamic framework, Alexander and his colleagues proposed that suppressed hostility and aggression, often originating in childhood, are typically released through competitive or physical activity. When these natural outlets for emotional expression are disrupted, the resulting sustained muscular tension associated with inhibited aggression may contribute to the onset of arthritis (Johnson et al., 1947).

The psycho-neuro-endocrine system provides a critical foundation for exploring the etiology of rheumatism. Understanding this system requires consideration of the patient's interpersonal relationships, occupational stressors, awareness of the illness, and external life events (Halliday, 1941). The mechanisms linking rheumatic disease and mental health are likely to be bidirectional and complex; rheumatic conditions influence and are influenced by psychological functioning. Multiple pathways contribute to the association between rheumatoid arthritis and mental health comorbidities, including cognitive, behavioral and affective processes, as well as inflammatory mechanisms and fatigue (Sturgeon et al., 2016).

Patient-reported outcomes (PROs) are health outcomes directly reported by patients without clinician interpretation and they offer a comprehensive view of disease status, particularly in assessing the impact of illness on daily life. As patients are generally regarded as the most accurate reporters of their own symptoms, PROs serve as essential tools for capturing all aspects of disease that are meaningful to patients. They are especially valuable in heterogeneous conditions such as rheumatic diseases (van Tuyl and Boers, 2015; Revicki et al., 2014).

PROs are widely utilized across rheumatic conditions to assess pain, physical functioning, and more general constructs such as patient global assessment of disease activity and health-related quality of life. Additionally, depression, anxiety, fatigue, coping, and pain are included in the core sets of outcomes for rheumatic diseases (van Tuyl and Boers, 2015).

Depression is highly prevalent in RA, affecting approximately 34.2–38.8% of patients and is associated with poorer disease outcomes. Meta-analyses have reported a prevalence of major depressive disorder of 16.8% among individuals with RA (Matcham et al., 2013). The risk of depression is also significantly higher among patients with psoriatic arthritis and spondyloarthritis compared with the general population. Furthermore, in PsA, depression has been linked to reduced therapeutic response and higher discontinuation rates of biologic agents (Patt et al., 2024). The pooled prevalence of depression in PsA ranges from 11.9-20%, while anxiety affects 19-33% of patients (Hernández-Rodríguez et al., 2024). Notably, depression in PsA has been proposed to function as an inflammatory comorbidity (Patt et al., 2024). In axSpA, reported depression prevalence range from 11% to 64%, depending on the assessment and the thresholds applied. Patients with comorbid depression exhibit significantly higher disease activity and greater functional impairment (Zhao et al., 2018).

Individuals with RA who also have comorbid major depression exhibit higher levels of anxiety compared with patients with RA without depression or in age-matched healthy controls (Sturgeon et al., 2016). The presence of depression and/or anxiety, regardless of assessment method, is associated with a lower likelihood of achieving sustained minimal disease activity in PsA (Wong et al., 2022).

In rheumatic diseases, anxiety and depression are the main contributors to fatigue (Iaquinta et al., 2022). There is currently no universally accepted definition of RA-related fatigue. The absence of a consensus definition and the diversity of measurement instruments used have hindered accurate prevalence estimation, with rates of clinically significant fatigue reported between 42% and over 80% (Cramp, 2019). One study found that fatigue prevalence reached 61% among patients with RA, PsA, and axial spondyloarthritis (Pilgaard et al., 2019). Generally, fatigue has a negative impact on daily functioning across chronic conditions (Nadinda et al., 2024). The mechanisms underlying fatigue in inflammatory rheumatic diseases may change over time and vary substantially among individuals (Davies et al., 2021).

Evidence for a consistent relationship between systemic inflammation and fatigue in RA is lacking; one possible explanation is that the influence of inflammation varies across disease stages (Davies et al., 2021). However, other studies have identified a positive correlation between disease activity and fatigue (Shen et al., 2021). Pain, mental health, disability, and sleep disturbances are consistent predictors of fatigue outcomes in RA (Druce and Basu, 2019).

Pain and fatigue share underlying mechanisms that contribute to their chronic persistence and frequently co-occur in various medical conditions (Nadinda et al., 2024). Moreover, pain has been identified as a primary determinant of fatigue and plays a critical role in shaping quality of life in RA (Shen et al., 2021). Patients with RA report substantially reduced *health-related quality of life* (HRQoL) compared with both the general population and individuals with other chronic illnesses, as evidenced by data from UK and US cohorts (Matcham et al., 2014). Across all rheumatic diseases, patients consistently demonstrate poorer HRQoL in all dimensions compared with the general population. Consequently, HRQoL should be considered a fundamental measure in rheumatology clinics to assess patient status and treatment outcomes across age groups, thereby enhancing understanding of the disease’s impact and the effectiveness of therapeutic interventions (Villalobos-Sánchez et al., 2024).

Coping is infrequently examined as an outcome variable in studies of rheumatic diseases (Savelkoul et al., 2003). Nonetheless, patients develop specific coping strategies to manage health-related stressors, which differ from those used in everyday life problems. These coping strategies vary across rheumatic diagnoses and are closely associated with HRQoL. Negative coping strategies, such as emotional, avoidant or evasive approaches, are linked to poorer physical and mental health outcomes (Peláez-Ballestas et al., 2015).

1.1.4 Psychological adaptation to rheumatic disease as a chronic condition

Following the medical diagnosis of a chronic illness, patients are confronted with unfamiliar circumstances that challenge their habitual coping mechanisms. Consequently, they must develop new strategies to adapt to their altered condition (de Ridder et al., 2008). The degree of psychological distress and the process of adaptation to chronic disease are influenced by both the nature of the stressors encountered and the personal and social resources available to the patient (Lazarus & Folkman, 1984). Immediately after diagnosis, broad forms of support, both emotional and instrumental, appear to play a crucial role in facilitating psychological adjustment. Over time, however, personal coping resources tend to assume greater importance in managing the ongoing demands of the illness (Evers et al., 1997).

The course of chronic diseases is shaped not only by biomedical or genetic determinants but also by the individual's psychological response to the illness. The personal meaning ascribed to the disease may be both conscious and unconscious, functioning as a "cognitive nucleus" that influences emotional and motivational reactions (Schüssler, 1992). During the formation of an illness representation, appraisal processes allow the individual to assess the potential significance of deviations from normal health. Such representations are both abstract and concrete and play a key role in directing coping efforts (Leventhal & Nerenz, 1983). Chronic disease introduces persistent stressors that elicit cognitive, emotional and behavioral responses, which in turn affect overall health outcomes. These responses are moderated by individual characteristics, as well as social and environmental factors (Dekker & de Groot, 2018). The term *psychological adjustment* refers to the dynamic psychological processes that occur in response to chronic disease and its treatment. Adjustment encompasses ongoing processes rather than fixed outcomes, responses that may promote well-being or, alternatively, contribute to psychological and physical decline (Dekker & de Groot, 2018). This adjustment process typically unfolds across several stages. The first stage, *representation*, involves the reception and interpretation of information to define the perceived health threat. The second stage, *coping or action planning*, concerns the selection, sequencing and implementation of possible responses. The third stage, *appraisal or monitoring*, entails evaluating coping effectiveness and modifying strategies as needed (Leventhal & Nerenz, 1983).

As illness extends its impact into various aspects of life, the perceived timeline often shifts from episodic to chronic, leading the individual to see the condition as increasingly permanent. When the disease becomes central to one's identity, when every activity is filtered through the lens of illness, the sense of being "chronically ill" can reinforce perceptions of incurability and hopelessness. Common symptoms such as fatigue, weakness or tiredness then serve to confirm this self-perception (Leventhal & Nerenz, 1983). Conversely, patients who appraise their illness as a challenge, a source of personal growth or something under internal control tend to engage in more adaptive coping processes such as cognitive restructuring. In contrast, perceiving illness as punishment, an enemy or a form of relief is associated with maladaptive, emotionally driven coping patterns (Schüssler, 1992). When coping attempts repeatedly fail, individuals may experience a sense of loss of control, diminished self-efficacy and the perception that the illness has overwhelmed or dominated the self (Leventhal & Nerenz, 1983).

Coping strategies encompass cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the person's resources, such as those associated with chronic disease (Folkman & Lazarus, 1988; Stanisławski, 2019). Individuals face two tasks: they need to solve the problem and regulate their emotions. It corresponds to two dimensions: problem coping, describing whether the person solves the problem or avoids the problem, and emotion coping, representing how the individual regulates their emotions under stress. Moreover, problem avoidance consists of the avoidance of thinking about the problem, reducing efforts to solve it, postponing the task, or giving up attempts to attain the goal (Stanisławski, 2019). Active and problem-focused coping strategies are associated with adaptive functioning involving active cognitive and behavioral efforts to deal with a problem, the use of cognitive transformations through reinterpretation that enable the elicitation of positive emotions and calming down. Using active coping might reflect a positive appraisal of the person's abilities to control problematic situations. Passive, avoidant and emotion-focused ways of coping are related to maladaptive functioning, including self-criticism when dealing with a problem, rumination on the negative aspects of a stressful situation and negative emotions, such as feeling of pressure or anger (Evers et al., 1997; Stanisławski, 2019; Sempértegui et al., 2017).

Rheumatic diseases are chronic conditions characterized by a progressive and unpredictable trajectory, often alternating between periods of activity and remission (Fournier et al., 2002). Upon diagnosis, patients typically experience significant disruption in their daily routines, necessitating a reorganization of multiple life domains (Evers et al., 1997). The disease itself functions as a psychological stressor; as symptoms intensify, individuals are more likely to resort to denial as a coping strategy, which can profoundly influence their mood and their physical and psychosocial functioning (Wróbel et al., 2023; Sturgeon et al., 2016). Nonetheless, moderate levels of denial may serve adaptive purposes. The combination of illness acceptance and mild denial can foster cognitive and emotional coping skills contributing greater emotional stability (Schüssler, 1992). In contrast, patients who rely heavily on emotion-focused coping tend to experience increased distress, whereas adaptive strategies, such as adjusting rest, exercise, and adherence to medication in response to disease fluctuations, may help to limit pain, joint damage and functional impairment (Fournier et al., 2002). Psychological adaptation may be indicated by decreased or stable levels of distress, even as the disease progresses (Evers et al., 1997). Lazarus and Folkman (1984) proposed that the effectiveness of coping cannot be assessed in isolation from the situational context in which it occurs. Coping with stress is a dynamic and evolving process, particularly for individuals living with chronic illness, often extending over many years. Various coping mechanisms have been identified, including confrontation, distancing, self-control, seeking social support, acceptance of responsibility, avoidance, problem-focused planning, and positive reappraisal (Wróbel et al., 2023). When the desired outcome is beyond one’s control, emotion-focused strategies that reduce emotional distress are more appropriate than problem-focused approaches (Folkman & Lazarus, 1988). Emotional coping is more common among individuals who struggle to accept their illness or view it as uncontrollable (Schüssler, 1992).

Coping has been conceptualized as a cognitive process aimed at reducing anxiety and other negative emotional states (Folkman & Lazarus, 1988). Regarding the relationship between coping and affect in rheumatic diseases, emotional well-being plays a crucial role in patients' adaptation to life with rheumatoid arthritis (Sturgeon et al., 2016). Depression and fatigue can undermine coping capacity, whereas active coping is essential for addressing most challenges effectively (Leventhal & Nerenz, 1983). In a review of RA, coping strategies were found to exert a stronger influence on mood than the reverse; avoidant and disengagement strategies predicted negative mood, increased disability and fatigue, underscoring their detrimental physical consequences (Ramjeet et al., 2008). Escape-avoidance coping has been linked to symptoms of depression and anxiety (Folkman & Lazarus, 1988), while passive coping strategies consistently correlate with lower functional status and greater depressive symptoms (Sempértegui et al., 2017). Furthermore, depression and anxiety are positively associated with emotion-oriented coping but negatively with task-oriented coping (Stanisławski, 2019).

Fatigue represents one of the most challenging symptoms for RD patients to manage (Katz, 1998). Conversely, fatigue can exacerbate stress and hinder coping (Beckers et al., 2023). It is often viewed as an outcome of coping failure under conditions of limited control (Hockey, 2013). Over time, a decline in coping resources may intensify fatigue (Davies et al., 2021). Sustained high effort or strain without adequate recovery can lead to diminished performance and an increased sense of exhaustion (Hockey, 2013).

1.1.5 The impact of rheumatic diseases on health-related quality of life

Quality of life (QoL) is a broad and multifaceted concept that has been used in diverse ways, leading to the development of the more specific term *health-related quality of life* (HRQoL) to emphasize aspects directly influenced by health and disease (Carr et al., 2001; Ferrans et al., 2005). HRQoL is a multidimensional construct encompassing subjective evaluations of symptoms, side effects and functional capacity across physical, psychological and social domains, as well as overall perceptions of life satisfaction and well-being (Revicki et al., 2014; Karimi & Brazier, 2016). This framework was designed to narrow the broader QoL concept to focus specifically on the effects of illness, treatment and health status on everyday life (Ferrans et al., 2005). Central to HRQoL is the patient's subjective perspective, obtained through direct self-report and measured across multiple dimensions (Revicki et al., 2014). Conceptually, HRQoL can be viewed as reflecting the disparity between individuals' expectations of health and their actual experiences (Carr et al., 2001).

Models of QoL illustrate that biological functioning (representing the functioning of organs) affects perceived symptom status, which in turn influences physical, psychological, and social well-being. These, collectively, shape one's general health perception and ultimately overall quality of life or subjective well-being (Ferrans et al., 2005). Subjective well-being itself comprises multiple elements, including positive and negative affect, general life satisfaction, and satisfaction across specific life domains. Conceptualizing health as the outcome of an adaptive process can thus be effectively achieved through the HRQoL framework (Dekker & de Groot, 2018).

Patient-reported outcomes used to assess QoL in rheumatic diseases can be divided into *generic* and *disease-specific* instruments. Examples include the Short Form-36 Health Survey (SF-36) as a generic measure, and the Ankylosing Spondylitis Quality of Life (ASQoL) as a disease-specific tool (Kwan et al., 2017). The SF-36, which has been extensively validated and translated across cultures, is among the most frequently used HRQoL measures in rheumatology. It has demonstrated sensitivity to treatment effects and effectively captures the impact of rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis on quality of life (Strand et al., 2009). Notably, as a self-reported instrument, the SF-36 may reveal discrepancies between patient and family perceptions of health. One study found that family members of individuals with rheumatic disease often underestimated patients' HRQoL, highlighting possible communication barriers and gaps in social support (Ramos-Remus et al., 2014).

Patients with inflammatory rheumatic diseases, including RA, PsA, and axSpA, show significantly reduced scores across all eight SF-36 domains and in both physical (PCS) and mental (MCS) component summaries compared with healthy controls. Physical health domains are generally more impaired than mental or social domains, with Physical functioning, Role limitations due to physical health and Bodily pain most severely affected. Among these conditions, RA patients exhibit the greatest overall impairment (Salaffi et al., 2009). A comparative analysis similarly reported that PCS scores were more reduced than MCS scores in all three diseases, with MCS values approximating population norms. Across conditions, women reported lower PCS and MCS scores than men, indicating sex-related differences in perceived quality of life (Landgren et al., 2023).

Systematic review consistently demonstrate that RA substantially diminishes HRQoL, underscoring the need for comprehensive management strategies (Matcham et al., 2014). Compared with the general population, RA patients report persistently lower physical and mental health scores, even after one year of follow-up (Gerhold et al., 2015). Some evidence suggests that physical HRQoL is particularly affected, while mental health scores are relatively preserved (Greenfield et al., 2017). A meta-analysis of SF-36 findings confirmed that RA patients score lowest in the *Role limitation due to physical health* domain, reflecting profound limitations in daily activities, whereas mental health domains are less affected, though still below normative levels. Differences between randomized controlled trials (RCTs) and observational studies were noted: RCTs generally showed reductions in both physical and mental components, whereas observational data indicated primarily physical deficits (Kingsley et al., 2011).

In axSpA, systematic review also reveals significant impairment across all SF-36 dimensions relative to the general population, with the physical component summary consistently lower than the mental component (Yang et al., 2016). Among physical domains, *Role limitation due to physical health* showed the lowest scores, while within mental domains, *Vitality* was most reduced. Additional studies using instruments such as the World Health Organization Quality of Life (WHOQOL) have confirmed that spondyloarthritis adversely affects all dimensions of QoL (Kwan et al., 2017). Consistent findings show that patients with radiographic axSpA have markedly lower scores across all SF-36 domains compared to controls (Law et al., 2018). Disease progression and spinal fusion are likely contributors to these impairments by limiting mobility and physical functioning (Bittar & Deodhar, 2025).

In PsA, both physical and mental aspects of HRQoL are reduced, reflecting the combined burden of joint and skin manifestations. The psychological impact of psoriasis contributes substantially to the deterioration in mental health among PsA patients (Gudu & Gossec, 2018).

HRQoL in rheumatic diseases is closely intertwined with other symptoms and clinical outcomes. In RA, physical QoL is primarily determined by fatigue, pain, physical functioning, and disease duration, while mental QoL is shaped by psychosocial variables such as anxiety, depression, and social functioning (Kojima et al., 2009). Disability has been significantly associated with both physical and mental HRQoL scores, whereas disease activity alone does not necessarily predict HRQoL (Kwan et al., 2014). Another study reported that disease activity and reduced work productivity have emerged as key determinants of HRQoL in both rheumatoid arthritis and spondyloarthritis (Carvalho et al., 2022).

In PsA, depressive symptoms predict poorer HRQoL even after accounting for disease severity (Howells et al., 2018). Similarly, in RA, both depression and anxiety are strongly correlated with diminished HRQoL (Nas et al., 2011; Sturgeon et al., 2016). Patients with comorbid anxiety report substantially worse physical and mental QoL, alongside higher disease activity at baseline and during follow-up (Machin et al., 2020). In PsA, anxiety primarily affects mental QoL rather than physical domains, emphasizing the psychological aspect of the disease (Bavière et al., 2020).

1.1.6 Sex and gender differences in rheumatic diseases

A recent review on sex and gender as modifiers of health and disease highlights that successful clinical care and translational research depend on clinicians' and scientists' awareness that diseases differ between women and men in epidemiology, pathophysiology, clinical presentation, psychological impact, progression and treatment response (Mauvais-Jarvis et al., 2020). While *sex* refers to biological attributes linked to being male or female, *gender* encompasses sociocultural norms that define roles, relationships and expectations. The ways in which gender influences health unfold within complex social contexts where these differences take shape

(Connell et al., 2012; Tarannum et al., 2022). Among the many determinants of illness, sex remains a key factor influencing disease incidence (Ferrans et al., 2005).

Conventional understandings of gender tend to emphasize difference, simplifying and distorting its inherent complexity (Hare-Mustin & Marecek, 1988). In contrast, the social constructionist perspective views gender as a dynamic process that both shapes and is shaped by systems of culture, power and inequality (Shields & Dicicco, 2011). Classical psychodynamic and feminist psychodynamic theories often overstate distinctions between men and women, portraying them as fixed, universal and enduring. Similarly, Parsons's sex role theory reinforces rigid, binary notions of gender by defining men as instrumental and task-oriented versus women as expressive and relationship-oriented. Conversely, systemic and structural family theories tend to minimize or overlook gender differences (Hare-Mustin & Marecek, 1988). Relational theory offers a more integrative view, conceptualizing gender as an embodied social structure in which complex, multidimensional relationships shape diverse health outcomes (Connell et al., 2012).

The onset, clinical phenotype, including comorbidities and disease course in rheumatology differ between sexes (Krasselt and Baerwald, 2019). Sex differences are well recognized in axial spondyloarthritis (Stovall et al., 2022). Male and female patients with psoriatic arthritis display both overlapping and distinct disease features. Although the causes remain unclear, both biological sex-related factors likely contribute to these differences (Nas et al., 2021). Consequently, a patient's sex plays an increasingly important role in individualized therapy decisions and comorbidity screening (Krasselt and Baerwald, 2019).

Radiographic axial spondyloarthritis is more prevalent in men than in women, with an estimated male-to-female ratio of approximately 3:1. However, when magnetic resonance imaging is used to detect early, non-radiographic forms of the disease, prevalence appears comparable between sexes (Bittar and Deodhar, 2025). Evidence also suggests that psoriatic arthritis tends to develop later in women, although sex-related differences in PsA risk and age at onset remain insufficiently explored (Tarannum et al., 2022; Patt et al., 2024).

In rheumatoid arthritis, disease presentation differs notably between sexes. Men are more likely to exhibit erosive disease and extra-articular manifestations, whereas women typically show higher measured disease activity despite similar radiographic joint damage (Krasselt and Baerwald, 2019). A comparable pattern is observed in PsA: although psoriasis is more common in men, and men more frequently develop axial involvement and radiographic joint damage, women experience greater overall disease burden, reporting higher disease activity and worse functional outcomes (Lubrano et al., 2023; Eder et al., 2013; Nas et al., 2021; Patt et al., 2024).

In radiographic axSpA, men tend to develop more severe radiographic damage over time (Nam et al., 2021; Tournadre et al., 2013; Webers et al., 2016). They also exhibit higher C-reactive protein (CRP) levels, more frequent positivity for human leukocyte antigen B27 (HLA-B27), and greater restriction of spinal mobility, whereas women typically present with higher erythrocyte sedimentation rates (ESR) (Cunha et al., 2022). Enthesitis and tender or swollen joint counts are both more frequent and more severe in women (Stovall et al., 2022; Wright et al., 2020; Mease et al., 2021). Several studies have reported higher Bath Ankylosing Spondylitis Functional Index (BASFI) scores in women, indicating greater functional impairment, although others found no significant sex-related differences (Tournadre et al., 2013; Garrido-Cumbrera et al., 2021). Sex-related differences in disease activity in axSpA appear to vary depending on the assessment tool. Women consistently report higher Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores, reflecting greater perceived disease activity, whereas Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein (ASDAS-CRP) values show little or no sex variation. This discrepancy likely arises because ASDAS-CRP incorporates an objective inflammatory marker (CRP) typically higher in men, while BASDAI relies solely on subjective measures. The absence of fatigue and enthesitis components in ASDAS-CRP calculations (as it is in BASDAI) further explains the lack of observed sex differences. Consequently, ASDAS-CRP may serve as a more balanced indicator of disease activity in both men and women with spondyloarthritis (Tournadre et al., 2013; Nam et al., 2021; Stovall et al., 2022; Cunha et al., 2022; Wright et al., 2020; Mease et al., 2021; Garrido-Cumbrera et al., 2021).

Women experience longer diagnostic delays in axSpA compared with men (Wright et al., 2020; Stovall et al., 2022; Cunha et al., 2022). Persistent perceptions of axSpA as a predominantly male disease may bias both clinical recognition and management. Female patients often undergo more consultations and a more complex diagnostic journey, even though their disease duration at diagnosis tends to be shorter (Garrido-Cumbrera et al., 2021).

Sex also influences treatment efficacy and adverse effects in RA, PsA, and axSpA (Stovall et al., 2022; Tarannum et al., 2022; Coates et al., 2023). In RA, men respond faster and more effectively to anti-TNF agents and are more likely to achieve drug-free remission (Krasselt and Baerwald, 2019). In PsA, men are three times more likely to achieve good or moderate TNF inhibitor responses within six months (Tarannum et al., 2022). In contrast, women with axSpA generally demonstrate reduced long-term response to anti-TNF therapy (Stovall et al., 2022) and receive pharmacologic and alternative treatments such as nonsteroidal anti-inflammatory drugs (NSAIDs) and biologics more frequently than men (Garrido-Cumbrera et al., 2021). Drug survival for TNF inhibitors is also poorer in women (Wright et al., 2020).

Women with RA have a fourfold higher risk of work disability compared to men. Lower education level, longer disease duration and poorer mental health are also independently associated with work disability (Wallenius et al., 2009). Women with axial PsA report worse quality of life, greater fatigue and higher levels of depression and anxiety (Nas et al., 2021). Similarly, women with axSpA experience more severe symptoms, including pain, fatigue, and disability, along with greater work and activity impairment and are less likely to work full-time (Mease et al., 2021). They also report higher rates of affective disorders and greater psychological distress (Garrido-Cumbrera et al., 2021).

1.1.7 Non-pharmacological interventions on fatigue and other disease-related outcomes

Fatigue is a prevalent and debilitating symptom in rheumatic diseases, distinct from ordinary tiredness by its severity, often disproportionate to exertion and persistent

(Davies et al., 2021; Matcham et al., 2015; Hewlett et al., 2005). Despite extensive research, no consensus has been reached regarding a precise definition of fatigue in these conditions (Beckers et al., 2023; Davies et al., 2021). Patients commonly describe fatigue as frequent, overwhelming, intrusive and draining both physical and mental energy. They report it as a multidimensional experience that pervades all areas of life, limiting social engagement and leading to increasing isolation. Although many individuals attempt self-management strategies, their success is often limited (Hewlett et al., 2005; Seifert & Baerwald, 2019). Several subtypes of fatigue have been proposed, including physical, emotional, mental and motivational dimensions (Hewlett et al., 2005; Davies et al., 2021). Thus, fatigue should not be viewed as a single, isolated symptom but rather as a multifaceted problem that broadly affects functioning (Esbensen et al., 2020). While patients often attribute their fatigue to inflammation, its underlying pathogenesis remains unclear (Hewlett et al., 2005; Davies et al., 2021). The mechanisms involved are likely multifactorial, encompassing biological, physiological, psychosocial and behavioural factors (Davies et al., 2021). Because fatigue is inherently subjective, its accurate and reliable measurement remains challenging and depends largely on self-report questionnaires. Moreover, without data on pre-morbid fatigue levels, it is difficult to determine whether fatigue worsens following the onset of inflammatory rheumatic disease (Davies et al., 2021).

Ongoing debate surrounds the mechanisms underlying fatigue in rheumatoid arthritis (Sturgeon et al., 2016). A recent scoping review of rheumatic diseases identified consistent associations between increased fatigue and higher disease activity, pain, depression and limitations in daily and social functioning (Beckers et al., 2023). Other studies suggest that fatigue in RA is largely influenced by factors beyond the direct effects of inflammation, such as obesity, physical inactivity or disability, poor mental health, sleep disturbance, and mood disorders, which together explain much of the variability in fatigue severity (Katz, 2017; Geenen & Dures, 2019). These interrelated factors form a dynamic biopsychosocial model in which biological, psychological and social processes interact reciprocally. Given the limited understanding of prognostic factors for poor fatigue outcomes and the generally inadequate management of fatigue, research should focus on mapping individual-specific networks of biopsychosocial contributors and developing tailored interventions that address the most relevant influencing factors for each person (Geenen & Dures, 2019; Druce & Basu, 2019).

Advances in disease assessment, therapeutic strategies, and the introduction of novel treatments have significantly improved prognoses for individuals with rheumatic diseases (Smolen et al., 2018). Recent guidelines from the American College of Rheumatology (ACR) (Fraenkel et al., 2021) and the European Alliance of Associations for Rheumatology (EULAR) (Smolen et al., 2023) emphasize the treat-to-target strategy, which focuses on tight control of disease activity, regular monitoring, and timely escalation of therapy when remission is not achieved (Di Matteo et al., 2023). Despite these therapeutic advances and the associated improvements in physical functioning and quality of life, current management often neglects the biopsychosocial dimensions of illness, focusing predominantly on biological factors (Gullick et al., 2019).

Pharmacological interventions, such as biologic disease-modifying antirheumatic drugs, have shown small to moderate beneficial effects on fatigue compared with placebo or usual care (Beckers et al., 2023). A recent systematic review also confirmed that biologic therapies, which aim to reduce disease activity, are generally effective and safe for managing fatigue in rheumatic diseases (Dures et al., 2024). In contrast, non-pharmacological approaches primarily focus on structured, time-limited physical activity and psychoeducational programs, which tend to be more therapeutically intensive than the provision of informational materials alone (Dures et al., 2024). Strong evidence supports the effectiveness of exercise and psychoeducational interventions in reducing fatigue, underscoring the importance of incorporating these strategies into routine clinical care (Santos et al., 2023). An umbrella review further indicated that physical activity and psychosocial interventions are most effective in improving functional ability and reducing fatigue. Exercise show additional benefits for overall disease impact and quality of life (Santos et al., 2019). Still, previous protocols for psychological interventions targeting fatigue in arthritis have typically outlined only the general framework of the intervention, offering limited or no detailed guidance on its practical implementation (e.g., Duarte et al., 2023; Hewlett et al., 2011).

Several studies have demonstrated that rheumatology health professionals can be trained to deliver brief, low-cost and effective cognitive-behavioural interventions that reduce both short- and long-term fatigue in inflammatory arthritis.

One study reported improvement in coping, self-efficacy and disability (Dures et al., 2022), whereas another found no significant changes in disease activity, depression, or quality of life (Hewlett et al., 2019a). Nevertheless, multidisciplinary rheumatology teams trained in delivering telephone-based cognitive-behavioral approaches and personalized exercise programs have successfully reduced the severity and impact of fatigue across multiple inflammatory rheumatic diseases (Bachmair et al., 2022). Similarly, in chronic fatigue syndrome, individual cognitive-behavioural therapy and graded exercise therapy, when combined with specialist medical care, are more effective than standard care alone (White et al., 2011). The evidence collectively suggests that effective fatigue management requires a flexible, individualized and holistic approach in rheumatic diseases (Dures et al., 2024).

1.2 AIMS

Building on the previously discussed importance of psychological factors in rheumatic diseases, this thesis seeks to address existing gaps in the literature concerning several unresolved questions. Specifically, this thesis aims to elucidate the interaction between clinical characteristics and psychological dimensions in individuals with rheumatic diseases by assessing the prevalence of psychological symptoms and related outcomes, including depression, anxiety, fatigue, coping strategies, and quality of life, and by identifying the underlying clinical factors associated with these outcomes. Based on the mechanisms identified, the project further aims to develop effective interventions to alleviate disease symptoms and improve overall outcomes.

Aim 1: Investigation of coping strategies

Aim 1.1 To explore whether specific coping strategies (problem-focused, emotion-focused, and dysfunctional coping) are associated with fatigue in patients with rheumatological diseases, and to determine whether this relationship is mediated by depression and anxiety.

Aim 1.2 To examine the potential moderating effects of variables such as diagnosis, disease activity, disease duration, and sex on these relationships.

Aim 2: Comparison and exploration of health-related quality of life

Aim 2.1 To compare the degree of impairment in health-related quality of life among patients with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis.

Aim 2.2 To investigate whether specific sociodemographic, psychological and clinical variables, including rheumatological treatments, depression and anxiety, are associated with impairment in the physical and mental domains of quality of life within each diagnostic group.

Aim 2.3 To examine whether fatigue mediates the relationship between disease activity and various dimensions of physical quality of life (including physical functioning, role-physical, bodily pain and general health) in patients with rheumatological conditions.

Aim 2.4 To assess whether sex and rheumatological treatment moderate these relationships and to determine whether comorbidity should be included as a covariate in the proposed models.

Aim 3: Exploration of sex differences in clinical and psychological features

Aim 3.1 To investigate sex differences in sociodemographic, psychological and clinical characteristics among patients with spondyloarthritis or psoriatic arthritis.

Aim 3.2 To explore how sociodemographic, psychological, and clinical factors influence both physical and mental quality of life in male and female patients.

Aim 4: Conceptualize a protocol for non-pharmacological interventions targeting fatigue and related outcomes

Aim 4.1 To assess and compare the effectiveness of cognitive-behavioural therapy plus usual care, a personalized exercise program plus usual care, and usual care alone in reducing fatigue.

Aim 4.2 Secondary objectives include evaluating the effectiveness of these non-pharmacological interventions in reducing disease activity, depression, anxiety, and pain, as well as in improving physical functioning, overall quality of life, and sleep quality among participants.

1.3 METHODOLOGICAL APPROACHES

The choice of study design should be guided by the specific research question and the overall purpose of the study (Mann, 2003). This section outlines the principal methodological approaches employed in the projects presented in this thesis, focusing on cross-sectional and randomized controlled study designs and mediation-moderation analysis.

In psychological research, the primary objectives are to assess the prevalence of specific constructs and to investigate causal relationships among variables (Igartua & Hayes, 2021). The **cross-sectional study design** is an observational approach frequently used to estimate the prevalence of health outcomes, identify determinants of health and describe population characteristics (Wang and Cheng, 2020). In such studies, all relevant variables, including patient characteristics, treatments and outcomes, are assessed at a single point in time (Mann, 2003). Cross-sectional studies are generally cost-effective, relatively easy to implement and capable of examining multiple outcomes simultaneously, often through the use of questionnaires (Wang and Cheng, 2020; Mann, 2003). However, because both exposure and outcome variables are measured concurrently, the ability to infer causal relationships is limited and observed associations may not reflect true cause-effect mechanisms (Mann, 2003). Despite these limitations, cross-sectional designs are valuable for generating novel insights and preliminary evidence and formulating hypotheses that can be further investigated through more advanced study designs, such as randomized controlled trials (Wang and Cheng, 2020; Stel et al., 2007; Sempértegui et al., 2017).

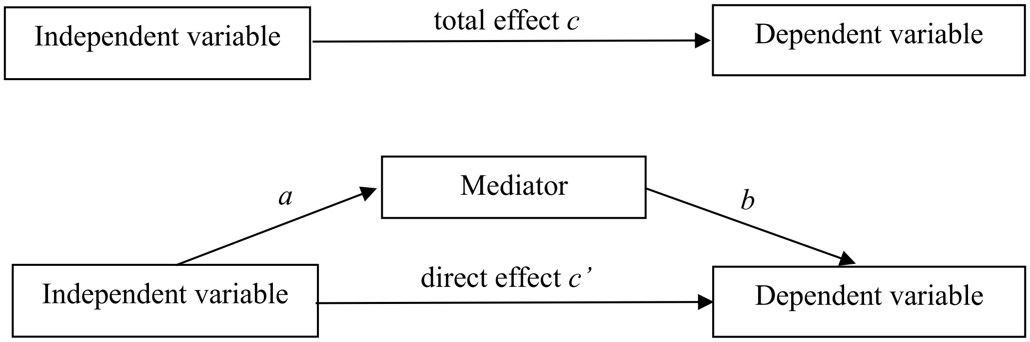
The **randomized controlled trial (RCT)** represents a specific form of cohort study in which participants are randomly allocated to an experimental group (exposed) or a control group (unexposed). For therapeutic research questions, the RCT is widely regarded as the most rigorous design, provided it is ethically acceptable, logistically feasible, and adequately powered (Stel et al., 2007). Randomization minimizes selection bias, while blinding enhances objectivity and reduces the influence of placebo effects (Simon, 2001; Stel et al., 2007). Nevertheless, RCTs may face limitations related to their artificial nature, restricted patient populations and practical difficulties in maintaining randomization or blinding - factors that can constrain the external validity and generalizability of findings (Simon, 2001). When feasible in terms of ethical considerations, participant availability, cost and follow-up, the RCT remains the most robust and credible approach for evaluating therapeutic interventions (Simon, 2001; Stel et al., 2007).

Beyond identifying correlations, further analyses seek to uncover the mechanisms driving these relationships by examining mediators and moderators that influence or modify the main effect. Such exploration should not rely solely on statistical methods but be grounded in strong theoretical frameworks and interpreted within a meaningful practical context (Igartua & Hayes, 2021). **Mediation analysis** explains how an independent variable (IV) influences a dependent variable (DV) through one or more intervening variables, known as mediators (M). This analysis assumes a theoretically or procedurally justified causal order among IV, M, and DV (Preacher & Hayes, 2008). A prerequisite for testing mediation is a significant association between the IV and DV (Holmbeck et al., 1997). To establish mediation, there must be significant relationships between (a) the IV and the mediator, and (b) the mediator and the DV (Baron & Kenny, 1986). When only one mediator is involved, the process is termed simple mediation; otherwise, it is a multiple mediation. In such a model, the total effect of IV on DV is partitioned into an indirect effect (through M) and a direct effect (path c'). Path a represents the effect of IV on M; path b reflects the effect of M on DV. The indirect effect is quantified as the product ab, and the total effect is expressed as $c = c' + ab$ (Preacher & Hayes, 2008). The extent to which the direct effect is reduced indicates the strength of the mediation (Holmbeck et al., 1997).

The conditions under which an effect occurs or varies in strength or direction are specified by a **moderation analysis**, where a moderator interacts with the IV to influence the DV (Holmbeck et al., 1997). Moderators are introduced when the relationship between a predictor and outcome is unexpectedly weak or inconsistent. They can be qualitative (e.g., gender) or quantitative (e.g., depression level) and determine how the IV-DV relationship changes across levels of the moderator (Baron & Kenny, 1986). Mediators and moderators can be integrated into a single model, allowing for mediation-moderation analyses (Holmbeck et al., 1997). The models in

Figure 1 illustrate the causal structure of a mediation analysis (Panel A) and a combined mediation-moderation framework - conditional mediation (Panel B).

Panel **A**: Mediation analysis



Panel **B**: Conditional mediation

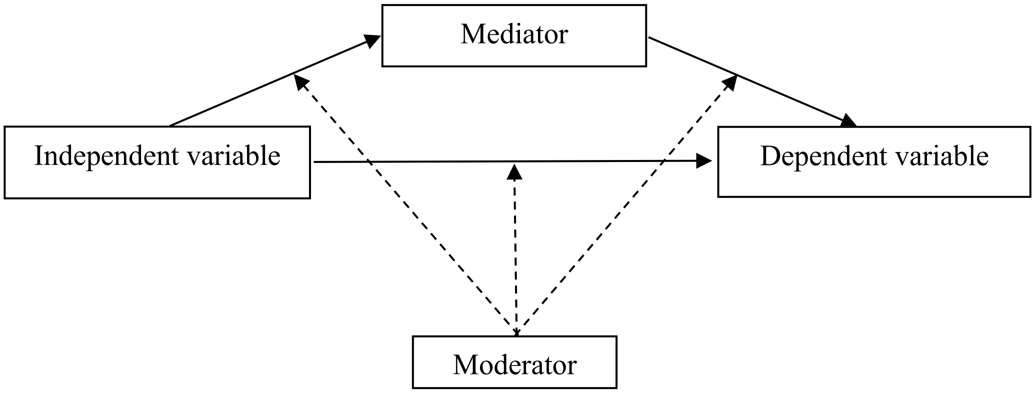


Fig. 1 (Panel **A**) Conceptual framework of the potential mediating effect of a mediator on the relationship between the independent and dependent variables. (Panel **B**) Conceptual framework of the potential effects of a moderator on the paths.

1.4 OUTLINE OF THE THESIS

The research conducted during my PhD program resulted in six scientific articles (five of which have been published or submitted to national or international peer-reviewed journals, while one is currently awaiting approval from the Ethics Committee). These works are organized into four thematic areas, corresponding to the major topics addressed and are presented in the following chapters (Chapters 2-5).

Chapter 2 explores the psychological adjustment to rheumatic disease as a chronic condition, emphasizing its role as a key factor influencing subsequent symptomatology. This chapter investigates the underlying mechanisms of this process. Specifically, our findings indicate that coping strategies are associated with fatigue and that this association is fully mediated by depression and anxiety.

Chapter 3 focuses on health-related quality of life among individuals with rheumatic diseases. It examines the levels and potential determinants of HRQoL in patients with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis. Furthermore, it investigates the mediating role of fatigue in the relationship between disease activity and quality of life.

Chapter 4 addresses sex differences among patients with psoriatic arthritis and axial spondyloarthritis. The results reveal that female patients exhibited lower scores across most clinical and psychological variables. Moreover, the diminished quality of life observed in women was primarily explained by fatigue, perceived stress, anxiety and pain.

Chapter 5 presents the protocol of the *FREE* project, which focuses on non-pharmacological interventions designed to reduce fatigue and other disease-related outcomes in individuals with rheumatic conditions. The project encompasses both psychological and physiotherapeutic approaches. A concise description of these interventions is provided within this chapter, while a complete and detailed account of the psychological intervention is included in Appendix E.

Chapter 6 presents an integrative discussion of all studies included in this thesis. It synthesizes and critically examines the main findings, outlines their implications for future research, policy, clinical practice and education, and discusses the strengths and limitations of the work. The chapter concludes with recommendations for future research.

Chapter 7 is the overarching conclusion of the thesis.

CHAPTER 2. COPING STRATEGIES AND MENTAL HEALTH IN RHEUMATIC DISEASES: UNDERSTANDING THE FATIGUE PATHWAY

This chapter presents the article for which I am the first author, currently under peer review in the *Journal of Psychosomatic Research*, entitled "*Coping Strategies, Depression, Anxiety, and Fatigue in Rheumatic Diseases: A Moderated Mediation Analysis*."

The present chapter contains *Supplementary material*, which can be found in Appendix A, consisting of tables with results from mediation and moderation analyses.

2.1 Introduction

Fatigue is a common and one of the most challenging symptoms in people with inflammatory rheumatic diseases, affecting between 40% and 80% of the patients (Matcham et al., 2015). In rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), fatigue is maintained by a network of biopsychosocial factors such as reduced physical functioning, poor mental well-being, depression, and anxiety, which is different between individuals (Davies et al., 2021).

The psychological approach to managing chronic disease and its components, including fatigue, involves coping strategies (Ramjeet et al., 2008). Coping is defined as cognitive or behavioural processes to effectively manage demands and reduce emotional distress. It can be categorised into problem-focused coping, which involves efforts to change the distressing situation, and emotion-focused coping, which focuses on regulating emotional responses (Folkman & Lazarus, 1988). Dysfunctional coping, a group of coping responses characterised by behavioural or mental avoidance to effectively deal with the stressors, is also noted (Carver et al., 1989). Patients' coping responses to arthritis are influenced by their perception of the disease; those who see it as uncontrollable are less likely to cope effectively with their physical symptoms than those with a more positive outlook (Sturgeon et al., 2016).

In rheumatic diseases, maladaptive coping can lead to perpetuated fatigue (Davies et al., 2021). In RA, greater use of avoidance coping predicted increased fatigue, while emotion-focused strategies like praying/hoping do not impact fatigue level (Scharloo et al., 1999). A previous review and meta-analysis reported that avoiding coping predicts negative mood and fatigue in patients with RA and other chronic disease, as shown in both cross-sectional and longitudinal studies (Ramjeet et al., 2008). Furthermore, there is strong evidence supporting the relationship between coping strategies and anxiety or depression in individuals with rheumatic diseases. Previous study shows that emotion-oriented coping is associated with high anxiety and depression, while task-oriented coping correlates with lower anxiety and depression (Cohan et al., 2006). In RA, wishful thinking, disengagement and avoidant coping predict negative mood, indicating adverse disease outcomes (Ramjeet et al., 2008). Depression and anxiety, as common comorbidities in rheumatic disease, predispose the patient to increased fatigue. Emotional distress significantly exacerbates fatigue in RA and SpA; however, the nature of this relationship remains unclear (Katz et al., 2017). Finally, previous research indicates that factors such as disease activity, disease duration, sex, and the diagnosis type in rheumatic diseases influence the relationship between coping mechanisms, psychological variables, and fatigue (Matcham et al., 2015; Peláez-Ballestas et al., 2015; Ray et al., 1995; Van Hoogmoed et al., 2010).

The mechanisms connecting different factors to the development or persistence of fatigue remain poorly understood (Davies et al., 2021). Beliefs about the causes and effects of fatigue and coping strategies significantly impact fatigue management Katz, 2017). Nerenz and Leventhal (Nerenz & Leventhal, 1983) proposed a self-regulation theory in chronic illness, which includes three stages: illness representation, selection and implementation of coping strategies based on that representation, and appraisal of coping effectiveness. All stages incorporate emotional control to adjust reactions and plans according to the illness and emotional state. In this adaptive system model, coping serves as the skill component, encompassing various factors that collectively influence the success or failure of an individual's adaptability. When a person identifies as "chronically ill," symptoms like pain, fatigue, and weakness can reinforce their belief in illness chronicity. The representation of these symptoms elicits a coping response that helps alleviate the emotional distress associated with the illness. Finally, fatigue may result not only from the debilitating effects of the illness itself but also from the onset of depression triggered by the illness's challenges (Nerenz & Leventhal, 1983; Rutter & Rutter, 2002). Additionally, confirmation of Nerenz and Leventhal theory comes from the common-sense model of self-regulation, showing that perceptions of illness influence coping strategies, which in turn affect health outcomes, with emotional factors and perceived control playing crucial roles (Hagger et al., 2017). Despite results on the correlations among coping strategies, depression, anxiety, and fatigue, to our knowledge, no studies have investigated the potential role of depression and anxiety as mediators in the relationship between coping strategies and fatigue, particularly with the proposed moderators. This study aimed to test whether depression and anxiety mediate the correlation between a specific coping strategy (problem-focused, emotion-focused, and dysfunctional coping) and fatigue in patients with rheumatological diseases. Moreover, the present study analyses the possible effect of specific moderators (diagnosis, disease activity, disease duration, and sex) on paths. The following hypotheses were proposed: 1) depression and anxiety have a mediating role between coping and fatigue, and 2) one or more paths among coping strategies, depression, anxiety, and fatigue are moderated by one or more characteristics among diagnosis, disease activity, disease duration, and sex.

2.2 Materials and methods

Clinical Sample

The current study recruited individuals diagnosed with Rheumatoid Arthritis, according to the ACR/EULAR criteria (Kay & Upchurch, 2012) or Psoriatic Arthritis, according to the CASPAR criteria or Axial Spondyloarthritis according to the ASAS criteria (Rudwaleit et al., 2010) treated at the Unit of Rheumatology of the Verona University Hospital Trust (Italy) over one year. The exclusion criteria were the diagnosis of other systemic diseases besides RA, PsA, or axSpA. Details regarding recruitment and assessment were reported elsewhere (Pezzato et al., 2021; Tosato et al., 2022). All participants provided written informed consent. The study protocol was approved by the Ethics Committee of the Provinces of Verona and Rovigo (CESC15840, 30/3/2016). The investigation was carried out in accordance with the Helsinki Declaration of 1975, as revised in 2013 (World Medical Association et al., 2013).

Measurements

Paper-based instruments were utilized in the hospital setting to gather socio-demographic and clinical information.

Coping strategies were assessed using the Coping Orientation to the Problems Experienced (COPE-NVI, Italian version), validated in the Italian population (Sica et al., 2008). This self-administered questionnaire evaluates 15 coping strategies for dealing with difficult or stressful events, categorized into"problem-focused coping", "emotion-focused coping", and "dysfunctional coping" (Carver et al., 1989). The COPE showed strong psychometric properties in Italian population (Sica et al., 2008).

Fatigue was assessed by the Chalder Fatigue Questionnaire (CFQ), a self-administered questionnaire for measuring fatigue severity. It consists of 11 items rated on a 4-point scale, resulting in scores that range from 0 to 33, with higher scores indicating greater levels of fatigue. The CFQ showed valid and reliable results for measuring fatigue (Chalder et al., 1999).

The severity of depressive symptoms was measured using the 16-item self-report Quick Inventory of Depressive Symptomatology (QIDS). Items are rated from 0 to 3, with a higher total score indicating more severe symptoms. The QIDS has demonstrated highly acceptable psychometric properties, underscoring its utility as a brief measure of depressive symptom severity in both clinical and research contexts (Rush et al., 2000).

Anxiety severity was measured using the 20-item State-Trait Anxiety Inventory (STAI-X1), which employs a 4-point Likert scale where higher scores indicate greater anxiety. The STAI-X1 demonstrated strong psychometric properties, proving to be a valuable tool for measuring anxiety (Oei et al., 1990).

Statistical analysis

Participants' demographic and clinical characteristics were given as frequency distribution (%) for categorical variables and mean and standard deviation (SD) for continuous variables. Comparisons among independent groups were performed by Chi-square test in the case of categorical variables and t-test (2 groups) and ANOVA (>2 groups) in the case of continuous variables. All tests were bilateral at $p<0.05$. Descriptives and tests were executed by SPSS 29.0.1.0 for Windows.

Multiple mediation analysis. A mediation analysis was performed to test whether the total effect (path c) of a specific coping strategy (problem-focused, emotion-focused, and dysfunctional coping), if statistically significant ($p<0.05$), is mediated by depression and anxiety (multiple mediation model). The total effect c comprises a direct effect (path c') of coping on fatigue and a mediated effect (path a1*b1 of depression as a mediator between coping and fatigue plus path a2*b2 of anxiety as a mediator between coping and fatigue). If c' is reduced but still significant, the mediation is called partial; if c' loses the statistical significance, the mediation is called total (Preacher &

Hayes, 2008). Figure 1A shows the conceptual framework of the multiple mediation model.

Conditional mediation analysis. First, the possible moderation effects (interactions) of each characteristic (among diagnosis, disease activity, disease duration, and sex) were estimated for each path of the multiple mediation model. Only characteristics which resulted statistically significant ($p<0.05$) for at least one path were retained as moderators (Preacher & Hayes, 2008). After that, each moderator was used to estimate the conditional mediation model. Figure 1B shows the conceptual framework of the conditional mediation model.

A bias-corrected bootstrapping procedure (5000 replications) was used to estimate the 95% confidence intervals for the point estimates of paths. Mediation, moderation, and conditional mediation analyses were executed by Jamovi version 2.3.28 for Windows (GLM Mediation Model 'jamm' modules).

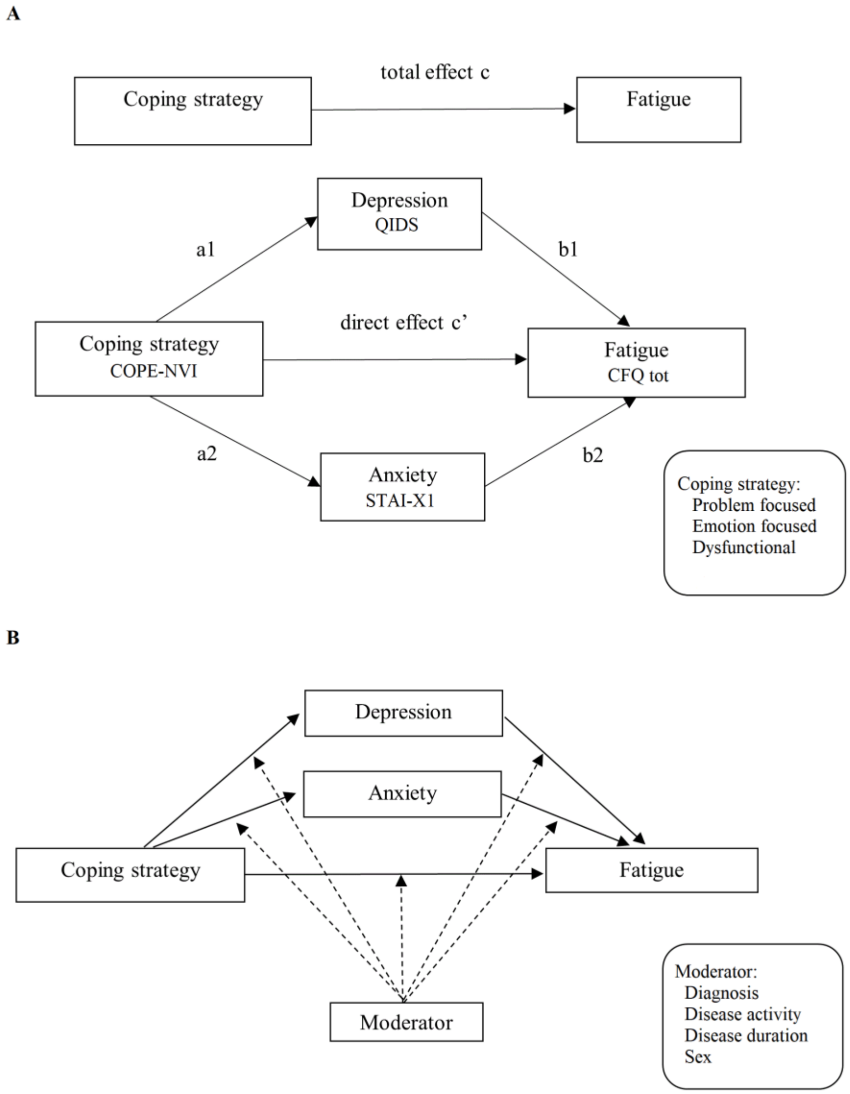


Figure 1 - Conceptual framework of multiple mediation and conditional mediation. (A) Multiple mediation of depression and anxiety on the relationship between coping strategy and fatigue. (B) Conditional mediation by the potential effects of a moderator (among diagnosis, disease activity, disease duration, sex) on the paths.

COPE-NVI: Coping Orientation to the Problems Experienced-new Italian version; CFQ: Chalder Fatigue Questionnaire; QIDS: Quick Inventory for Depressive Symptomatology; STAI-X1: State-Trait Anxiety Inventory-State Anxiety.

2.3 Results

Sample characteristics

The study sample comprised 807 patients, primarily women (N= 570, 70.6%), with a mean age of 57.3 years (SD 12.5 years). Most patients are married (N= 593, 73.5%), and more than 50% have a low educational level and are not employed. By considering the diagnosis, patients were affected by Rheumatoid Arthritis (60.7%), Psoriatic Arthritis (24.5%), and Ankylosing Spondylitis (14.7%). Disease activity showed a mean level of 2.8 (SD 1.0) for RA, 15.1 (SD 8.7) for PsA, and 2.5 (SD 1.1) for axSpA, respectively. The mean disease duration was more than 10 years (SD 8.9). The CFQ mean score was 4.3 (SD 4.2). The mean score for the QIDS was 6.9 (SD 4.4) and for STAI-X1 was 40.7 (SD 11.4). Problem-focused, emotion-focused, and dysfunctional coping strategies showed mean levels of 47.6 (SD 10.7), 45.4 (SD 8.9), and 22.5 (SD 5.2), respectively (Table 1).

Table 1 - Socio-demographic and clinical characteristics of patients (n=807).

Socio-demographic characteristics	Total sample N=807
Age (yrs), mean (sd)	57.3 (12.5)
Female, n (%)	570 (70.6%)
Married, n (%)	593 (73.5%)
Low education, n (%)	447 (55.4%)
Employed, n (%)	422 (52.3%)
Clinical characteristics	
Diagnosis, n (%)	
Rheumatoid arthritis	490 (60.7%)
Psoriatic arthritis	198 (24.5%)
Axial Spondyloarthritis	119 (14.7%)
Disease activity, mean (sd)	
Rheumatoid arthritis[1]	2.8 (1.0)
Psoriatic arthritis[2]	15.1 (8.7)
Axial Spondyloarthritis[3]	2.5 (1.1)

Disease duration (yrs), mean (sd)	11.2 (8.9)
CFQ score, mean (sd)	4.3 (4.2)
QIDS score, mean (sd)	6.9 (4.4)
STAI-X1 score, mean (sd)	40.7 (11.4)
COPE-NVI score, mean (sd)	
Problem focused	47.6 (10.7)
Emotion focused	45.4 (8.9)
Dysfunctional coping	22.5 (5.2)

[1]DAS28-CRP: Disease Activity Score in 28 joints with C-Reactive Protein. [2]DAPSA: Disease Activity in Psoriatic Arthritis. [3]ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein. CFQ: Chalder Fatigue Questionnaire; QIDS: Quick Inventory for Depressive Symptomatology; STAI-X1: State-Trait Anxiety Inventory; COPE-NVI: Coping Orientation to the Problems Experienced - New Italian Version.

Multiple mediation analysis

First, the total effect c was estimated for each coping strategy (problem-focused, emotion-focused, and dysfunctional) assumed as the independent variable (IV) on fatigue, which is the dependent variable (DV). By considering problem-focused, the point estimate for c was 0.006 [SE 0.01; 95% CI (-0.02 to 0.03), p=0.63], thus not permitting to proceed with mediation. Analogously, emotion-focused revealed a non-significant point estimate for c of 0.01 [SE 0.01, 95% CI (-0.01 to 0.05), p=0.27]. On the contrary, the dysfunctional strategy had a statistically significant point estimate for c of 0.20 [SE 0.02, 95% CI (0.14 - 0.25), p<0.001]. Thus, the multiple mediation model was estimated for this IV (dysfunctional coping strategy), with depression and anxiety as mediators for fatigue (DV) (Figure 2).

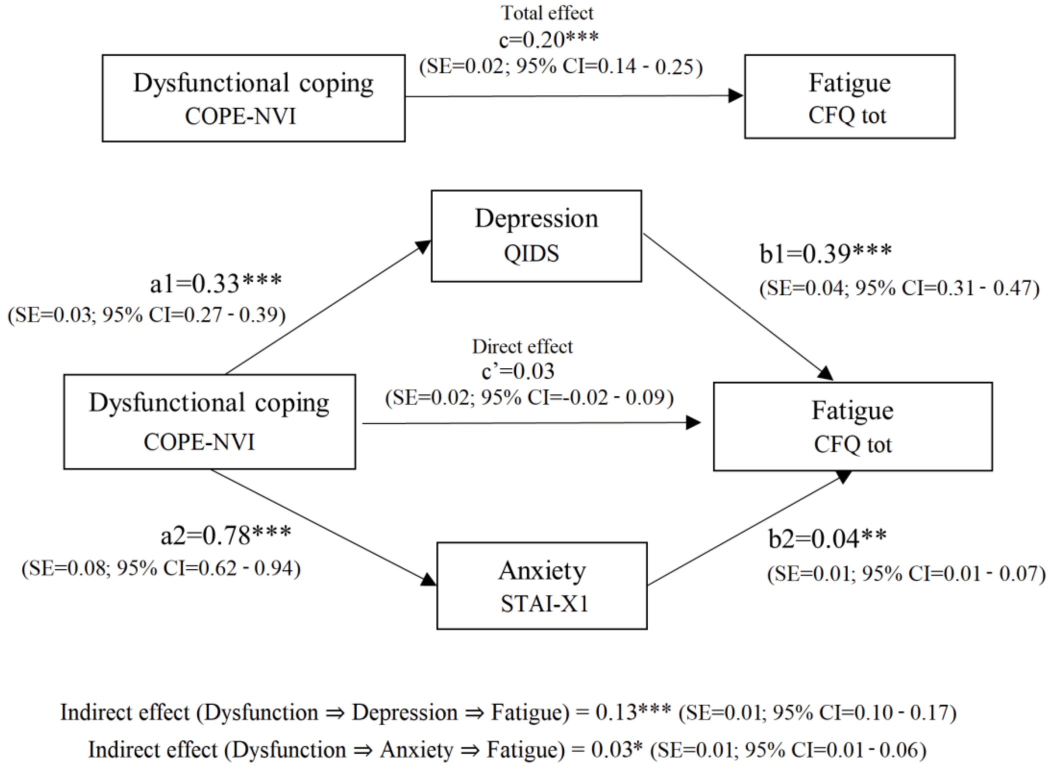


Figure 2 - Estimated mediating effects of depression and anxiety on the relationship between dysfunctional coping and fatigue.

**P*<0.05; ***P*<0.01; ****P*<0.001; CI 95%: Confidence Interval computed with 5000 times bias-corrected bootstrap; SE: Standard Error; COPE-NVI: Coping Orientation to the Problems Experienced-new Italian version; CFQ: Chalder Fatigue Questionnaire; QIDS: Quick Inventory for Depressive Symptomatology; STAI-X1: State-Trait Anxiety Inventory-State Anxiety.

The simple path coefficients (a1, b1, a2, and b2) and the indirect paths (a1*b1 and a2*b2) were all statistically significant ($p<0.05$). The direct effect c'=0.03 of dysfunctional coping on fatigue was no more significant [SE 0.02; 95% CI (-0.02 to 0.09), $p=0.22$], thus suggesting that depression and anxiety totally mediate the relationship between IV and DV. The proportion of the total effect mediated was 83%.

Conditional mediation analysis

The estimated moderation effect of each characteristic (among diagnosis, disease activity, disease duration, and sex) for each path of the multiple mediation model with dysfunctional coping strategy as IV and fatigue as DV showed that disease activity and disease duration do not moderate mediation paths (p>0.05 for each path; data available from the Authors), while diagnosis (axSpA vs RA on the direct path) and sex (M vs F on the simple path a1) moderate one path each (p<0.05) (Figure 3; Appendix A1, A2 and A3).

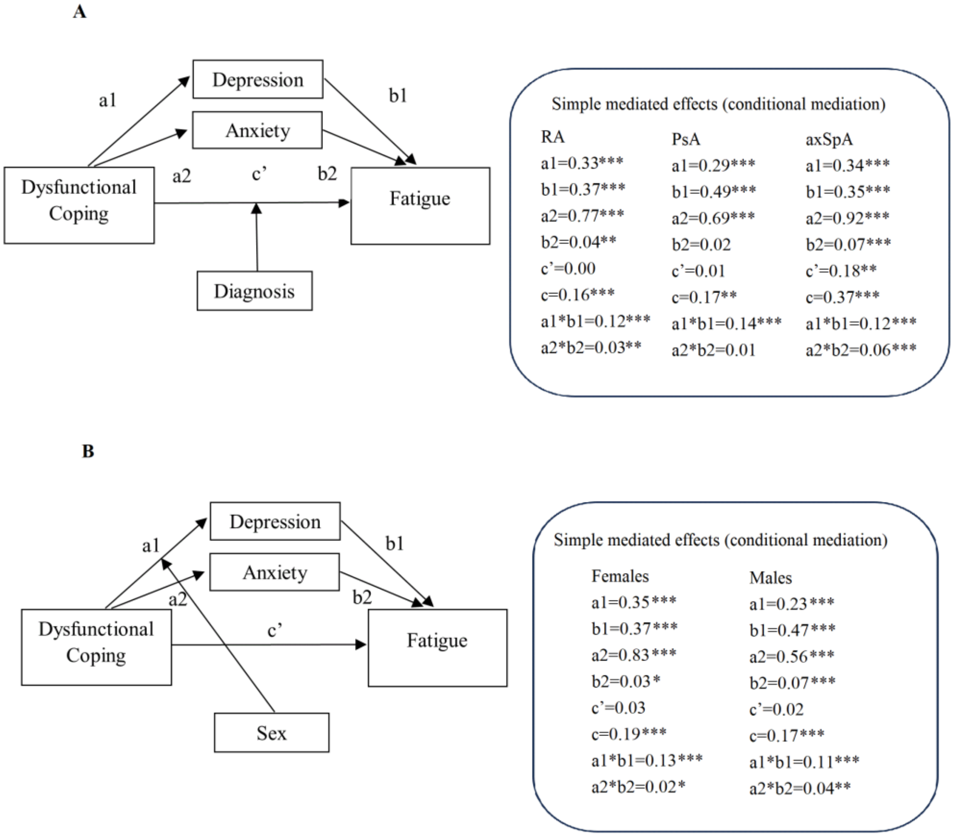


Figure 3 - The estimated moderation effect of diagnosis and sex for each path of the multiple mediation model with dysfunctional coping strategy as an independent variable and fatigue as a dependent variable. (A) Estimated conditional mediation of diagnosis. (B) Estimated conditional mediation of sex.

**P*<0.05; ***P*<0.01; ****P*<0.001.

By considering diagnosis, when dysfunctional coping affects fatigue, its effect depends on the diagnostic category. In detail, the estimate of the direct path c' was 0.006 [SE 0.03, 95% CI (-0.05 to 0.07), p=0.84] for rheumatoid arthritis, 0.017 [SE 0.05, 95% CI (-0.08 to 0.11), p=0.74] for psoriatic arthritis, and 0.18 [SE 0.06, 95% CI (0.06 - 0.31), p=0.004] for axial spondyloarthritis (Figure 3A; Appendix A4). A graphical representation of the interaction of diagnosis with dysfunctional coping in predicting fatigue is given in Figure 4A, which shows that the line for axial spondyloarthritis is steeper, thus suggesting, together with the statistical significance of c’ (which, in turn, leads to a partial mediation of depression and anxiety), that for patients affected by axSpA the level of dysfunctional coping has a stronger effect on fatigue.

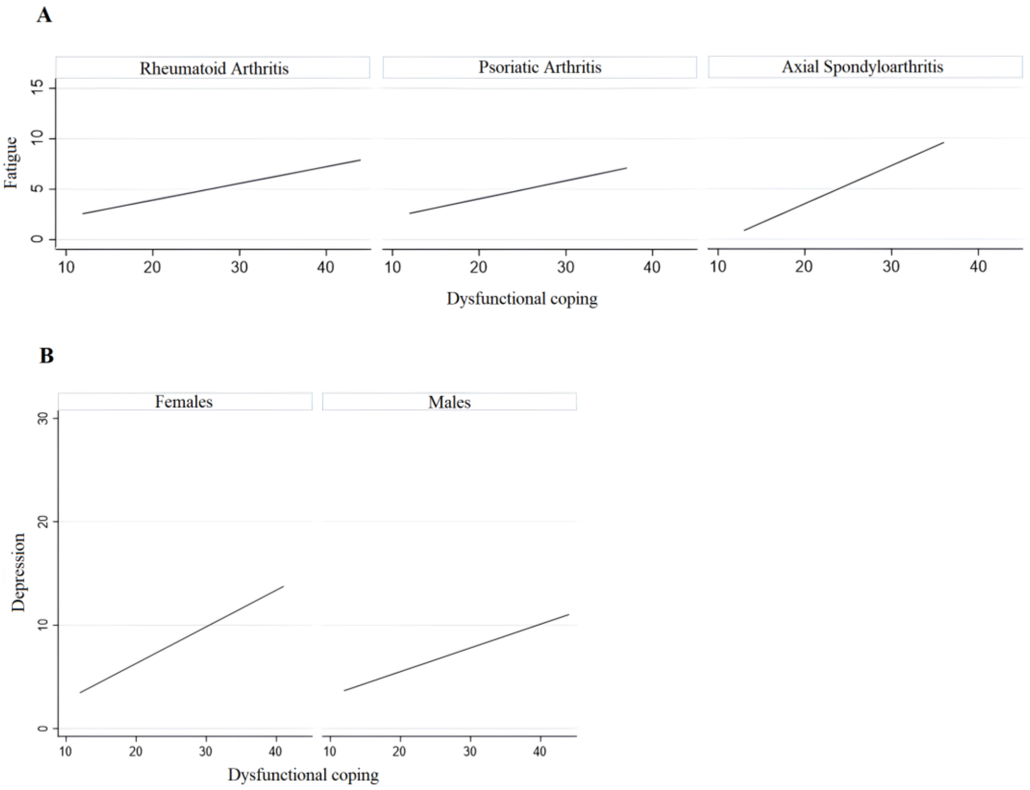


Figure 4 - Interaction of diagnosis with dysfunctional coping in predicting fatigue and sex with dysfunctional coping in predicting depression. (A) Moderating influence of diagnosis on the effect of dysfunctional coping on fatigue. (B) Moderating influence of sex on the effect of dysfunctional coping on depression.

Regarding sex, when dysfunctional coping affects depression, its effect depends on it. In detail, the estimate of path a1 was 0.23 [SE 0.05, 95% CI (0.13 - 0.32), p<0.001] for males and 0.35 [SE 0.03, 95% CI (0.28 - 0.42), p<0.001] for females (Figure 3B; Appendix A5). The graphical representation of the interaction of sex with dysfunctional coping in predicting depression shows that the line for females is steeper, thus suggesting that the level of dysfunctional coping for females has a more substantial effect on depression (Figure 4B).

2.4 Discussion

This study investigated, in a large and epidemiologically representative 1-year cohort of rheumatic disease patients, two hypotheses: 1) the role of depression and anxiety as mediators in the relationship between coping strategies (problem-focused, emotion-focused, and dysfunctional coping) and fatigue (multiple mediation analysis), and 2) the possible moderating effects of characteristics such as diagnosis, disease activity, disease duration, and sex on the paths of the mediation model (conditional mediation analysis).

The first hypothesis was confirmed only for dysfunctional coping as the independent variable. For this coping strategy, depression and anxiety act as mediators in the relationship with fatigue; moreover, depression and anxiety totally mediate the relationship. No significant correlation was found between the other coping strategies (problem-focused and emotion-focused) and fatigue. Prior research on RA patients indicates that active coping styles can enhance psychological well-being, while the use of passive coping or focusing on emotions increases the likelihood of depressive and anxiety symptoms (Sturgeon et al., 2016; Scharloo et al., 1999; Zairko et al., 2014). Given that adaptive coping strategies are expected to contribute to improved functioning in chronic diseases (Fournier et al., 2002), our findings that adaptive coping does not directly influence fatigue raise concerns about addressing maladaptive strategies for fatigue management, especially since positive coping seems ineffective.

By considering the mediation, Carver et al. (1989) suggested that dysfunctional strategies are based on the feeling of hopelessness, avoidance of facing stressors, or venting emotions, factors that impede adaptation in rheumatoid arthritis (Ziarko et al., 2014), thus contributing to the persistence of fatigue. Additionally, ruminating on fatigue in RA could be induced by a dysfunctional strategy toward the disease burden (Van Hoogmoed et al., 2010). In contrast, RA patients with healthy coping strategies have a feeling of control over their RA symptoms (Sturgeon et al., 2016). Previous research has also shown that in PsA patients, dysfunctional coping predicted depression, while self-blame predicted anxiety (Fournier et al., 2002). Other studies reported that individuals with RA and a history of depression demonstrate less effective coping strategies (Sturgeon et al., 2016). The frequent use of dysfunctional coping strategies, supported by strong emotional reactions to the disease, contributes to high levels of depression in RA (Ziarko et al., 2014). Previous study conclude that dysfunctional strategies could be harmful to patients with RA, increasing emotional distress (Tosato et al., 2023).

Previous studies also demonstrated that anxiety and depression are strongly related to fatigue in rheumatic diseases (Davies et al., 2021; Katz, 2017; Bixio et al., 2024). Specifically, a history of affective disorder directly impacts current fatigue levels in RA patients (Jump et al., 2004). A study on PsA patients showed that an approach to concealing distress from others exacerbates fatigue (Chisholm et al., 2016). Fatigue is a common symptom of major depressive disorder, making it challenging to differentiate between pure fatigue symptoms and those related to depression (World Health Organization, 2022). Corfield et al. (2016) indicate that fatigue and depression are distinct from overlapping symptomatology, and our sample seems to confirm this result, with 12% of patients exhibiting moderate to severe depressive symptoms, and 49% reporting significant fatigue (Bixio et al., 2024; Ristic et al., 2023). While fatigue in rheumatic diseases is commonly correlated with depression more than anxiety (Matcham et al., 2015; Sturgeon et al., 2016), the present study shows that also anxiety impacts fatigue. This finding is significant, given that anxiety symptoms are more prevalent than depression in arthritis (Hewlett et al., 2011). Eventually, the relationship between depression and fatigue, as well as anxiety and fatigue, is complex, complicating the determination of whether depression or anxiety causes fatigue or vice versa (Treharne et al., 2007; Katz, 2017).

The second hypothesis, that is the conditional mediation due to possible moderators (diagnosis, disease activity, disease duration, and sex), was confirmed only for sex and diagnosis. Disease activity and duration did not moderate in the mediation model. While previous research found that higher disease activity correlates with increased passive coping in RA and SpA (Peláez-Ballestas et al., 2015), one study suggests coping strategies may be independent of disease activity in axSpA (van Lunteren et al., 2020). Regarding disease duration, Ray et al. (1995) indicated that in rheumatic diseases, coping resources may decline over time, making disease duration a key factor in how coping strategies relate to fatigue. Nevertheless, Boonen et al. (2004) concluded that changes in coping strategies are independent of disease duration in axSpA patients. By considering the moderating effects of sex, in both females and males depression and anxiety completely moderate the relationship between dysfunctional coping and fatigue. However, dysfunctional coping has a more significant impact on depression in females than in males, with women considerably more likely to use dysfunctional coping and experience depressive symptoms. In rheumatic diseases, females tend to seek emotional support more frequently, especially during periods of high disease activity, while men are more inclined to resort to denial and emotional discharge (Wrobel et al., 2023). Nevertheless, both genders employ coping strategies, including adjustment, avoidance, interaction, and acceptance, to manage their condition (Ostlund et al., 2018). Research shows that women often engage in passive coping strategies in response to stress, focusing on their own symptoms, which contributes to a higher depression rate compared to men with RA (Carmona et al., 2023). Additionally, female patients with axSpA and PsA face longer diagnostic delays, poorer treatment adherence, and a lower quality of life than males, which explains a higher prevalence of depression among women (Ristic et al., 2024; Tarannum et al., 2022). Thus, given the differences in clinical presentation and disease course, women have more difficulties coping with rheumatic conditions, making them more vulnerable to depression.

By considering the moderating effects of diagnosis, in axSpA patients, dysfunctional coping has a more pronounced impact on fatigue than in those with RA and PsA, even though axSpA patients use dysfunctional coping less often. The significant effect holds even when accounting for depression and anxiety as mediators, indicating that high levels of dysfunctional coping in axSpA are only partially mediated by these factors. Previous studies indicate that individuals with SpA not only develop various coping strategies and demonstrate greater resilience than the general population but also report better quality of life compared to those with other rheumatic diseases (Ristic et al., 2023; Tekaya et al., 2024). Nevertheless, our analysis indicates that axSpA patients who rely on dysfunctional coping strategies experience more significant fatigue. Previous studies reported that coping strategies in SpA are typically stable over time (Tekaya et al., 2024). A qualitative study suggests that to alleviate fatigue in SpA, individuals need to engage in physical activity, modify their habits, and face challenges, approaches often lacking in those who predominantly utilize dysfunctional coping strategies (Pearson et al., 2022).

Some strengths and limitations should be considered in the present study. The first strength is a large and epidemiologically representative 1-year cohort of patients from daily practice, comprised of three common inflammatory rheumatic diseases that affect psychological outcomes differently, providing a comprehensive view of the disease burden. The second strength of the study is its introduction of an original theoretical model that has been empirically validated, offering potential practical applications in clinical settings.

Conversely, several limitations must be acknowledged. The first limitation pertains to the cross-sectional study design, which does not allow to infer causality but only to estimate correlation among variables. The second limitation involves the intricate interplay between coping, fatigue, and emotional distress, which can be bidirectional; the directionality of influence may diverge from the interpretations proposed in this study. For instance, prior research indicates that depressive symptoms can adversely affect maladaptive coping strategies (Sturgeon et al., 2016) and that fatigue may serve as a significant predictor of self-reported depression in individuals with arthritis (Katz, 2017). The third limitation is that the sample comprises mainly individuals with a prolonged disease duration (exceeding 11 years), which may not accurately reflect the coping strategies employed by patients experiencing the recent onset of illness (Remjeet et al., 2008).

The current study has significant clinical implications. It finds that depression and anxiety mediate the association between dysfunctional coping and fatigue, suggesting that interventions should address these mediators in addition to coping, as previous research has shown that current depression is related to or precipitates present fatigue (Hewlett et al., 2011). Previous studies have demonstrated that cognitive-behavioral stress management and resilience therapies effectively improve self-management and coping skills in patients with rheumatic diseases (Evers et al., 2011). A longitudinal study revealed that a 2-year cognitive-behavioral treatment program improved coping with fatigue in RA patients, and self-management skills became integrated into their daily lives (Hewlett et al., 2019). Additionally, self-monitoring fatigue and developing protective coping behaviours are crucial for energy conservation in RA before becoming completely exhausted (Koike et al., 2000). Finally, effective coping plays a crucial role in long-term adaptations, and support programs can enhance self-management for those with limited coping skills (Evers et al., 2011). Overall, the present study contributes to a clearer understanding of how psychological interventions targeting maladaptive coping strategies and emotional distress enhance outcomes in rheumatic diseases, particularly regarding fatigue.

In conclusion, we suggest that understanding the pathway between coping strategies and fatigue opens a broader perspective toward psychological approaches and interventions. Psychological interpretation, adaptation, and response to the disease could be the initial part of the underlying mechanism where depression and anxiety further maintain fatigue, with sex and diagnosis as possible moderators. Rheumatologists and other health professionals need to build a holistic approach that can help them optimally assess and manage fatigue and other psychological outcomes of rheumatic disease. Finally, our models serve as a starting point for further exploration, emphasizing the need to examine how additional variables may mediate the relationship between coping strategies and outcomes in rheumatic diseases.

CHAPTER 3. QUALITY OF LIFE IN RHEUMATIC DISEASES: PATTERNS AND THE ROLE OF FATIGUE

3.1 DETERMINANTS AND DIFFERENCES OF QUALITY OF LIFE IN RHEUMATIC DISEASES

This subchapter presents the article for which I am the first author, published in the *Journal of Psychosomatic Research*, entitled "*Comparison and Potential Determinants of Health-Related Quality of Life Among Rheumatoid Arthritis, Psoriatic Arthritis, and Spondyloarthritis: A Cross-Sectional Study*" (DOI: 10.1016/j.jpsychores.2023.111512). The final authenticated version is available online at: https://www.sciencedirect.com/science/article/pii/S0022399923003690?via%3Dihub .

This subchapter contains *Supplementary material*, which can be found in Appendix B.

3.1.1 Introduction

Rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloarthritis (SpA) are chronic, inflammatory, and autoimmune rheumatic diseases (Smolen et al., 2018; FitzGerald et al., 2021; Braun et al., 2021) having a strong impact on the physical, psychological and social aspect of patient's life (Haugeberg et al., 2021). Health-related quality of life (HRQoL) represents one of the main outcomes of rheumatic diseases and treatment is particularly focused on it (Torre-Alonso et al., 2018; Gerhold et al., 2015). The HRQoL is defined as a multidimensional concept that includes subjective reports of symptoms, side effects, functioning in multiple life domains, and general perceptions of life satisfaction and quality (Revicki et al., 2014). It is important to assess the quality of life in rheumatic diseases because the chronic and debilitating nature reflects on the everyday functioning and well-being of the patients. Thus, a comprehensive approach toward rheumatic diseases needs to include the assessment of quality of life as a substantial factor (Moraes et al., 2021; Gudu & Gossec, 2018; Matcham et al., 2014).

In rheumatic diseases, HRQoL is deteriorated with respect to the general population (Strand et al., 2012). The number of studies comparing the quality of life among different rheumatic diseases is modest, results are not uniform, and differences do not lead to a clear conclusion. Generally, in rheumatic diseases physical domains of HRQoL are more impaired than mental ones (Smolen et al., 2018; Matcham et al., 2014; Salaffi et al., 2009; Landgren et al., 2023). Comparing HRQoL of rheumatoid arthritis patients with spondyloarthritis ones, the physical quality of life was worse in RA patients (Chen et al., 2017; Ovayolu et al., 2011; Chorus et al., 2003; Kiltz et al., 2009), while the mental quality of life was found similar (Kiltz et al., 2009), worse in RA patients (Chen et al., 2017) or worse in SpA patients (Chorus et al., 2003). Previous studies reported that the quality of life in RA and PsA is reduced, but without significant difference (Sokoll et al., 2001; Husted et al., 2001; Borman et al., 2007).

To the best of our knowledge, only two studies compared the quality of life among RA, PsA, and SpA. One was conducted more than a decade ago (Salaffi et al., 2009), and it found that patients affected by rheumatoid arthritis had the lowest scores. Still, no details about rheumatological treatments and psychiatric assessment were included. The other study was published recently (Landgren et al., 2023), and it presented that after age matching, RA, PsA and SpA scores of physical quality of life were without differences, and RA and PsA scores of mental quality of life were similar, but no analysis about the association between quality of life and clinical variables was done. Thus, the present study aims to compare the impairment in health-related quality of life among rheumatoid arthritis, psoriatic arthritis and spondyloarthritis. Furthermore, it explores if specific socio-demographic and clinical variables, including rheumatological treatments, depression and anxiety, are associated with impairment in physical and mental quality of life domains for each diagnostic group.

3.1.2 Materials and methods

Clinical sample

This observational, cross-sectional study examined the differences in health-related quality of life among patients affected by rheumatoid arthritis, psoriatic arthritis and spondyloarthritis. The sample consisted of a cohort of patients, aged 18 years or older, who were diagnosed as following: rheumatoid arthritis - according to the ACR/EULAR classification criteria (Kay & Upchurch, 2012), psoriatic arthritis - according to the CASPAR criteria (Taylor et al., 2006), and spondyloarthritis - according to the ASAS classification criteria (Sieper & Poddubnyy, 2017). All participants, in charge at the Unit of Rheumatology, University Hospital of Verona, Italy, were already diagnosed and they were assessed once clinical stability was achieved. Written informed consent was provided after the description of the study. The recruitment was carried out sequentially during a routine outpatient visit, in the period of one year. Exclusion criteria were: diagnosis of fibromyalgia, connective tissue diseases (Systemic Lupus Erythematosus, Sjogren, sclerodermas, dermatomyositis, polymyositis), vasculitis, gout, infective arthritis, rheumatic polymyalgia or other severe systemic diseases (Pezzato et al., 2021; Tosato et al., 2023). No other exclusion criteria were applied (for example, a specified level of disease activity, and defined disease duration). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki (World Medical Association, 2013) and approved by the Ethics Committee of the Provinces of Verona and Rovigo (Ref. CESC15840, 2016).

Measurements

Standardized instruments were used to collect socio-demographic and clinical data.

The health-related quality of life was estimated by using the self-reported Medical Outcomes Study 36-item Short Form Survey (SF-36; Italian version) (Apolone & Mosconi, 1998), which is the most widely used instruments (Matcham et al., 2014). The instrument consists of 36 items summarized in eight dimensions representing eight health concepts: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Those dimensions are further aggregated on two summary measures: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Lower scores on each dimension and on summary measures indicate worse HRQoL and higher scores for better quality of life (Ware, 2000).

Disease activity was assessed with the specific instrument for each disease as it is recommended in clinical practice (Duarte-García et al., 2019). Specifically, it was assessed by the Disease Activity Score in 28 joints with C-Reactive Protein (DAS28-CRP) in RA, the Disease Activity in PSoriatic Arthritis (DAPSA) in PsA and the Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein (ASDAS-CRP) in SpA.

The DAS28-CRP score includes tender and swollen joint count (based on a 28-joint assessment), level of C-reactive protein (mg/dl) and the general health assessment scored on a visual analog scale (VAS, 0 – 10) (van Riel & Renskers, 2016). The DAPSA score includes tender joints count (out of 68), swollen joints count (out of 66), level of C-reactive protein (mg/dl) and patient's assessment of disease activity and pain (0-10) (Schoels et al., 2010). The ASDAS-CRP score includes back pain (0-10), duration of morning stiffness (0-10), patient global assessment of disease activity (0-10), peripheral pain/swelling (0-10) and level of C-reactive protein (mg/dl) (van der Heijde et al., 2009).

As done before (Tosato et al., 2022), pharmacological treatment was categorized as first-line therapy [conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and/or anti-TNF (anti–tumor necrosis factor drugs)] and second-line therapy [biological disease-modifying antirheumatic drugs (bDMARDs), targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) with or without csDMARDs]. The use of glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDS) were also collected.

Depressive and anxious symptomatology was assessed using the Hospital Anxiety and Depression Scale (HADS) (Zigmond et al., 1983). The HADS is a self-reported questionnaire, quick and easy to complete. It is composed of two scales, one for depression (HADS-D) and one for anxiety (HADS-A), each constituted by seven items. Higher scores indicate more severe symptoms.

Statistical analysis

Variables were described by absolute frequencies and percentages if categorical and means (SDs) if continuous. The comparisons among the three diagnostic groups were performed by Chi-square tests (categorical variables) and ANOVAs with Bonferroni's post-hoc comparisons (continuous variables). The associations between each characteristic (independent variable) and each of the two SF-36 summary measures (Physical Component Score PCS and Mental Component Score MCS) were explored by univariate linear regression models. After that, independent characteristics associated at $p<0.10$ in the univariate models entered the multivariate linear regression models with each SF-36 summary measure as dependent variable. Adjusted Beta coefficients and p-values were estimated. Adjusted R^2 for each model was shown. Effect size wasfor estimated by Eta squared (for each model) and partial eta squared (for each independent variable). Partial eta squared values are interpreted by a rule of thumb as follows: 0.01 small effect, 0.06 medium effect, ≥0.14 large effect. All tests were bilateral with the significant level at $p<0.05$. Analyses were performed by SPSS 28 for Windows.

3.1.3 Results

Socio-demographic and clinical characteristics

The study sample consisted of 807 patients affected by RA (n=490, 60.7%), PsA (n=198, 24.5%) and SpA (n=119, 14.8%). With respect to socio-demographics, the three diagnostic groups significantly differed in all characteristics, with the exception of marital status (Table 1).

Table 1. Socio-demographic characteristics (n=807)

Socio-demographic variables	**RA (n=490)**		**PsA (n=198)**		**SpA (n=119)**		**p-value**
	Mean or %	**SD or N**	**Mean or %**	**SD or N**	**Mean or %**	**SD or N**	
Age, years	59.5	12.2	56.8	11.6	48.9	11.6	<0.001^{a}
Gender							
Female	80.0%	392	62.6%	124	45.4%	54	<0.001^{b}
Male	20.0%	98	37.4%	74	54.6%	65	
Marital status							
Single	11.6%	57	11.6%	23	21.8%	26	
Married	72.4%	355	76.8%	152	72.3%	86	0.002^{b}
Widowed	7.8%	38	4.0%	8	0%	0	
Separated/Divorced	8.2%	40	7.6%	15	5.9%	7	
Educational level							
Primary (age 6-10 yrs.)	23.0%	113	16.7%	33	6.7%	8	
Secondary (age 11-13 yrs.)	38.0%	186	35.3%	70	31.1%	37	<0.001^{b}
Vocational qualification / Diploma (age 14-18 yrs.)	33.6%	165	40.0%	79	50.4%	60	
Degree	5.4%	26	8.0%	16	11.8%	14	
Employment							
No	60.8%	298	48.0%	95	24.4%	29	<0.001^{b}
Yes	39.2%	192	52.0%	103	75.6%	90	

RA rheumatoid arthritis; PsA psoriatic arthritis; SpA spondyloarthritis.

a: ANOVA; Bonferroni's post-hoc comparisons (age): RA> PsA; RA>SpA; PsA>SpA; b: Chi-square test.

Briefly, RA patients were mostly females (80%), married (72%), with secondary or vocational qualification educational level (71%) and no employment (61%). Moreover, the RA group was the oldest (mean 59.5 years, SD 12). On the contrary, the SpA patients were the youngest (mean 49 years, SD 12) and showed the highest proportions of males (55%), they were mostly married (72%), with secondary or vocational qualification educational level (81%) and employed (about 76%).

Regarding disease activity, 36% of RA and 49% of PsA had a moderate or high level of activity, while 63.1% of SpA patients had a high or very high level of activity (Table 2).

Table 2. Clinical characteristics (n=807)

Clinical variables	**Rheumatoid arthritis (n=490)**		**Psoriatic arthritis (n=198)**		**Spondylarthritis (n=119)**		**p value**
	Mean or %	**SD or N**	**Mean or %**	**SD or N**	**Mean or %**	**SD or N**	
Clinical (rheumatology)							
DAS28-CRP	2.8 (M)	1.0 (SD)					
Remission or Low (<3.3)	63.8%	313					
Moderate or High (>=3.3)	36.2%	177					
DAPSA			15.1 (M)	8.7 (SD)			
Remission or Low (<15)			51.0%	101			
Moderate or High (>=15)			49.0%	97			
ASDAS -CRP					2.5 (M)	1.1(SD)	
Inactive or Moderate(<2.2)					36.9%	44	
High or Very high (>=2.2)					63.1%	75	
Disease duration (yrs.)	12.5	9.5	8.8	6.9	10.0	8.2	<0.001[a]
Comorbidity							
No	9.2%	45	9.6%	19	16.8%	20	0.046[b]
Yes	90.8%	445	90.4%	179	83.2%	99	
Cardio-circulatory§							
No	38.2%	170	46.9%	84	47.5%	47	0.060
Yes	61.8%	275	53.1%	95	52.5%	52	
Endocrinological§§							
No	71.5%	318	76.5%	137	87.9%	87	0.003
Yes	28.5%	127	23.5%	42	12.1%	12	
Cancer§§§							
No	87.0%	387	88.3%	158	92.9%	92	0.252
Yes	13.0%	58	11.7%	21	7.1%	7	
Respiratory°							
No	90.3%	402	87.2%	156	90.9%	90	0.450
Yes	9.7%	43	12.8%	23	9.1%	9	
Neurological°°							
No	98.0%	436	97.2%	174	98.0%	97	0.831
Yes	2.0%	9	2.8%	5	2.0%	2	
Gastroenterological°°°							
No	67.6%	301	73.2%	131	65.7%	65	0.311
Yes	32.4%	144	26.8%	48	34.3%	34	

Osteoarticular^							
No	51.0%	227	57.5%	103	66.7%	66	0.013
Yes	49.0%	218	42.5%	76	33.3%	33	
Other^^							
No	45.8%	204	29.1%	52	49.5%	49	<0.001
Yes	54.2%	241	70.9%	127	50.5%	55	
Rheumatological treatment							
First-line therapy[1]	75.7%	371	78.3%	155	84.0%	100	0.143^b
Second-line therapy[2]	24.3%	119	21.7%	43	16.0%	19	
Glucocorticoid treatment							
No	50.6%	248	77.3%	153	79.8%	95	$<0.001^b$
Yes	49.4%	242	22.7%	45	20.2%	24	
NSAID treatment[3]							
No	78.8%	386	68.7%	136	58.8%	70	$<0.001^b$
Yes	21.2%	104	31.3%	62	41.2%	49	
Clinical (psychiatry)							
HADS -D	5.9 (M)	3.9 (SD)	5.6 (M)	3.7 (SD)	5.0 (M)	3.5 (SD)	0.059^a
Normal or Mild (<11)	85.7%	420	91.4%	181	91.6%	109	0.048^b
Moderate or Severe (>=11)	14.3%	70	8.6%	17	8.4%	10	
HADS -A	7.1 (M)	3.9 (SD)	6.7 (M)	3.9 (SD)	6.5 (M)	4.1 (SD)	0.273^a
Normal or Mild (<11)	80.2%	393	81.3%	161	79.0%	94	0.878^b
Moderate or Severe (>=11)	19.8%	97	18.7%	37	21.0%	25	
Antidepressant therapy							
No	93.9%	460	92.9%	184	94.1%	112	0.878^b
Yes	6.1%	30	7.1%	14	5.9%	7	

a: ANOVA; Bonferroni's post comparisons for Disease duration: RA>PsA (p<0.001); RA>SpA (p<0.001). Bonferroni's post comparisons for HADS-D (depression): NS. Bonferroni's post comparisons for HADS-A (anxiety): NS. b: Chi-square test.

1: csDMARDs and/or anti-TNF; 2: anti-IL6 / bDMARDs / tsDMARDs with or without csDMARDs; 3: used in last ten days.

RA rheumatoid arthritis; PsA psoriatic arthritis; SpA spondyloarthritis; cDMARDs conventional disease-modifying antirheumatic drugs; anti-TNF anti-tumor necrosis factor; NSAID treatment non-steroidal anti-inflammatory drug treatment; DAS28-CRP disease activity score in 28 joints with c-reactive protein; DAPSA disease activity in psoriatic arthritis; ASDAS-CRP ankylosing spondylitis disease activity score with c-reactive protein; HADS-D hospital anxiety and depression scale – depression; HADS-A hospital anxiety and depression scale – anxiety.

§ heart attack, ischemic heart disease, hypertension, atrial flutter, heart failure, peripheral vascular disease, hypercholesterolemia.

§§ diabetes, hypothyroidism, hyperthyroidism.

§§§ breast, uterus, prostate, lung, skin.

° obstructive pulmonary disease, emphysema, asthma.

°° dementia, stroke, Parkinson disease.

°°° hepatitis, cirrhosis, irritable colon, gastritis, Crohn disease.

^ osteoporosis, femur fracture, other fracture, arthrosis.

^^ psoriasis, enthesitis, uveitis, asthenia, fever, weight loss.

Disease duration was significantly different among diseases since RA patients have been diagnosed about 12 years ago (SD 9), PsA patients about 9 years ago (SD 7), and SpA patients 10 years ago (SD 8). Groups were significantly different with having one or more comorbidities, since about 91% of RA patients, about 90% of PsA patients, and about 83% of SpA patients had comorbidities. Leading comorbidities across the groups were cardio-circulatory, osteoarticular, and gastroenterological ones. By considering medications, the diagnostic groups did not differ concerning rheumatological prescriptions, while mostly RA patients were treated with glucocorticoids (49%), and mostly SpA patients were treated with NSAIDs (41%). Patients mainly had normal or mild levels of depression (86-92%) and anxiety (79-81%) and were not under antidepressant therapy (about 94%).

Health-related quality of life and its determinant

The SF-36 Physical component was different among the three groups, with SpA patients showing the highest score (RA: 36.0 SD 10.3, PsA: 36.9 SD 10.0, SpA: 38.6 SD 10.2, p=0.037 ANOVA; Bonferroni's post hoc: RA<SpA). The Mental component did not differ among the three groups (RA: 46.1 SD 10.1, PsA: 46.3 SD 10.9, SpA: 48.0 SD 9.5, p=0.189 ANOVA). Comparisons of the dimensions among rheumatic diseases are given in Appendix B.

Univariate linear regression analysis was performed to explore the association between each socio-demographic and clinical variable (independent variable), and each physical and mental quality of life (dependent variable) distinguished by diagnostic group.

Table 3. Unadjusted Beta coefficients between each summary measure of quality of life (PCS and MCS) as the dependent variable and each socio-demographic and clinical characteristic as the independent variable in RA, PsA and SpA (Univariate linear regression models).

	Dependent variables											
Independent variables	**Rheumatoid arthritis**				**Psoriatic arthritis**				**Spondyloarthritis**			
	PCS		**MCS**		**PCS**		**MCS**		**PCS**		**MCS**	
	Coeff	p-value	Coeff	p-value	Coeff	p-value	Coeff	p-value	Coeff	p-value	Coeff	p-value
Socio-demographic												
Age	-0.23	<0.001	-0.02	0.723	-0.14	0.018	0.04	0.502	-0.37	<0.001	-0.15	0.112
Female	-0.14	0.001	-0.09	0.036	-0.25	<0.001	-0.14	0.042	-0.26	0.004	-0.16	0.073
High education	0.11	0.019	-0.03	0.566	0.13	0.069	0.03	0.674	0.22	0.014	0.19	0.043
Employed	0.21	<0.001	0.06	0.203	0.15	0.038	-0.13	0.064	0.39	<0.001	0.28	0.002
Clinical (rheumatology)												
DAS28-CRP	-0.42	<0.001	-0.20	<0.001								
DAPSA					-0.61	<0.001	-0.23	0.001				
ASDAS-CRP									-0.68	<0.001	-0.36	<0.001
Disease duration (yrs.)	-0.14	0.002	0.01	0.798	0.03	0.716	0.08	0.252	-0.04	0.649	0.08	0.365
Comorbidity	-0.22	<0.001	-0.06	0.158	-0.18	0.010	0.03	0.650	-0.05	0.586	-0.03	0.748
Pharmacological treatment Second-line therapy[1]	-0.17	<0.001	-0.06	0.176	-0.18	0.011	-0.04	0.599	-0.12	0.207	-0.21	0.025
Glucocorticoid treatment	-0.29	<0.001	-0.07	0.095	-0.22	0.002	-0.13	0.057	-0.32	<0.001	-0.21	0.020
NSAID treatment[2]	-0.19	<0.001	-0.09	0.035	-0.32	<0.001	-0.08	0.272	-0.17	0.066	-0.17	0.068
Clinical (psychiatry)												
HADS -D	-0.32	<0.001	-0.60	<0.001	-0.37	<0.001	-0.66	<0.001	-0.43	<0.001	-0.77	<0.001
HADS -A	-0.18	<0.001	-0.62	<0.001	-0.28	<0.001	-0.61	<0.001	-0.37	<0.001	-0.77	<0.001
Antidepressant therapy	0.06	0.587	0.03	0.777	-0.19	0.006	0.02	0.284	-0.18	0.046	-0.12	0.177

1: anti-IL6 / bDMARDs / tsDMARDs with or without csDMARDs; 2: used in last ten days.

PCS physical component score; MCS mental component score; cDMARDs conventional disease-modifying antirheumatic drugs; anti-TNF anti-tumor necrosis factor; NSAID treatment non-steroidal anti-inflammatory drug treatment; DAS28-CRP disease activity score in 28 joints with c-reactive protein; DAPSA disease activity in psoriatic arthritis; ASDAS-CRP ankylosing spondylitis disease activity score with c-reactive protein; HADS-D hospital anxiety and depression scale – depression; HADS-A hospital anxiety and depression scale – anxiety.

As shown in Table 3, a worse physical component was associated, for all diagnostic groups, with being older, female, employed, with a higher disease activity, having been prescribed glucocorticoids, and having higher depressive and anxiety symptoms. Indeed, some characteristics were associated to a worse physical quality of life depending on a specific diagnosis: in detail, comorbidity, second-line therapy and NSAIDs (for RA and PsA), higher education (for RA and SpA), and antidepressant therapy (for PsA and SpA).

By considering the mental component of SF-36, a worse quality of life was associated, for all diagnostic groups, with a higher disease activity and more severe depressive and anxiety symptoms. Being female (for RA and PsA), with higher education, employed, taking a second line therapy, and having been prescribed glucocorticoids (for SpA) were characteristics associated to a worse quality of life for the specified diagnoses.

Significant at p<0.10, independent variables (socio-demographic and clinical characteristics) entered the multivariate linear regression model estimated for each diagnostic group, thus giving adjusted Beta coefficients, as presented in Table 4.

Table 4. Adjusted Beta coefficients between each summary measure of quality of life (PCS and MCS) as the dependent variable and socio-demographic and clinical characteristics as independent variables in RA, PsA and SpA (Multivariate linear regression models; only independent variables significantly associated at p<0.10 in univariate linear regression models entered the multivariate ones)

	Dependent variables											
Independent variables	**Rheumatoid arthritis**				**Psoriatic arthritis**				**Spondyloarthritis**			
	PCS		**MCS**		**PCS**		**MCS**		**PCS**		**MCS**	
	Coeff (p)	Partial η2	Coeff (p)	Partial η2	Coeff (p)	Partial η2	Coeff (p)	Partial η2	Coeff (p)	Partial η2	Coeff (p)	Partial η2
Socio-demographic												
Age	-0.08 (0.091)	0.006	-	-	-0.90 (0.152)	0.011	-	-	-0.09 (0.235)	0.013	-	-
Female	-0.07 (0.078)	0.006	0.03 (0.363)	0.002	-0.10 (0.058)	0.019	-0.03 (0.626)	0.001	-0.01 (0.887)	0.000	0.03 (0.584)	0.003
High education	0.02 (0.592)	0.001	-	-	-0.02 (0.682)	0.001	-	-	0.06 (0.421)	0.006	0.06 (0.279)	0.011
Employed	0.00 (0.860)	0.000	-	-	-0.00 (0.896)	0.000	-0.17 (0.002)	0.048	0.12 (0.130)	0.021	0.05 (0.411)	0.006
Clinical (rheumatology)												

DAS28-CRP	-0.29 (<0.001)	0.104	-0.10 (0.006)	0.016								
DAPSA					-0.44 (<0.001)	0.243	-0.06 (0.277)	0.006				
ASDAS-CRP									-0.51 (<0.001)	0.263	0.05 (0.491)	0.004
Disease duration (yrs.)	-0.10 (0.007)	0.015	-	-	-	-	-	-	-	-	-	-
Comorbidity	-0.12 (0.003)	0.018	-	-	-0.08 (0.119)	0.013	-	-	-	-	-	-
Pharmacological treatment Second-line therapy[1]	-0.10 (0.007)	0.015	-	-	-0.11 (0.028)	0.026	-	-	-	-	0.02 (0.723)	0.001
Glucocorticoid treatment	-0.15 (<0.001)	0.029	0.01 (0.735)	0.000	-0.12 (0.017)	0.031	-0.09 (0.097)	0.014	-0.06 (0.407)	0.006	-0.13 (0.828)	0.000
NSAID treatment[2]	-0.09 (0.019)	0.012	0.00 (0.988)	0.000	-0.20 (<0.001)	0.071	-	-	-0.04 (0.525)	0.004	-0.12 (0.035)	0.040
Clinical (psychiatry)												
HADS -D	-0.25 (<0.001)	0.045	-0.31 (<0.001)	0.076	-0.21 (0.006)	0.040	-0.43 (<0.001)	0.143	-0.19 (0.087)	0.027	-0.43 (<0.001)	0.176
HADS -A	0.06 (0.297)	0.002	-0.40 (<0.001)	0.121	0.01 (0.909)	0.000	-0.27 (<0.001)	0.066	0.08 (0.422)	0.006	-0.001 (<0.001)	0.183
Antidepressant therapy	-	-	-	-	-0.07 (0.164)	0.010	-	-	-0.05 (0.461)	0.005	-	-
Model η2	**0.347**		**0.443**		**0.528**		**0.499**		**0.536**		**0.695**	

1: (anti-IL6, bDMARDs, tsDMARDs) with or without csDMARDs; 2: used in last ten days. PCS physical component score; MCS mental component score; cDMARDs conventional disease-modifying antirheumatic drugs; anti-TNF anti-tumor necrosis factor; NSAID treatment non-steroidal anti-inflammatory drug treatment; DAS28-CRP disease activity score in 28 joints with c-reactive protein; DAPSA disease activity in psoriatic arthritis; ASDAS-CRP ankylosing spondylitis disease activity score with c-reactive protein; HADS-D hospital anxiety and depression scale – depression; HADS-A hospital anxiety and depression scale – anxiety.

A worse physical component remained associated, for all diagnostic groups, with a higher disease activity. By considering the specificity of each diagnosis, in the RA patients disease duration, the presence of comorbidity, having been prescribed a second-line therapy, glucocorticoids and NSAIDs, and declaring more severe depressive symptoms were further associated to a worse physical quality of life. In the PsA group, taking a second-line therapy, glucocorticoids and NSAIDs, and having a higher depression severity were all associated to a lower physical component score. No more characteristics, otherwise disease activity, were associated to a worse physical quality of life in the SpA cohort.

By considering the mental component, a worse quality of life was associated, for all diagnostic groups, with more severe depressive and anxiety symptoms. In the RA patients, a higher disease activity was associated to a lower score of MCS, in the PsA patients, employment was related to a lower MCS score, and in the SpA patients, NSAID treatment was negatively related to a score of MCS.

The proportion of the total variance in a dependent variable explained by the models ranged from $\eta2=0.347$ to $\eta2=0.536$ for the physical component and from $\eta2=0.443$ to $\eta2=0.695$ for the mental component. Considering partial eta squared, mainly disease activity in PCS models, and depression and anxiety in MCS models have medium or large effect size, while other variables have small effect size.

3.1.4 Discussion

To date, this is a study, performed in a large cohort of patients, comparing the impairment in health-related quality of life among rheumatoid arthritis, psoriatic arthritis and spondyloarthritis, and its specific associated socio-demographic and clinical characteristics. The first main finding is that the score on the physical component of quality of life is higher in SpA than in RA patients, while there are no differences in the mental component among the diagnostic groups. The second main finding is that a worse physical component is associated, for all diagnostic groups, with a higher disease activity while a worse mental component is with more severe depressive and anxiety symptoms.

In the current study, SpA patients when compared with RA patients had higher scores in physical quality of life (PCS), and in some domains as physical functioning and role limitation due to physical health. Previous findings are in line with these results (Salaffi et al., 2009; Chen et al., 2017; Ovayolu et al., 2011). Physical functioning and role limitation due to physical health in established rheumatic diseases are central outcomes (Kwan et al., 2017; Radner et al., 2011), their impairment is caused by inflammation and structural damage (Braun et al., 2021), as indicated by disease activity and disease duration (Radner et al., 2011). In the sample of the current study, RA patients had a lower disease activity than SpA patients, but significantly longer disease duration, older age, and more comorbidities, characteristics related to physical functioning (Radner et al., 2011; Dominick et al., 2004). In the present study, PsA patients were not significantly different in comparison with RA and SpA patients within domain of physical quality of life, thus reinforcing previous studies (Sokoll et al., 2001; Borman et al., 2007). Still, in one study quality of life was less reduced in PsA patients than in RA patients (Strand et al., 2012), while other studies found slight differences among the separate dimensions of physical quality of life (Husted et al., 2001; Michelsen et al., 2018). In the present study mental quality of life (MCS) did not differ among rheumatic diseases, as some authors conclude that adequate rheumatological care among rheumatic disease generates a similar impact on wellbeing (Chorus et al., 2003). That is in accordance with some previous studies (Landgren et al., 2023; Singh & Strand, 2009), while other studies found opposite results, where patients with RA had lower (Ovayolu et al., 2011) or higher (Chorus et al., 2003) MCS score in comparison with PsA and SpA. In the present study RA patients had lower mental health, a dimension of MCS, compared to SpA, while PsA did not significantly differ from the other two clinical groups. The reduced dimension of mental health in rheumatic disease can be caused by emotional problems and fatigue (Landgren et al., 2023), but the clinical groups of the current study did not differ in respecting psychological distress, and comparison of fatigue was not included in the study. Finally, comparing impairment of quality of life among chronic rheumatic diseases in our study is noteworthy, presenting practical everyday problems of physical and emotional functioning in rheumatic patients and revealing the particularity of each clinical group. In the present study, results suggest that physical quality of life (PCS) primarily correlates with rheumatological characteristics, where disease activity stands out as the only variable significantly related to PCS among all the groups, and with a large effect size across the models. Other variables significantly associated with worse PCS have small or medium effect size, and those variables are second-line therapy, glucocorticoids, NSAIDs, and depression both in RA and PsA, and disease duration and comorbidity only in RA. In the current study disease activity scores had different distributions among rheumatic diseases, while most of the RA patients and half of the PsA patients were in remission or with low disease activity, SpA patients predominantly had high or very high disease activity. Groups also had different age and gender distribution, and different disease duration, which makes the comparison of their disease activity challenging. Nevertheless, disease activity across inflammatory rheumatic diseases was invariably negatively associated with physical component, as previously confirmed (Moraes et al., 2021; Englbrecht et al., 2013; Kotsis et al., 2014). The disease activity score is mainly used as a clinical marker in clinical practice, through which the improvement is monitored. Thus, it is intuitive that patients with lower disease activity had higher quality of life, because having a more controlled form of the disease they are more able to carry out daily activities. Swelling and the progressive destruction of the joints are one of the main hallmarks of inflammatory rheumatic diseases and can have a substantial negative impact on physical function, activity limitation, and bodily pain - dimensions of physical quality of life (FitzGerald et al., 2021; Singh et al., 2009; Sparks et al., 2019). Additionally, the worse clinical status was found associated with a loss of work productivity (Ramonda et al., 2016; de Hooge et al., 2016) and reduced social activities (Moraes et al., 2021), which justified the negative impact on quality of life. The practical implication is that with the control of the illness, over the correct approach, such as early diagnosis, effective and appropriate treatment, and involvement of a multidisciplinary health team, physical quality of life of patients will improve.

It was also found that RA and PsA patients who were taking second-line therapy, glucocorticoids, or NSAIDs had worse physical quality of life. Since in the sample of the current study second-line therapy was prescribed when patients did not respond to first-line therapy, it implies an uncontrolled form of the disease, the disappointment of not achieving the remission, increased necessity, and concern beliefs toward medication (Tosato et al., 2022), and in those difficult circumstances, lower quality of life is expected. This is in contrast with recent reports of improvement in quality of life even with multiple rheumatological treatment failures (Gerhold et al., 2015) and that this effect has been maintained over time (Keystone et al., 2017). Their longitudinal study design gives them more reasons to conclude correctly in comparison with the cross-sectional design of the present study. Few studies found that the association between therapy and quality of life could be mediated by disease activity, disease duration (Overman et al., 2014), or comorbidities (Danve & Deodhar, 2022), and in the present study patients had long disease duration and comorbidities, that possibly decreased therapy effect on quality of life.

Contrary to PCS, multivariate models of MCS in the present study were poorly explained by rheumatological variables, demonstrating the advantage of separately understanding and approaching the physical and mental quality of life. The worse MCS among rheumatic diseases was principally correlated with symptoms of depression and anxiety, and their effect size in the models is large or medium. Employment, disease activity, and NSAID treatment are variables associated with the worse MCS in some of the models, but the effect size was small. Several studies in RA, PsA, and SpA pointed out the contribution of depression and anxiety in the explanation of poorer mental (Isnardi et al., 2021; Hakkou et al., 2011), or both mental and physical quality of life (Kotsis et al., 2012; Xu et al., 2016), and association could be bidirectional (Seifert & Baerwald, 2019). The detrimental effect of chronic illness is often followed by depressive and anxiety symptoms, its prevalence is steadily confirmed in rheumatic disease (Kotsis et al., 2012; Xu et al., 2016), and present finding of the association between psychological distress and mental quality of life points to the necessity of intervention for these treatable outcomes. It encourages physicians to incorporate an assessment of depressive and anxiety symptoms into their clinical practice and to include mental health professionals in the management of the disease. Eventually, exploration of variables related to physical and mental quality of life in rheumatic diseases is applicable because accurate identification of correlates of worse HRQoL may guide clinical practice and the understanding of the key drivers of RA, PsA and SpA disease burden (Carvalho et al., 2022).

Discussing quality of life, it should be taken into account that in the present study clinical groups were significantly different regarding socio-demographic characteristics, such as age, gender, marital status, educational level, and employment. Considering the literature, it was expected that older (Alsaleh et al., 2022; Dominick et al., 2004), female (Matcham et al., 2014; Tarannum et al., 2022; Webers et al., 2016), low-educated (Kiltz et al., 2009), and unemployed (Ramonda et al., 2016) patients have a worse quality of life. Among socio-demographic variables in the current study, only employment was significantly negatively related to mental quality of life in PsA, but with a small effect size. Employment declined with disease duration in rheumatic disease (Kiltz et al., 2009) and in the present sample, PsA and SpA had significantly lower disease duration and more employed patients than RA patients. The fact that employed PsA patients had lower mental quality of life could be explained by reduced work productivity (Ramonda et al., 2016) experiencing considerable difficulties in carrying out their jobs because of the disease. Still, employment is an advantage for the patient, contributes to autonomy and self-esteem, gives the sense of accomplishing the social role, and mitigates the financial burden of chronic disease (De Craemer et al., 2023), so it stayed unclear why it did not have a positive impact on quality of life.

The present study has some strengths. First, the sample consisted of a large cohort of patients affected by the three most frequent inflammatory rheumatic diseases, recruited from the clinical practice setting. Patients were consecutively recruited, thus minimizing a possible selection bias. Second, patients were stable and without changes in prescribed pharmacotherapy in the last three months, so the association between treatment and quality of life was not influenced by intensive changes. Third, in all the sample assessment of the quality of life was done with the same validated questionnaire, and it allowed comparing absolutely the same concepts across diseases. The subjective quality of life was examined because it is the perceived impact of disease on a patient's life satisfaction. Fourth, the analysis included most of the basic clinical variables essential for clinical practice, which is reflected in effect size among the models (0.347 – 0.695).

The study has also some limitations. The main limitation of the study was the cross-sectional design, which permitted only to explore the association between a set of characteristics and the health-related quality of life. Longitudinal study would reveal the direction of influence between quality of life and clinical variables, and a better understanding of the causal relationships would lead to more precise practical implications. Second, even if the explained proportion of variance in models of quality of life among diseases was high, there must be additional significant factors that could be added as independent variables. It would be advantageous to include in the model fatigue, pain, disability, work productivity, or an extended range of data about disease progression, which would improve the explanation of quality of life. Third, the comorbidity index was not evaluated, not permitting comparison among different diseases and related disabilities. With it, the present study would benefit from the exploration of the influence of different comorbidities on quality of life.

In conclusion, the current study indicates that quality of life in RA, PsA and SpA, even with underlined differences, could be considered as similar in a wider perspective of disease outcomes. Health-related quality of life is an important and complex outcome in inflammatory rheumatic diseases and comparison among RA, PsA and SpA could reveal consequences of disease burden useful for clinical practice. Further studies should focus on the association between disease activity and quality of life, to develop a better understanding of that interaction and to base treatment strategies on it. In general, following the predictors of quality of life in early diagnosis patients would guide the development of interventions to improve quality of life among rheumatic diseases.

3.2 FATIGUE'S ROLE IN QUALITY OF LIFE AMONG RHEUMATIC DISEASES

This subchapter presents the article for which I am the first author, currently under peer review in the *Journal of Behavioral Medicine*, titled "*Examining fatigue as a factor linking rheumatic diseases to health-related quality of life: A mediation-moderation analysis*."

This subchapter contains *Supplementary material*, which can be found in Appendix C.

3.2.1 Introduction

Rheumatic diseases are chronic, inflammatory, autoimmune conditions that primarily affect the musculoskeletal system but may also involve other tissues and internal organs. The most prevalent forms include rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA) (Smolen et al., 2018; Ristic et al., 2023). These conditions impose a substantial burden on individuals and society, contributing to progressive disability, reduced work capacity, premature mortality, and considerable socioeconomic costs (Smolen et al., 2016).

Compared with the general population, patients with rheumatic diseases experience marked impairments in both physical and mental health-related quality of life (HRQoL). Rheumatic diseases typically have a greater impact on physical HRQoL than mental well-being, primarily affecting physical functioning, limitations due to physical function, and bodily pain (Salaffi et al., 2009; Matcham et al., 2014). Disease activity has a particularly pronounced impact, being a powerful predictor of HRQoL both in RA and axSpA (Matcham et al., 2014; Smolen et al., 2018; Kotsis et al., 2014; Ma et al., 2025). Modeling approaches further suggest that disease activity indirectly affects HRQoL via functional limitations (Shen et al., 2021).

Fatigue is one of the most common and debilitating symptoms of rheumatic diseases. It is strongly associated with disease-related and psychological factors, including psychological distress, coping, and common mental disorders (Matcham et al., 2015). The relationship between fatigue and disease activity is complex and varies across disease stages (Davies et al., 2021; Shen et al., 2021). Multidimensional models in RA indicate that disease activity influences fatigue both directly and indirectly through mood disturbance (Nicassio et al., 2012). In RA, PsA and axSpA, there is the consistent finding that higher levels of fatigue are strongly correlated with higher levels of disease activity, poorer HRQoL and worse overall health status (Stebbings et al., 2014; Gado et al., 2021; Cross et al., 2008).

HRQoL in rheumatic diseases is also shaped by sex, treatment, and comorbidities. Women typically report greater disease activity, poorer physical and mental HRQoL, and higher rates of fatigue and anxiety compared with men, highlighting the importance of sex differences in disease outcomes (Ristic et al., 2025). in RA, anti-TNF-α therapy substantially reduces fatigue, with improvements predicted by baseline quality-of-life measures, whereas in PsA, biological disease-modifying antirheumatic drugs demonstrate only limited effects on fatigue (Druce et al., 2015; Reygaerts et al., 2018). Comorbidities, present in up to 90% of patients (Ristic et al., 2023), further impair HRQoL by increasing disease activity, functional limitations, and mortality (Zhao et al., 2020; Azevedo et al., 2019; Salaffi et al., 2009). While physical health is consistently affected, mental health outcomes appear less sensitive to comorbidity burden (Radner et al., 2011). Depression, however, is the only comorbidity consistently and independently associated with fatigue and poorer HRQoL in RA (Pollard et al., 2006).

The HRQoL framework developed by Ferrans and colleagues provides a comprehensive theoretical basis for understanding these relationships (Ferrans et al., 2005; Bakas et al., 2012). In this model, biological functioning influences symptoms, which in turn affect functional status and general health, ultimately shaping overall HRQoL conceptualized as subjective well-being. Individual and environmental characteristics can further modify each stage of this pathway. Within this framework, disease activity and comorbidities represent biological functioning, fatigue is conceptualized as a symptom, treatment is linked to symptom management, and sex is classified as an individual characteristic (Ferrans et al., 2005; Kanters et al., 2015).

To our knowledge, no study has yet examined fatigue as a mediator between disease activity and quality of life in RA, PsA, and axSpA; only one comparable study has addressed this question in systemic lupus erythematosus (Thibault et al., 2023). Guided by Ferrans' model, the present study therefore aims (1) to test whether fatigue mediates the relationship between disease activity and HRQoL, (2) to investigate whether sex and rheumatological treatment moderate this mediation model, and (3) to explore comorbidity as a covariate within the model.

3.2.2 Materials and methods

Clinical Sample

In this cross-sectional study, eligible participants were adults (≥18 years) diagnosed with rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis, according to

ACR/EULAR (Kay and Upchurch, 2012), CASPAR, or ASAS criteria (Rudwaleit et al., 2010), respectively. Recruitment occurred sequentially during routine outpatient visits at the Rheumatology Unit, University Hospital of Verona, Italy over one year. All patients were assessed once clinically stable and after obtaining written informed consent. Exclusion criteria included fibromyalgia, connective tissue diseases (e.g., systemic lupus erythematosus, Sjögren's syndrome, scleroderma, dermatomyositis, polymyositis), vasculitis, gout, infectious arthritis, polymyalgia rheumatica, or other severe systemic diseases (Pezzato et al., 2021). The study followed the Declaration of Helsinki (World Medical Association, 2013) and received ethics approval from the Committee of Verona and Rovigo (CESC15840).

Measurements

Socio-demographic and clinical data were obtained with questionnaires and/or standardized instruments.

Disease activity was assessed using validated, disease-specific instruments. For rheumatoid arthritis, we used the Disease Activity Score in 28 joints with C-Reactive Protein (DAS28-CRP), which includes the tender and swollen joint count, C-reactive protein (CRP) level, and patient global health assessment measured on a visual analog scale. Psoriatic arthritis was evaluated with the Disease Activity in PSoriatic Arthritis (DAPSA) score, which incorporates the tender joint count, swollen joint count, CRP level, and patient assessment of disease activity and pain. Axial spondyloarthritis was measured with the Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP), which includes back pain, duration of morning stiffness, patient global assessment of disease activity, peripheral pain/swelling, and CRP level.

Health-related quality of life was assessed with the self-reported Medical Outcomes Study 36-item Short Form Survey (SF-36; Italian version) (Apolone and Mosconi, 1998). It is a commonly used instrument in research and clinical practice in rheumatic diseases (Matcham et al., 2014). The SF-36 comprises 36 items covering eight dimensions, categorized into physical or mental quality of life, which are further summarized into two component scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The mental quality of life domains includes vitality, social functioning, role limitations due to emotional problems, and mental health, reflecting energy level, emotional stability, and social functioning. To avoid redundancy, since these domains overlap with fatigue (Hewlett et al., 2011), we excluded the mental quality of life domains and MCS score from the analysis. The physical quality of life includes physical functioning (PF), role limitations due to physical health (RP), bodily pain (BP), and general health (GH). We included both the physical quality of life domains and the PCS score in our analyses. Lower scores on each dimension and on the summary scores indicate worse HRQoL, whereas higher scores indicate better HRQoL (Ware, 2000).

Fatigue was measured with the Chalder Fatigue Questionnaire (CFQ), a self-administered tool assessing fatigue severity over the past month. It captures both physical and mental fatigue, combined into a global score. The CFQ consists of 11 items rated on a 4-point scale, recoded using a binary method (0, 0, 1, 1), yielding a total score from 0 to 11, with higher scores indicating greater fatigue. The CFQ has demonstrated validity and reliability in patients with rheumatic diseases (Chalder et al., 1993; Hewlett et al., 2011).

Comorbidities were assessed with the Rheumatic Disease Comorbidity Index (RDCI), a validated tool measuring the burden of comorbid conditions and their association with long-term health outcomes in patients with rheumatic diseases. The RDCI is predictive of functional status and mortality and performs well with both self-report and administrative data. Scores (range 0-9) were calculated using the original formula: 2 × lung disease + [2 × (heart attack, other cardiovascular disease, or stroke) or 1 × hypertension] + fracture + depression + diabetes + cancer + (ulcer or stomach symptom) (England et al., 2015; Dolomisiewicz et al., 2023).

Data on rheumatological treatment were also collected. Treatments were categorized as: first-line therapy [conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and/or anti-TNF (anti–tumor necrosis factor drugs)] and second-line therapy [biological disease-modifying antirheumatic drugs (bDMARDs) and, targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) with or without csDMARDs] (see Tosato et al., 2022 for details).

Statistical analysis

Demographic and clinical characteristics of participants were given as frequency distributions (%) for categorical variables, and as mean values with standard deviations (SD) for continuous variables. Comparisons between independent groups were carried out using the t-test (2 groups) for continuous variables. All tests were two-tailed, with statistical significance set at $p<0.05$. Descriptives and tests were conducted using Jamovi version 2.6.26 for Windows.

Mediation analysis

Mediation analysis was conducted to examine whether the total effect (path c) of a given disease activity (DAS28-CRP, DAPSA and ASDAS-CRP) on physical quality of life dimensions (PCS, PF, RP, BP, GH), if statistically significant ($p<0.05$), was mediated by fatigue. The total effect (c) comprises both the direct effect of disease activity on physical quality of life (path c') and the indirect effects through the mediator path a*b for fatigue. Mediation was classified as partial if c' decreased but remained significant, and as full (or total) if c' was no longer statistically significant (Preacher and Hayes, 2008). The conceptual structure of this mediation model is presented in Figure 1A.

Conditional mediation analysis

To explore potential moderating effects, interactions between participant characteristic (sex and rheumatological treatment) and each path of the mediation model (a, b, c') were first tested. It was retained only moderator which reached the statistical significance ($p<0.05$) in at least one path (Preacher and Hayes, 2008). The variable was then incorporated into conditional mediation models. The conceptual framework of this approach is presented in Figure 1B.

Covariance structure analysis

To assess a potential covariation effect, the comorbidity index (RDCI) was added to the model as a second independent variable. We examined whether the total effect (path

c) of comorbidity (RDCI) on physical quality of life dimensions (PCS, PF, RP, BP, and GH), if statistically significant ($p<0.05$), was mediated by fatigue. Specifically, we evaluated whether comorbidity contributed to a covariation effect within the mediation model. The conceptual structure of this covariation analysis is illustrated in Figure 1C.

Bootstrapping procedure

Bias-corrected bootstrapping with 5,000 replications was used to estimate 95% confidence intervals for all path coefficients. Mediation, moderation, conditional mediation and covariance analyses were performed using Jamovi version 2.6.26 for Windows (GLM Mediation Model, jamm module).

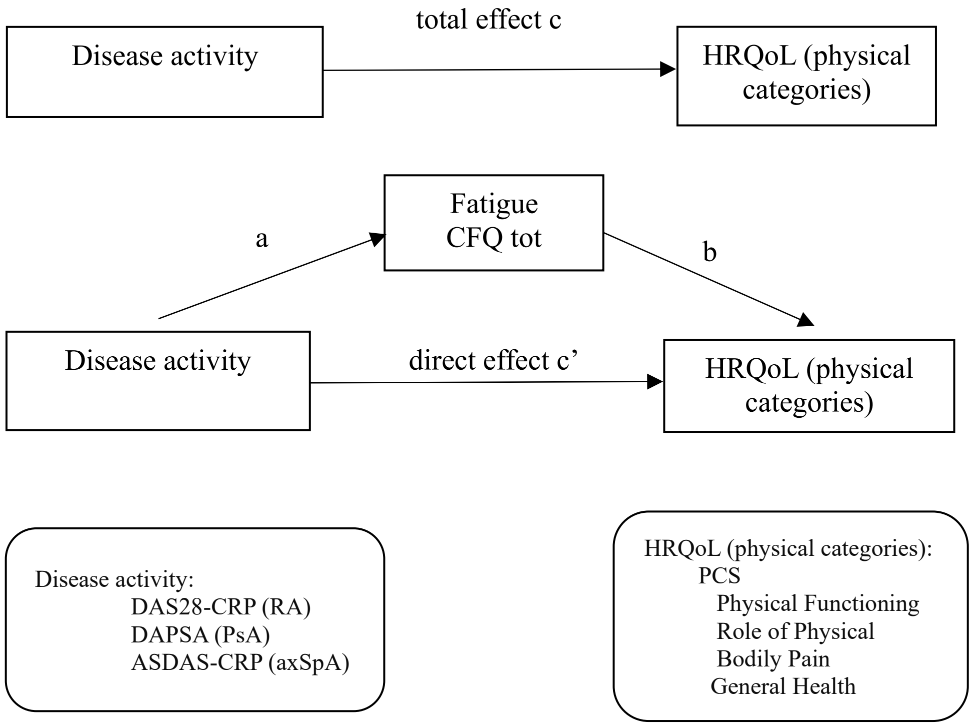


Fig. 1a Conceptual framework: the mediation of fatigue on the relationship between disease activity and categories of physical quality of life. RA rheumatoid arthritis, PsA psoriatic arthritis, axSpA axial spondyloarthritis, DAS28-CRP disease activity score in 28 joints with C-reactive protein, DAPSA disease activity in psoriatic arthritis, ASDAS-CRP ankylosing spondylitis disease activity score with C-reactive protein, CFQ chalder fatigue questionnaire, HRQoL health-related quality of life, PCS physical component summary.

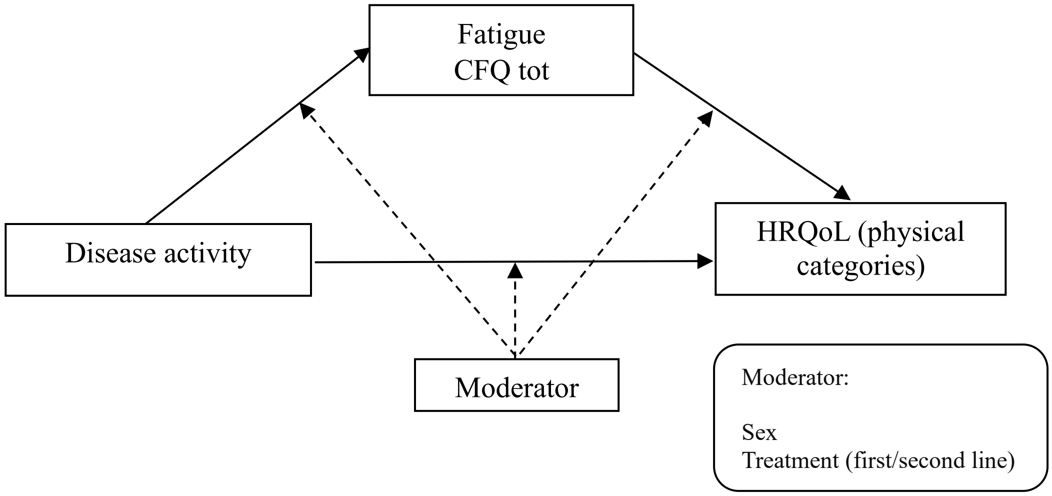


Fig. 1b Conceptual framework: conditional mediation by the potential moderator on the paths. CFQ chalder fatigue questionnaire, HRQoL health-related quality of life.

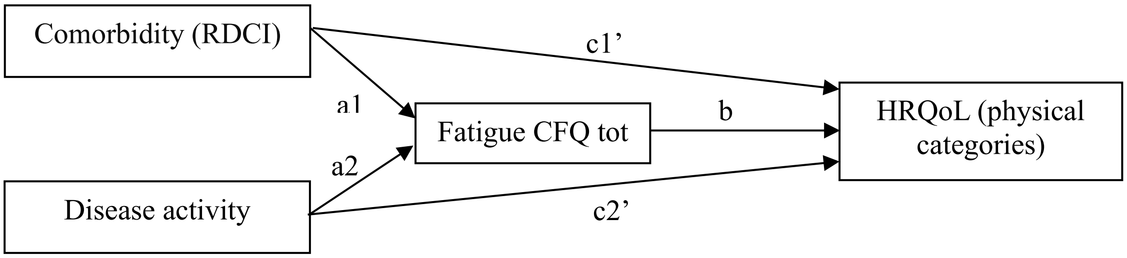


Fig. 1c Conceptual framework: Covariation effect of comorbidity. RDCI rheumatic disease comorbidity index, CFQ chalder fatigue questionnaire, HRQoL health-related quality of life.

3.3.3 Results

Sample characteristics

A total of 807 patients were enrolled in the study. The sample was predominantly constituted by females (N=570, 70.6%) and had a mean age of 57.3 years (SD=12.5). Most participants were married (N=593, 73.5%), while more than half reported a low level of education and were unemployed. In terms of clinical characteristics, rheumatoid arthritis was the most common diagnosis (60.7%), followed by psoriatic arthritis (24.5%) and axial spondyloarthritis (14.7%). Average disease activity scores were 2.8 (SD=1.0) for RA, 15.1 (SD=8.7) for PsA, and 2.5 (SD=1.1) for axSpA. The mean comorbidity score, based on the RDCI, was 1.8 (SD=1.5). Fatigue levels, assessed using the CFQ, showed a mean value of 4.3 (SD=4.2). With respect to treatment, the majority of patients (N=626, 77.6%) were receiving first-line therapy, while the remaining 181 participants (22.4%) were undergoing second-line treatment (see Table 1).

Table 1 - Socio-demographic and clinical characteristics of patients (n=807).

Socio-demographic characteristics	Total sample N=807
Age (yrs), mean (sd)	57.3 (12.5)
Female, n (%)	570 (70.6%)
Married, n (%)	593 (73.5%)
Low education, n (%)	447 (55.4%)
Employed, n (%)	422 (52.3%)
Clinical characteristics	
Diagnosis, n (%)	
Rheumatoid arthritis	490 (60.7%)
Psoriatic arthritis	198 (24.5%)
Axial Spondyloarthritis	119 (14.7%)
Disease activity, mean (sd)	
Rheumatoid arthritis[1]	2.8 (1.0)
Psoriatic arthritis[2]	15.1 (8.7)
Axial Spondyloarthritis[3]	2.5 (1.1)
Comorbidity (RDCI), mean (sd)	1.8 (1.5)
CFQ score, mean (sd)	4.3 (4.2)
Rheumatological treatment, n (%)	
First-line treatment[4]	626 (77.6%)
Second-line treatment[5]	181 (22.4%)

[1]DAS28-CRP Disease Activity Score in 28 joints with C-Reactive Protein. [2]DAPSA Disease Activity in Psoriatic Arthritis. [3]ASDAS-CRP Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein. [4] csDMARDs and/or anti-TNF; [5] anti-IL6 / bDMARDs / tsDMARDs with or without csDMARDs; RDCI Rheumatic Disease Comorbidity Index; CFQ Chalder Fatigue Questionnaire.

Mediation analysis

The total effect of the disease activity of each rheumatic disease (rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis), as an independent variable (IV), on each of the dimensions of physical quality of life (physical component summary, physical functioning, role limitations due to physical health, bodily pain and general health), as a dependent variable (DV), was statistically significant (p<0.001). When considering the physical component summary as the DV, the total effect of disease activity (as IV) was -4.08 [-4.87 to -3.29] for rheumatoid arthritis (DAS28-CRP), -0.69 [-0.82 to -0.56] for psoriatic arthritis (DAPSA), and -6.33 [-7.56 to -5.10] for axial spondyloarthritis.

The significant associations between IVs and DVs justified conducting mediation analyses for each of the fifteen combinations (three diseases × five quality-of-life domains), with fatigue total score as the mediator (M). In all models, the indirect effect (a: disease activity → fatigue; b: fatigue → quality of life) was statistically significant (p<0.001). However, the direct effect of disease activity on quality of life also remained significant, indicating that fatigue acted as a partial mediator. In other words, the impact of disease activity on quality of life was partly explained by fatigue, but a direct effect persisted.

The percentages of total mediated effect varied between 13.3% and 40.5%. The highest proportion of explained variance for each disease was observed in models where role limitations due to physical health served as the dependent variable: 40.5% for rheumatoid arthritis, 30.7% for psoriatic arthritis, and 30.7% for axial spondyloarthritis (see Table 2).

Tble 2 Effect of disease activity in rheumatoid arthritis[1], psoriatic arthritis[2] and axial spondyloarthritis[3] on different dimensions of physical quality of life through fatigue[4] score as a mediator [Estimate [95% CI]].

Disease activity (IV)	**Dimensions of Physical Quality of Life** (DV)	**Fatigue** (M)	**Indirect effect** (IV ⇒ M ⇒ DV)	**Component a** (IV ⇒ M)	**Component b** (M ⇒ DV)	**Direct effect** c' (IV ⇒ DV)	**Total effect** c (IV ⇒ DV)	**% total mediated effect**
DAS28-CRP	**PCS**	CFQ	-0.92 *** [-1.29 to -0.56]	0.99 *** [0.66 to 1.33]	-0.93 *** [-1.12 to -0.74],	-3.16 *** [-3.90 to -2.41]	-4.08 *** [-4.87 to -3.29]	22.6%
DAS28-CRP	PF	CFQ	-2.11 *** [-2.10 to -1.22]	0.99 *** [0.66 to 1.33]	-2.12 *** [-2.65 to -1.59]	-6.85 *** [-8.93 to -4.78]	-8.96 *** [-11.10 to -6.83]	23.5%
DAS28-CRP	RP	CFQ	-4.24 *** [-5.88 to -2.60]	0.99 *** [0.66 to 1.33]	-4.26 *** [-5.06 to -4.47]	-6.21 *** [-9.33 to -3.08]	-10.45 *** [-13.80 to -7.10]	40.5%
DAS28-CRP	BP	CFQ	-2.24 *** [-3.10 to -1.38]	0.99 *** [0.66 to 1.33]	-2.25 *** [-2.66 to -1.84]	-9.08 *** [-10.70 to -7.47]	-11.32 *** [-13.06 to -9.58]	19.7%
DAS28-CRP	GH	CFQ	-1.55 *** [-2.21 to -0.89]	0.99 *** [0.66 to 1.33]	-1.56 *** [-1.96 to -1.16]	-3.97 *** [-5.55 to -2.39]	-5.52 *** [-7.13 to -3.90]	28.0%
DAPSA	**PCS**	CFQ	-0.13 *** [-0.20 to -0.06]	0.18 *** [0.11 to 0.24]	-0.74 *** [-0.99 to -0.49]	-0.56 *** [-0.69 to -0.43]	-0.69 *** [-0.82 to -0.56]	18.9%
DAPSA	PF	CFQ	-0.32 *** [-0.49 to -0.15]	0.18 *** [0.11 to 0.24]	-1.82 *** [-2.50 to -1.13]	-1.34 *** [-1.68 to -0.99]	-1.65 *** [-1.20 to -1.31]	19.3%
DAPSA	RP	CFQ	-0.72 *** [-1.06 to -0.39]	0.18 *** [0.11 to 0.24]	-4.12 *** [-5.25 to -2.99]	-1.63 *** [-2.2 to -1.07]	-2.36 *** [-2.95 to -1.76]	30.7%
DAPSA	BP	CFQ	-0.32 *** [-0.47 to -0.17]	0.18 *** [0.11 to 0.24]	-1.81 *** [-2.33 to -1.29]	-1.13 *** [-1.39 to -0.87]	-1.45 *** [-1.72 to -1.18]	21.9%
DAPSA	GH	CFQ	-0.22 *** [-0.36 to -0.07]	0.18 *** [0.11 to 0.24]	-1.25 *** [-1.91 to -0.60]	-0.60 *** [-0.93 to -0.27]	-0.82 *** [-1.14 to -0.50]	26.8%
ASDAS-CRP	**PCS**	CFQ	-0.90 ** [-1.53 to -0.26]	1.47 *** [0.87 to 2.08]	-0.61 *** [-0.96 to -0.26]	-5.44 *** [-6.72 to -4.15],	-6.33 *** [-7.56 to -5.10], 0.63	14.1%

ASDAS-CRP	PF	CFQ	-1.97 * [-3.65 to -0.28]	1.47 *** [0.87 to 2.08]	-1.33 ** [-2.34 to -0.33]	-12.00 *** [-15.68 to -8.32]	-13.96 *** [-17.44 to -10.49]	14.0%
ASDAS-CRP	RP	CFQ	-5.56 *** [-8.76 to -2.37]	1.47 *** [0.87 to 2.08]	-3.77 *** [-5.30 to -2.25]	-12.50 *** [-18.08 to -6.91]	-18.06 *** [-23.68 to -12.44]	30.7%
ASDAS-CRP	BP	CFQ	-2.13 ** [-3.50 to -0.75]	1.47 *** [0.87 to 2.08]	-1.44 *** [-2.16 to -0.72]	-13.78 *** [-16.42 to -11.14]	-15.90 *** [-18.48 to -13.33]	13.3%
ASDAS-CRP	GH	CFQ	-2.53 ** [-4.14 to -0.93]	1.47 *** [0.87 to 2.08]	-1.72 *** [-2.55 to -0.89]	-7.14 *** [-10.19 to -4.10]	-9.68 *** [-12.66 to -6.69]	26.1%

*p<0.05; **p<0.01; ***p<0.001; CI 95% confidence interval computed with 5000 times bias-corrected bootstrap, SE standard error, 1 DAS28-CRP disease activity score in 28 joints with C-reactive protein, 2 DAPSA disease activity in psoriatic arthritis, 3 ASDAS-CRP ankylosing spondylitis disease activity score with C-reactive protein, 4 CFQ chalder fatigue questionnaire, IV independent variable, DV dependent variable, M mediatior, PCS physical component summary, PF physical functioning, RP role of physical, BP bodily pain, GH general health.

Conditional mediation analysis

The moderation analysis examined the effects of sex and rheumatological treatment on each path of the mediation models, with disease activity scores as IV, physical quality of life dimensions as DV and fatigue as M. Results indicated that sex did not moderate any of the mediation pathways (all p>0.05; data available upon request). In contrast, rheumatological treatment (first-line vs. second-line) significantly moderated the direct effect in one model (p<0.05; see Table 3A; Appendix C1).

Table 3A: Moderation effects (interactions) of treatment (first-line treatment, second-line treatment) on paths in psoriatic arthritis

Interaction	**Estimate**	**95% CI**
DAPSA*Treatment (first vs second) ⇒ Fatigue	-0.04	-0.20 to 0.11
DAPSA*Treatment (first vs second) ⇒ Bodily Pain	0.65 *	0.07 to 1.23
Fatigue*Treatment (first vs second) ⇒ Bodily Pain	-0.47	-1.50 to 0.55

*p<0.05; **p<0.01; ***p<0.001. CI 95%: confidence interval computed with 5000 times bias-corrected bootstrap, DAPSA disease activity in psoriatic arthritis.

Specifically, when considering disease activity in psoriatic arthritis (DAPSA) as a predictor of bodily pain, the strength of the direct effect varied by treatment group. For patients receiving first-line treatment, the estimated path c' was -1.48 [95% CI (-1.64, -1.31), p<0.001], whereas for those on second-line treatment, the estimate was -1.04 [95% CI (-1.28, -0.80), p<0.001] (see Table 3B; Appendix C2).

Table 3B: Conditional mediation for treatment in psoriatic arthritis

	Effect	**First-line treatment**		**Second-line treatment**	
		Estimate	**95% CI**	**Estimate**	**95% CI**
DAPSA ⇒ Fatigue ⇒ Bodily Pain	Indirect	-0.30 ***	-0.39 to -0.22	-0.23 ***	-0.35 to -0.10
DAPSA ⇒ Fatigue	Component (a)	0.16 ***	0.13 to 0.20	0.15 ***	0.08 to 0.21
Fatigue ⇒ Bodily Pain	Component (b)	-1.86 ***	-2.20 to -1.52	-1.59 ***	-2.12 to -1.06
DAPSA ⇒ Bodily Pain	Direct	-1.48 ***	-1.64 to -1.31	-1.04 ***	-1.28 to -0.80
DAPSA ⇒ Bodily Pain	Total	-1.78 ***	-1.95 to -1.61	-1.27 ***	-1.52 to -1.02

*p<0.05; **p<0.01; ***p<0.001. CI 95%: confidence interval computed with 5000 times bias-corrected bootstrap; DAPSA disease activity in psoriatic arthritis.

The graphical representation of the interaction between DAPSA and rheumatological treatment in predicting bodily pain shows that the slope is steeper for first-line treatment. This indicates that lower disease activity in patients receiving first-line treatment has a stronger impact on reducing bodily pain (increasing the score, since higher scores represent no pain), given the inverse relationship between DAPSA and bodily pain (see Figure 2).

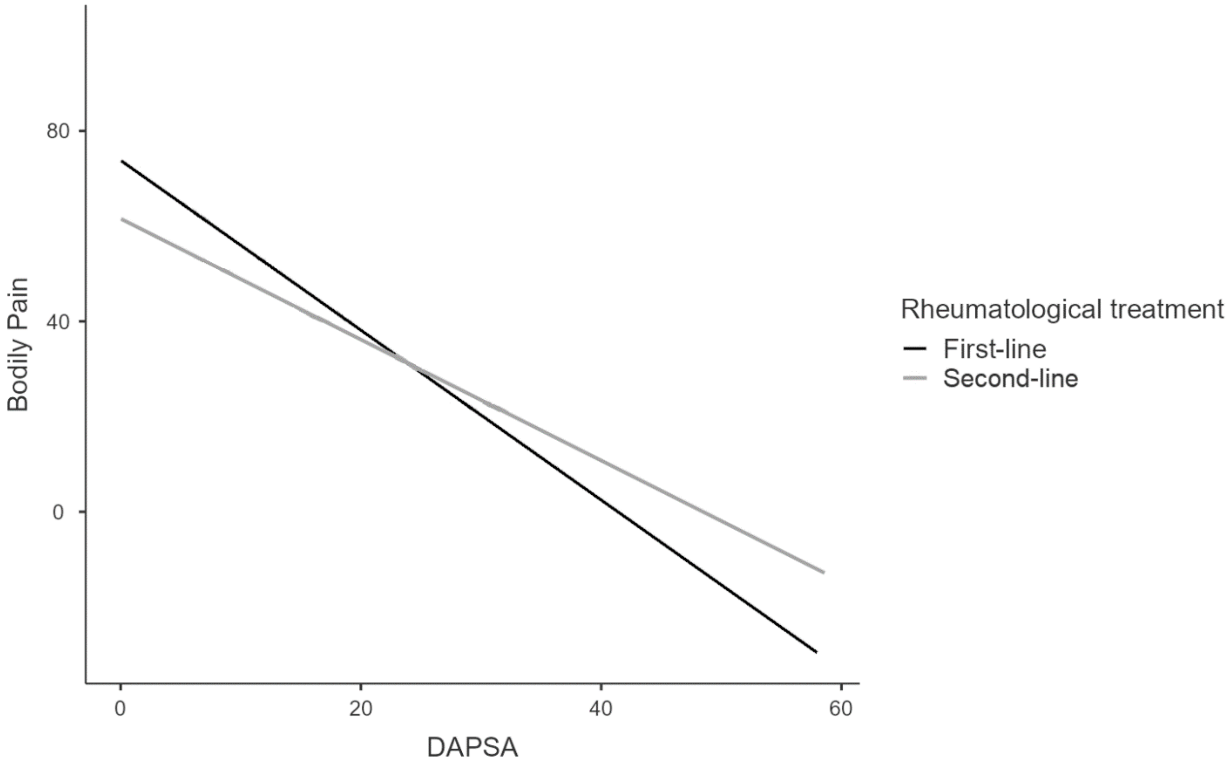


Fig. 2 Moderating influence of rheumatological treatment on the effect of DAPSA on Bodily Pain in psoriatic arthritis. DAPSA disease activity in psoriatic arthritis, first-line: conventional synthetic disease-modifying antirheumatic drugs and/or anti-TNF, second-line therapy: biological disease-modifying antirheumatic drugs and, targeted synthetic disease-modifying antirheumatic drugs with or without csDMARDs.

Covariance structure analysis

When comorbidity (RDCI) was included as a covariate in the mediation models, it demonstrated a statistically significant total effect on several dimensions of physical quality of life across models for all three disease activity scores. However, in all models where this total effect was significant, comorbidity was not associated with fatigue (p>0.05) - no indirect effect through fatigue was observed. Thus, suggesting that comorbidity did not act as a covariate in the proposed mediation framework (data available upon request).

3.2.4 Discussion

In the present study, three principal findings are reported. First, in rheumatic diseases, disease activity was associated with both all physical domains and the physical component summary of health-related quality of life, with fatigue mediating this relationship. Second, this mediation model was moderated by rheumatological treatment, altering the association between disease activity and bodily pain, the HRQoL domain, in patients with psoriatic arthritis. Third, neither sex, serving as a moderator, nor comorbidity, included as a covariate, exerted a significant influence on the mediation pathways.

First main finding considers the mediation models, results were consistent across rheumatic diseases, but the mediating effect of fatigue on the association between disease activity and HRQoL domains varied depending on the specific domain. The strongest mediated effect of fatigue was observed in the Role-Physical domain, which evaluates problems with work or daily activities due to physical health (Ware, 2000). Rheumatic diseases are among the leading causes of work-related health problems in Europe (Bevan, 2015; McCormack et al., 2018). Non-remission levels of disease activity are strongly associated with work and activity impairment, highlighting the importance of remission for maintaining work performance and activity (Kim et al., 2017). Fatigue has been shown to independently affect absenteeism and presenteeism at work, productivity loss, and activity impairment in RA and SpA (Druce et al., 2018). In RA, fatigue has been reported to affect multiple aspects of work performance, leading to difficulties at work and limited understanding from colleagues and employers (Connolly et al., 2015). Taken together, our findings suggest that subjective perceptions of physical health related to work are negatively influenced by disease activity, largely explained by fatigue, which accounts for up to 40% of this relationship.

In models with General Health (a HRQoL domain) as the dependent variable, reflecting self-evaluations of health as poor and likely to deteriorate (Ware, 2000), fatigue showed a substantial mediation effect across all three diseases. This aligns with prior theoretical models of chronic symptoms, which highlight the key role of expectations and beliefs about disease-related symptoms in chronic somatic conditions (Nadinda et al., 2024). Illness perceptions encompass beliefs about how the disease affects the body, life activities and experiences. In RA, negative illness representations are associated with greater symptom burden, stronger perceptions of consequences and chronicity, and reduced perceived control (Norton et al., 2014). Thus, our results show that general health perception is influenced not only by disease activity but also by disease-related symptoms such as fatigue.

In models with Physical Functioning (a HRQoL domain) as the dependent variable, fatigue showed a modest to moderate mediation effect. Although physical functioning is thought to perpetuate fatigue in arthritis (Davies et al., 2021), the impact of rheumatic diseases on physical limitations is multifactorial and cannot be fully explained by fatigue alone, but rather by the interplay of physical and psychological factors (Ormseth et al., 2015). Moreover, the direct association between disease activity and the Physical Functioning domain of HRQoL has been reported as particularly strong (Ma et al., 2025). In the case of models with Bodily Pain domain, fatigue was expected to exert a strong mediating effect, given evidence of shared mechanisms between pain and fatigue in arthritis (Davies et al., 2021). However, the effect was only modest in the current study. This is opposite to earlier findings suggesting that, in arthritis, fatigue is primarily related to pain and only secondarily to disease activity (Pollard et al., 2006).

Finally, models with the Physical Component Summary of HRQoL as the dependent variable showed a weaker mediation effect compared to most individual domains of physical quality of life. This supports recommendations by the authors of the SF-36 that, in addition to relying on summary measures, analyses should consider individual domains to draw more reliable conclusions (Ware & Kosinski, 2001).

The second main finding concerns the moderator in our mediation model, showing that rheumatological treatment influences the relationship between disease activity and bodily pain in psoriatic arthritis. First-line therapy reduced the impact of disease activity on pain, in line with previous evidence (Wilsdon et al., 2019), while second-line therapy also alleviated pain (Keskin et al., 2020), - but less effectively, as expected since it is prescribed after failure of first-line treatment and thus reflects more severe disease and greater concerns about medication (Tosato et al., 2022). However, in our sample, treatment did not moderate the relationship between disease activity and domains of physical quality of life (other than Bodily Pain) in other models, which differs from findings in rheumatoid arthritis and spondyloarthritis (Di Matteo et al., 2023; Deodhar et al., 2025).

The third main finding is that sex did not moderate any pathway in the tested mediation models. This result is somewhat unexpected, as previous research has consistently shown that males and females experience different levels of disease burden in terms of disease activity, fatigue, and quality of life (Ristić et al., 2025). The possible explanations could be that we did not include the mental quality of life, where sex differences manifest more frequently (Matcham et al., 2014).

Moreover, comorbidity was not a significant covariate in the mediation models. Our sample exhibited a moderate comorbidity burden, with approximately 90% of patients reporting at least one comorbid condition. In the model, comorbidities were not associated with fatigue levels as a moderator. In contrast, a previous study reported a strong association between comorbidities and fatigue (Tournadre et al., 2019), suggesting that comorbidities may contribute to fatigue directly or indirectly by exacerbating health problems, thereby increasing the likelihood of fatigue in arthritis.

Implication

Rheumatic diseases substantially reduce quality of life, and therapeutic strategies have traditionally focused on rheumatological treatment aimed at reducing disease activity (Smolen et al., 2016). The present finding that, across three rheumatic diseases, the effect of disease activity on quality of life is mediated by fatigue suggests that targeting fatigue may represent an additional pathway to improving quality of life. Given that quality of life enhancement is one of the key indirect outcomes of treatment (Di Matteo et al., 2023), incorporating fatigue management into therapeutic approaches may provide meaningful benefits for patients. Moreover, previous research on non-pharmacological interventions for fatigue in arthritis has demonstrated further positive effects on quality of life (Bachmair et al., 2022).

Strengths

To the best of our knowledge, this is the first study to examine the relationship between disease activity and quality of life through the mediating role of fatigue in rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. Second, we analyzed a large cohort of clinically stable patients with rheumatological diseases who were recruited during routine outpatient visits. This sampling strategy enhances the external validity of our findings and supports the generalizability of the results to everyday clinical practice. Third, we included three different rheumatic diseases and employed three corresponding disease activity scores. This approach allowed us to test whether the mediation-moderation model was consistent and valid across multiple disease contexts, thereby strengthening the robustness of our conclusions.

Limitations

The first limitation is the cross-sectional design, which does not allow causal inferences to be drawn. Since mediation-moderation models are conceptually based on causal assumptions, our findings should be confirmed in longitudinal studies. The second, our model did not account for environmental factors that may influence quality of life, as previously emphasized in the literature (Ferrans et al., 2014). Considering these contextual elements may provide a more comprehensive understanding of the determinants of quality of life in rheumatic diseases. Finally, we did not include sleep quality as a variable, even though sleep disturbances have been suggested to moderate the relationship between disease activity and fatigue (Nicassio et al., 2012). Future studies should therefore consider sleep quality to refine the mediation-moderation framework.

3.2.5 Conclusion

The present study extends current knowledge regarding the substantial impact of rheumatic diseases, (including rheumatoid arthritis, psoriatic arthritis and axial spondyloarthritis), on health-related quality of life. Elevated disease activity was associated with diminished outcomes across all domains of physical quality of life, with fatigue emerging as a significant mediator, accounting for up to 40% of this relationship. In PsA, rheumatologic treatment moderated the effect of disease activity on bodily pain, a domain of physical quality of life. Comorbidities did not function as covariates within the mediation model, as they exerted no significant influence on fatigue. Overall, these findings underscore the necessity of comprehensive therapeutic strategies in rheumatic diseases, emphasizing that, alongside the management of disease activity, targeted interventions addressing fatigue may further contribute to optimizing patients' quality of life.

CHAPTER 4. SEX DIFFERENCES ACROSS CLINICAL AND PSYCHOLOGICAL OUTCOMES IN RHEUMATIC DISEASES

4.1 SEX DIFFERENCES IN CLINICAL FEATURES AND QUALITY OF LIFE IN RHEUMATIC DISEASES

This subchapter presents the article for which I am the first author, published in the journal *Reumatismo*, entitled "*Gender differences in clinical features and quality of life in patients with spondyloarthritis and psoriatic arthritis*" (DOI: 10.4081/reumatismo.2024.1779).

The final authenticated version is available online at: https://www.reumatismo.org/reuma/article/view/1779 .

4.1.1 Introduction

Gender differences are a relevant and substantial source of variation in a number of clinical and subclinical conditions, affecting risk factors, prevalence, age of onset, clinical presentation, symptomatology, prognosis, and treatment effectiveness. Since disease experience and responses to therapeutic interventions are often significantly different in women compared to those of men (Legato et al., 2016), personalized preventive and therapeutic strategies are being sought, taking into account gender differences (Cirillo et al., 2020).

A group of inflammatory rheumatic diseases, such as axial spondyloarthritis (SpA) and psoriatic arthritis (PsA) affect male and female patients differently, giving rise to divergent clinical presentation, disease course, and response to treatment (Stovall et al., 2022; Tarannum et al., 2022).

Considering clinical features, female patients with spondyloarthritis have a higher disease burden due to a longer diagnostic delay, higher disease activity, and lower efficacy of treatment, but male patients have more radiographic damage (Rusman et al., 2020). Women with PsA tend to have worse functioning, higher disease burden (Lubrano et al., 2023), higher number of swollen joints, and increased functional disability scores than men (Nas et al., 2021). Due to the diverse nature of the disease, understanding how gender influences disease outcomes will help clinicians to optimally tailor management strategies for individual patients (Braaten et al., 2019) and increase patients' quality of life.

Health-related quality of life (HRQoL) is a self-administered questionnaire that quantifies how health status affects the quality of life, specifically the self-perceived well-being related to the presence of the disease or treatment (Karimi et al., 2016). Patients with axial SpA had a substantially lower HRQoL than the general population (Yang et al., 2016), while gender-based differences in axial SpA are vague. In some studies (Law et al., 2018; Webers et al., 2016), women had the worst quality of life, and in other studies (Enginar et al., 2023; Neuenschwander et al., 2020; Andreasen et al., 2019), scores tend to be similar in both genders, while in one study (de Carvalho et al., 2012), male patients had lower scores. Impaired health-related quality of life reported in women with axial SpA can be explained by outcomes such as fatigue, pain, sleep disturbances, and increased disease activity, all of which have been shown to affect women more than men (Marzo-Ortega et al., 2022). Patients with psoriatic arthritis experienced reduced quality of life in comparison to the general population (Husted et al., 2001), and women with PsA often experience worse quality of life, higher pain, fatigue, and functional disability than men (Tarannum et al., 2022, Eder et al., 2012).

The existence of gender differences in HRQoL is strongly influenced by the methodology of the study, specifically whether data collection is done at baseline or over time (Stovall et al., 2022), whether HRQoL's physical or mental aspect is evaluated and by the measure of the quality of life which has been used (Webers et al., 2016).

To our knowledge, there are few studies analyzing gender differences in clinical characteristics and health-related quality of life in both spondyloarthritis and psoriatic arthritis. Therefore, the present study aims to compare (1) the sociodemographic and clinical features and (2) the dimensions of health-related quality of life between female and male patients with spondyloarthritis and psoriatic arthritis. Specifically, we hypothesized that both axial SpA and PsA women would have more severe disease activity and consequently more aggressive therapy and reduced HRQoL.

4.1.2 Materials and methods

Study design and clinical sample

This observational, cross-sectional study included patients with axial SpA and with PsA. All patients were 18 years or older, clinically stable, and already have diagnosed with axial SpA, according to the Assessment of Spondyloarthritis International Society (ASAS) classification criteria (Sieper et al., 2009), or PsA – according to the Classification criteria for Psoriatic ARthritis (CASPAR) criteria (Taylor et al., 2006). Exclusion criteria were the diagnosis of fibromyalgia, connective tissue diseases (Systemic Lupus Erythematosus, Sjogren, sclerodermas, dermatomyositis, polymyositis), vasculitis, gout, infective arthritis, rheumatic polymyalgia or other severe systemic diseases. Recruitment was done during a routine outpatient visit at the Unit of Rheumatology, University Hospital of Verona, during a period of 1 year (Pezzato et al., 2021; Tosato et al., 2023; Ristic et al., 2023).

Measurements

Clinical data were collected by standardized instruments. Disease activity was assessed by the Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein (ASDAS-CRP) for the patients with spondyloarthritis (Smolen et al., 2015), and by the Disease Activity in PSoriatic Arthritis (DAPSA) for the patients with psoriatic arthritis (Smolen et al., 2015). Disease duration, comorbidity, familiarity, body mass index (BMI), erosion, and pro-radiographic symptoms were also recorded. Rheumatological treatment was categorized as first-line therapy [conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and/or anti-TNF (anti–tumor necrosis factor drugs)] and second-line therapy [biological disease-modifying antirheumatic drugs (bDMARDs) and, targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) with or without csDMARDs] according to Tosato et al. (2022). The use of glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) was also recorded. HRQoL was evaluated using the self-reported Medical Outcomes Study 36-item Short Form Survey (SF-36; Italian version) (Apolone & Mosconi, 1998). The instrument assesses eight dimensions of health status: physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Lower scores on each dimension indicate worse HRQoL and higher scores indicate better quality of life (Ware, 2000). Previous studies confirm the SF-36 as a valid and reliable measure of health-related quality of life for use in patients with SpA and PsA at a single time point (Kwan et al., 2016; Husted et al., 1997).

Statistical analysis

The characteristics were presented as frequencies (%) for categorical variables and as means (standard deviations) for continuous variables. Comparisons between females and males within spondyloarthritis and psoriatic arthritis, respectively, were performed using Fisher's exact test (2 categories), Chi-square test (>2 categories) for categorical variables, and *t*-test (independent samples) for continuous variables. All tests were bilateral, with a significant level of 0.05. Statistical analyses were performed using SPSS 22 for Windows.

4.1.3 Results

A total of 119 patients with spondyloarthritis (54 females and 65 males), and 198 with psoriatic arthritis (124 females, and 74 males) were assessed. Socio-demographic characteristics of women and men are presented in Table I. The mean age was not significantly different between male and female patients as well as marital status and education. Instead, female patients were less employed than male patients, both in spondyloarthritis (females: 61.1% *versus* males: 87.7%; p=0.001), and in psoriatic arthritis (females: 44.4% *versus* males: 64.9%; p=0.006).

Table I - Socio-demographic characteristics of the patients with spondyloarthritis and psoriatic arthritis, stratified and compared by gender.

	Spondyloarthritis (n=119)			**Psoriatic arthritis (n=198)**		
Socio-demographic characteristics	**Females (n=54)**	**Males (n=65)**	**p-value**	**Females (n=124)**	**Males (n=74)**	**p-value**
Age(yrs.), mean (sd)	51.1 (12.1)	47.2 (11.1)	0.072[c]	57.3 (11.5)	56.1 (12.0)	0.481[c]
Marital status, n (%)						
Single	9 (16.7%)	17 (26.2%)	0.439[b]	13 (10.5%)	10 (13.5%)	0.234[b]
Married	42 (77.8%)	44 (67.7%)		93 (75.0%)	59 (79.7%)	
Separated/ Divorced/Widowed	3 (5.6%)	4 (6.2%)		18 (14.5%)	5 (6.8%)	
Education, n (%)						
Low	18 (33.3%)	27 (37.8%)	0.448[a]	67 (54.0%)	36 (48.6%)	0.557[a]
High	36 (66.7%)	38 (58.5%)		57 (46.0%)	38 (51.4%)	
Employment, n (%)						
No	21 (38.9%)	8 (12.3%)	0.001[a]	69 (55.6%)	26 (35.1%)	0.006[a]
Yes	33 (61.1%)	57 (87.7%)		55 (44.4%)	48 (64.9%)	

a: Fisher's exact test. b: Chi-square test. c: *t*-test.

Table II shows clinical and treatment characteristics in spondyloarthritis and psoriatic arthritis, stratified and compared by gender. In both SpA and PsA disease activity was higher in female patients than in male patients (ASDAS-CRP: females: 2.9, SD 1.0; males: 2.2, SD 1.1; p<0.001; DAPSA: females: 16.6; males: 12.8; p=0.003). Disease duration was shorter in female patients with psoriatic arthritis (females: 8.1 yrs. SD 7.0; males: 10.1 yrs. SD 6.7; p=0.048), while in patients with spondyloarthritis, there was no gender difference in disease duration (p=0.083).

Considering comorbidity and familiarity, and scores of body mass index and erosion, female and male patients were similar.

Table II - Clinical and treatment characteristics of the patients with spondyloarthritis and psoriatic arthritis, stratified and compared by gender.

	Spondyloarthritis (n=119)			**Psoriatic arthritis, n=198**		
Clinical characteristics	**Females (n=54)**	**Males (n=65)**	**p-value**	**Females (n=124)**	**Males (n=74)**	**p-value**
Disease activity						
ASDAS-CRP, mean (sd)	2.9 (1.0)	2.2 (1.1)	<0.001[c]			
Inactive (<1.3)	6 (11.1%)	15 (23.1%)	0.012[b]			
Moderate (>=1.3 and <2.1)	6 (11.1%)	17 (26.2%)				
High (>=2.1 and <=3.5)	26 (48.1%)	25 (38.5%)				
Very high (>3.5)	16 (29.6%)	8 (12.3%)				
DAPSA, mean (sd)				16.6 (9.5)	12.8 (7.0)	0.003[c]
Remission (<=4)				7 (5.6%)	5 (6.8%)	0.033[b]
Low (>4 and <=14)				47 (37.9%)	42 (56.8%)	
Moderate (>14 and <=28)				55 (44.4%)	24 (32.4%)	
High (>28)				15 (12.1%)	3 (4.1%)	
Disease duration, mean (sd), yrs.	8.6 (7.3)	11.2 (8.8)	0.083[c]	8.1 (7.0)	10.1 (6.7)	0.048[c]
Comorbidity, n (%)						
No	6 (11.1%)	14 (21.5%)	0.147[a]	14 (11.3%)	5 (6.8%)	0.331[a]
Yes	48 (88.9%)	51 (78.5%)		110 (88.7%)	69 (93.2%)	
Familiarity, n (%)						
No	41 (75.9%)	46 (70.8%)	0.542[a]	79 (63.7%)	53 (71.6%)	0.278[a]
Yes	13 (24.1%)	19 (29.2%)		45 (36.3%)	21 (28.4%)	
BMI, mean (sd)	25.4 (5.7)	26.2 (2.9)	0.301[c]	26.2 (5.0)	27.1 (3.6)	0.200[c]
Erosion, n (%)						
No	48 (88.9%)	61 (93.8%)	0.509[a]	102 (82.3%)	63 (85.1%)	0.695[a]
Yes	6 (11.1%)	4 (6.2%)		22 (17.7%)	11 (14.9%)	
Pro-radiographic, n (%)						
No	27 (50.0%)	41 (63.1%)	0.193[a]	58 (46.8%)	49 (66.2%)	0.008[a]

Yes	27 (50.0%)	24 (36.9%)		66 (53.2%)	25 (33.8%)	
Treatment characteristics						
Rheumatological treatment, n (%)						
First-line therapy[1]	41 (75.9%)	59 (90.8%)	0.043[a]	97 (78.2%)	58 (78.4%)	0.564[a]
Second-line therapy[2]	13 (24.1%)	6 (9.2%)		27 (21.8%)	16 (21.6%)	
Glucocorticoid treatment, n (%)						
No	37 (68.5%)	58 (89.2%)	0.006[a]	91 (73.4%)	62 (83.8%)	0.115[a]
Yes	17 (31.5%)	7 (10.8%)		33 (26.6%)	12 (16.2%)	
NSAID treatment[3], n (%)						
No	33 (61.1%)	37 (56.9%)	0.710[a]	84 (67.7%)	52 (70.3%)	0.753[a]
Yes	21 (38.9%)	28 (43.1%)		40 (32.3%)	22 (29.7%)	

a: Fisher’s exact test. b: Chi-square test. c: *t*-test.

ASDAS-CRP ankylosing spondylitis disease activity score with c-reactive protein; DAPSA disease activity in psoriatic arthritis; BMI body mass index. NSAID treatment non-steroidal anti-inflammatory drug treatment. 1: csDMARDs and/or anti-TNF; 2: anti-IL6 / bDMARDs / tsDMARDs with or without csDMARDs; 3: used in last ten days.

Female patients with spondyloarthritis were more frequently under second-line therapy (p=0.043) and glucocorticoid treatment (p=0.006), contrary to NSAID treatment where gender differences were not expressed (p=0.710). Female and male patients with psoriatic arthritis were similar in treatment characteristics.

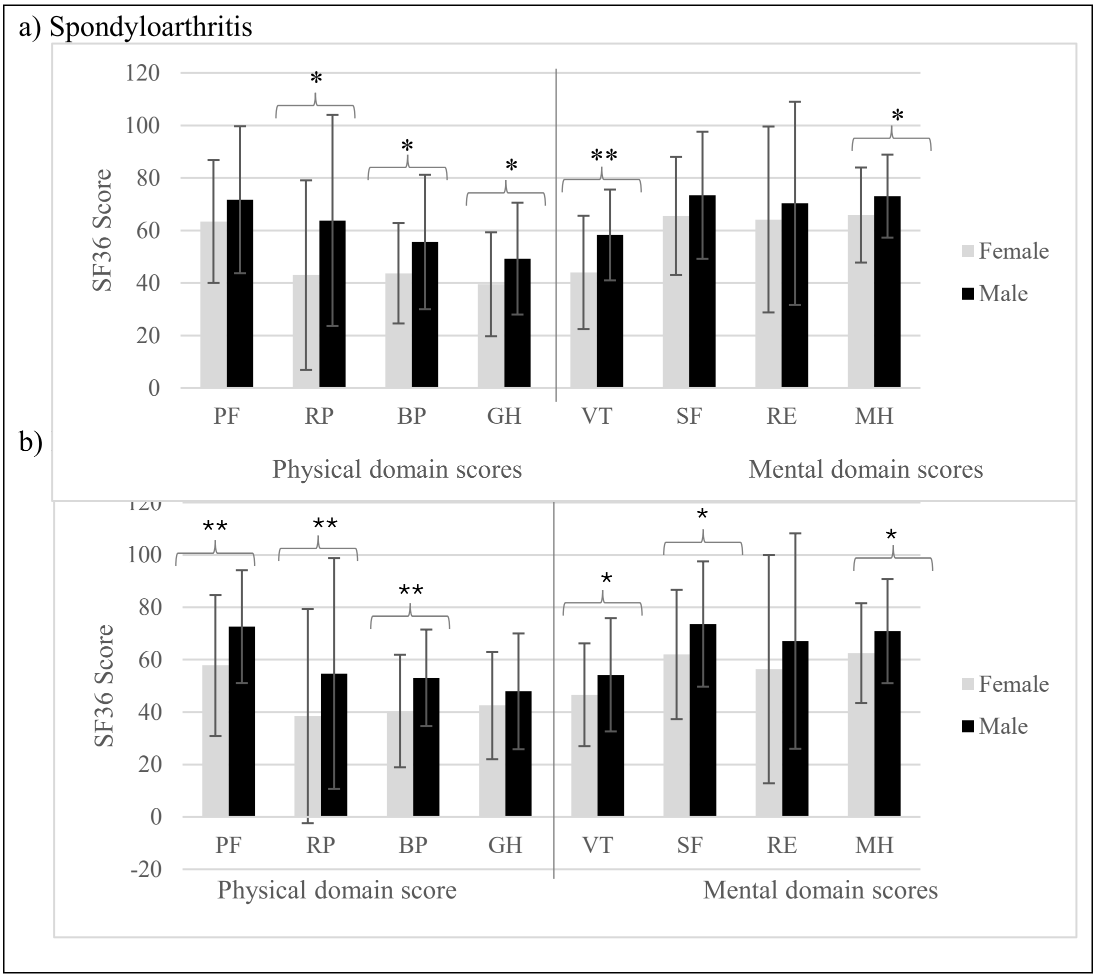


Figure 1 - Physical and mental domains of health-related quality of life (Short form-36 SF-36) in spondyloarthritis (females, n=54; males, n=65) (a), and psoriatic arthritis (females, n=124; males, n=74) (b), stratified and compared by gender. Mean and standard deviation are shown. The SF36 domains score between 0 and 100 with 0 – worse and 100 – best health. *T*-test is used to compare gender differences. PF physical functioning; RP role limitations due to physical health; BP bodily pain; GH general health; VT vitality; SF social functioning; RE role limitations due to emotional problems; MH mental health. * p<0.05, ** p<0.01, *** p<0.001.

As shown in Figure 1, female patients had lower scores than males in most of the dimensions of quality of life. Considering patients with spondyloarthritis, in three of four dimensions of physical quality of life, females had lower scores than males, specifically in Role limitation due to physical health (p=0.004), Bodily pain (p=0.006), and General health (p=0.011). In the dimension of Physical functioning, there was no gender difference (p=0.087). In two of four dimensions of mental quality of life, females had lower scores than males, specifically in Vitality ($p<0.001$) and Mental health ($p=0.022$). No statistically significant differences were determined in the following dimensions: Social functioning ($p=0.068$) and Role limitations due to emotional problems ($p=0.379$). Considering psoriatic arthritis, female patients had lower scores in three of four dimensions of physical quality of life: Physical functioning ($p<0.001$), Role limitations due to physical health ($p=0.009$), and Bodily pain ($p<0.001$). As regards mental quality of life, females had lower scores than males in three of four dimensions: vitality ($p=0.012$), social functioning ($p=0.001$), and mental health ($p=0.004$).

4.1.5 Discussion and conclusion

The results of the present study indicate two main findings: i) worse clinical and treatment features; and ii) lower quality of life in female patients with axial SpA and PsA. These results confirmed the proposed hypothesis of more severe disease activity, more aggressive therapy, and reduced quality of life in women with axial SpA and PsA when compared to men.

The first main finding of the present study is the presence of worse clinical features in males, such as more severe disease activity in both axial SpA and PsA, more radiographic progression in PsA, and more frequent second-line therapy and glucocorticoid treatments. In particular, women with axial SpA and PsA had a higher level of perceived disease activity. Previous findings on axial SpA mostly showed the same results (Neuenschwander et al., 2020; Nam et al., 2021), except in one study where gender differences in disease activity depended on the used measure (Webers et al., 2016). Indeed, women with PsA tended to report worse scores of disease activity (Nas et al., 2017). More severe disease activity in both women with axial SpA and PsA may be due to sex differences in immune mechanisms and to a greater disease burden due to the more extensive involvement of peripheral joints and entheses (Stovall et al., 2022; Tarannum et al., 2022, Webers et al., 2016). Results of the present study showed that female and male patients with axial SpA had similar age and disease duration, while even though women and men with PsA did not differ in age, males had longer disease duration, indicating an older age at the diagnosis of PsA in females. This could be due to a biological difference between women and men, but it might also suggest delays in diagnosis, probably because of the misinterpretation of early symptoms of PsA in women (Tarannum et al., 2022).

In the present study, erosion and radiographic progression were not different between female and male patients with axial SpA, differently from previous studies, which found fewer radiologic abnormalities in women with axial SpA (Stovall et al., 2022; Tournadre et al., 2013; Wright et al., 2020). Even with lower radiographic severity in females with axial SpA, after adjusting for radiographic spinal damage, women were found to report worse functioning at any given level of radiographic damage (Lee et al., 2007). In the current study, females with PsA were not different from males in the erosion of the bones but had significantly more radiographic progression. Previous studies found opposite results, where males with PsA were more likely to develop more severe radiographic structural damage (Tournadre et al., 2013; Nas et al., 2017; Nas et al., 2021) and a more erosive disease (Tournadre et al., 2013).

In the current study, a higher number of women with axial SpA were under second-line therapy, which is prescribed when the patients do not respond to first-line therapy, such as anti-TNF. Few studies have shown significantly poorer responses to TNF inhibitor therapies in women with axial SpA (Neuenschwander et al., 2020; Wright et al., 2020). The present analysis did not find gender differences related to the rheumatological treatment of PsA patients. However, a previous study showed a higher response to anti-TNF at 6 months in men with PsA (Tarannum et al., 2022). The results of the present study showed that female axial SpA patients more often use glucocorticoids. This finding may be explained by worse disease activity in women, as short-term use of glucocorticoids is recommended to treat inflammation (Ramiro et al., 2023).

The second main finding in the current study is that the physical and mental dimensions of HRQoL were reduced in female patients with axial SpA and PsA. The higher disease activity in females with axial SpA and PsA could explain these differences since a previous study showed that female patients were more likely to report a high impact of disease activity on quality of life (Nam et al., 2021). In addition, it was found that the presence of pro-radiographic features in women with

PsA could decrease their quality of life (Nas et al., 2021). Several studies have emphasized that women with axial SpA and PsA report a greater impairment in quality of life (Tarannum et al., 2022; Nas et al., 2021; Braaten et al., 2019; Tournadre et al., 2013; Wright et al., 2020).

Considering specific dimensions of physical quality of life, PF is worse in female patients with PsA, as previously reported (Wallenius et al., 2009). Since a low score on the PF dimension is defined as being limited in performing all physical activities (Ware, 2000) and SF-36PF is the best instrument for measuring functional disability in PsA (Leung et al., 2008), the results of the present study are in line with previous findings, showing PsA women as more likely to have physical activity limitations (Nas et al., 2017). In the present study, in patients with axial SpA, the PF scores tend to be similar in both genders. Due to the progressive loss of spine mobility, physical limitations appear to be prevalent among axial SpA patients (Yang et al., 2016), but with conflicting results concerning gender differences, which range from a greater functional impairment in females to no gender differences (Stovall et al., 2022). The dimension of the SF-36 role limitation due to physical health refers to problems with work or other daily activities because of physical health (Ware, 2000). In the present study, physical health was worse in females with axial SpA and PsA, and female patients were less often employed than male patients. Previous studies found that work disability associated with axial SpA and PsA occurs more often in women than in men of the same age (Tarannum et al., 2022; Yang et al., 2016; Wallenius et al., 2009), and that involvement of peripheral joints of the hands and feet, higher levels of pain, fatigue, and physical limitations could all contribute to it (Tarannum et al., 2022). One study recently showed that being employed was associated with a decreased probability of having low quality of life and depression in male patients with axial SpA (Nam et al., 2021). Previous papers highlighted that the educational level was strongly related to the type of job, and the work-disabled patients had a lower level of education, indirectly indicating that the work-disabled patients might have more physically demanding jobs (Braaten et al., 2019; Wallenius et al., 2009). In the present study, there was no gender difference with respect to the level of education, thus suggesting that women's working capacity is reduced more by variables associated with the disease than by the level of education.

In the current study, bodily pain, another physical dimension in SF-36, was worse in female patients both in axial SpA and PsA (Ware, 2000). Pain is a substantial symptom of axial SpA and the most common complaint in patients (Yang et al., 2016). Women with axial SpA and PsA often report more intense pain and experience it at more sites, with a greater level of severity, a higher frequency, and a longer duration than men (Stovall et al., 2022; Tarannum et al., 2022; Braaten et al., 2019). Finally, women with axial SpA had lower scores on the dimension of general health, defining personal health as poor (Ware, 2000).

Considering the dimensions of mental quality of life, in the present study, lower scores in vitality were reported both in female patients with axial SpA and PsA than in their male counterparts. In SF-36, a low score on vitality is defined as a feeling of being tired and worn out (Ware, 2000), and SF-36 vitality is used to measure fatigue both in axial SpA and PsA (Lim et al., 2021; Tan et al., 2020). Previous studies revealed that more than half of axial SpA patients reported fatigue induced by the disease (Yang et al., 2016), and in axial SpA and PsA women, the level of fatigue was higher compared to men (Tarannum et al., 2022; Braaten et al., 2019; Law et al., 2018). These results can be explained by higher physical limitations and mental dysfunction in women, as determined by SF-36 (Nas et al., 2021), and in the present study, these values were decreased. Mental health, a dimension of SF-36, was lower in female patients, both in axial SpA and PsA, which referred to higher individual feelings of anxiety and depression (Yang et al., 2016). In a previous study on axial SpA patients, the mental health dimension was reduced, suggesting that the impact of axial SpA on mental health was considerable (Yang et al., 2016). Results from a recent meta-analysis on axial SpA (Park et al., 2020) showed that there were no differences in the risk of depression among men and women, while men have more than a two-fold increased risk for incident anxiety. Indeed, the risk of anxiety and depression is higher in women with PsA (Tarannum et al., 2022; Nas et al., 2021; Braaten et al., 2019). Thus, the results of the present study suggest that a lower level of mental health in female patients can be due to the presence of depression and anxiety. In the current study, women with PsA had lower scores on the dimension of social functioning since they more frequently felt interference with ordinary social activities due to physical and emotional problems (Ware, 2000).

The present study has several strengths. First, two inflammatory rheumatic diseases were considered, thus providing a broader perspective toward the understanding of gender-specific differences in arthritis. Second, the sample was composed of outpatients recruited during a routine visit without any restriction due to disease severity or treatment, enabling the findings to be generalizable to the axial SpA and PsA populations. A few limitations have to be mentioned. First, axial SpA was not considered in the categories of ankylosing spondylitis and non-radiographic axial SpA, even if previous research found clinical and quality of life differences between them (Hong et al., 2019). Contrarily, predominantly axial versus peripheral PsA was not significantly different in the dimensions of SF-36 (Mease et al., 2011). Second, the sample size was small when the axial SpA and PsA patients were stratified by gender, thus suggesting caution in data interpretation.

In conclusion, the present study revealed gender differences in clinical characteristics, treatment, and HRQoL in axial SpA and PsA, where women had worse scores in most of the variables. Quantifying the impact of disease on daily life in women and men is essential for developing an effective, precise, and gender-specific approach to these patients. The causes of gender differences in disease expression and outcomes are still unknown, but the presence of the differences supports the idea that working on appropriate rheumatological and psychological treatment targets according to gender could be the central point for improving the quality of life.

4.2 SEX DIFFERENCES IN PSYCHOLOGICAL FEATURES AND DETERMINANTS OF QUALITY OF LIFE IN RHEUMATIC DISEASES

This subchapter presents the article for which I am the first author, published in the journal *BMC Psychology*, entitled "*Gender differences in psychological features and determinants of quality of life in axial spondyloarthritis and psoriatic arthritis: a cross-sectional study*" (DOI: 10.1186/s40359-025-02889-5).
The final authenticated version is available online at:
https://bmcpsychology.biomedcentral.com/articles/10.1186/s40359-025-02889-5 .

This subchapter contains *Supplementary material* which can be found in Appendix D.

4.2.1 Introduction

Axial **s**pondyloarthritis (axSpA) is an inflammatory chronic disease with different manifestations in female and male patients due to gender variations in the immunological, hormonal and genetic responses or sex differences in body anatomy or psychological functioning (Garrido-Cumbrera et al., 2021; Stovall et al., 2022). Specifically, women with axSpA generally had reduced quality of life and experienced higher levels of fatigue and pain and more impaired functional status than men (Wright et al., 2020).

Psoriatic arthritis (PsA) is a common, debilitating arthritic condition associated with severe comorbidities and reduced life expectancy (McArdle et al., 2018). Several differences in PsA manifestations between men and women are stated both in clinical conditions and disease outcomes (Braaten et al., 2019; Korsakova et al., 2024). Recent studies have shown that female patients experience a more severe course of PsA, higher levels of disease activity with higher levels of pain and fatigue, lower quality of life and increased functional limitations and work disability than male patients (Braaten et al., 2019; Tarannum et al., 2022; Lubrano et al., 2023; Scriffignano et al., 2024).

Anxiety and depression are common in both axSpA and PsA (Tarannum et al., 2022; Park et al., 2020), and the risk of developing anxiety and depression is higher in women with PsA than in men (Tarannum et al., 2022; Toledano et al., 2024). In axSpA, men have an increased risk of anxiety than women, while no apparent gender differences were found for the risk of depression (Park et al., 2020). Fatigue is a persistent problem for people with axial spondylarthritis and psoriatic-arthritis (Overman et al., 2016), with female patients experiencing a higher level than men (Toledano et al., 2024; Pilgaard et al., 2019). Pain is a common symptom in patients with rheumatic diseases (Atzeni et al., 2015; Sarzi-Puttini et al., 2015). Compared with male patients with inflammatory arthritis, females have worse pain scores that persist throughout the disease course (Barnabe et al., 2012; Vogel et al., 2023). Some studies showed that health-related quality of life is more detrimental in female patients both in PsA and axSpA (Webers et al., 2016; Eder et al., 2013), while other studies did not find gender differences (Enginar et al., 2023; Nas et al., 2017).

SpA and PsA substantially adversely affect health-related quality of life (FitzGerald et al., 2021; Yang et al., 2016). Female gender is related to impaired quality of life in psoriatic arthritis but not in axial spondyloarthritis (Yang et al., 2016; Eder et al., 2024). In male and female patients with PsA, significant predictors for impairment of the quality of life are pain, number of affected joints, and restricted joint mobility (Nas et al., 2017). In women and men with axSpA, worse physical and mental quality of life were associated with high disease activity and living without a partner (Law et al., 2018), while only lower mental quality of life was related to fatigue (Law et al., 2018; Nam et al., 2021).

The above-mentioned differences in disease expression in males and females need to be examined through the lens of gender theoretical concepts, using a coherent and integrated approach (Schmitz et al., 2010; Barsky et al., 2001; Hammarström et al., 2014). The conventional understanding of gender often emphasizes inherent psychological differences between males and females, suggesting these distinctions are deeply rooted, natural, and carry significant personal and social implications. Conversely, the social constructionist perspective states differences between genders are social constructs and cannot fully represent reality, indicating that gender theories serve as frameworks that shape our understanding and influence social and scientific practices (Hare-Mustin et al., 1988; Schields et al., 2011). Moreover, systems and structural theories tend to disregard gender altogether, positioning generation/age as the primary organizing principle within the family while other theories emphasize gender distinctions (Schields et al., 2011). For instance, psychodynamic theories portray masculinity and femininity as oppositional, arising from divergent responses to challenges during the preoedipal and oedipal stages, while recent feminist psychodynamic theories accentuate profound and enduring dichotomies between women and men (Schields et al., 2011; Washburn et al., 1994). Parsons's sex role theory posits that gender roles are fixed, separate, and dichotomous, whereas social role theory suggests that shared behavioural expectations are shaped through socialization processes, evident in the differential ways genders manage dependency and distress, with women generally more inclined to seek medical assistance (Barsky et al., 2001; Schields et al., 2011; Newman et al., 2020). Additionally, social support theory highlights the importance of social networks in health, noting that women, being more interpersonally oriented, are more prone to seek help and talk about their distress, resulting in better health outcomes. Conversely, societal norms often discourage boys from expressing discomfort, resulting in the denial of pain and avoid admitting weakness (Barsky et al., 2001). Hegemonic masculinity emphasizes male power through traits such as physical strength and autonomy, reinforcing male dominance over women, while andronormativity in medicine prioritizes male health issues, often neglecting those of females (Samulowitz et al., 2018). Despite this, women generally experience more frequent and intense bodily symptoms than men, leading to a poorer perception of physical health and somatic well-being, which may be attributed to their heightened sensitivity to subtle bodily signals and greater bodily vigilance (Barsky et al., 2001).

To our knowledge, no study has specifically examined psychological factors, in addition to clinical and treatment variables, as potential determinants of physical and mental quality of life in patients with axial spondyloarthritis and psoriatic arthritis, focusing on gender differences. The present study aimed 1) to compare psychological characteristics between females and males affected by spondyloarthritis or psoriatic arthritis and 2) to explore which features (with a special focus on psychological characteristics) are associated with impaired physical and mental quality of life in both female and male patients. Based on the psychological theories, we hypothesize that women will score lower on psychological variables and general well-being.

4.2.2 Methods

Clinical sample

Adult patients (≥ 18 years) with previously diagnosed axSpA - according to the Assessment of SpondyloArthritis international Society (ASAS) classification criteria or PsA - according to the ClASsification for Psoriatic ARthritis (CASPAR) criteria were included in this large cohortstudy with a cross-sectional design (Sieper et al., 2017). The exclusion criteria included the presence of fibromyalgia, connective tissue diseases (such as Lupus Erythematosus, Sjögren's syndrome, scleroderma, dermatomyositis, and polymyositis), vasculitis, gout, infectious arthritis and polymyalgia rheumatica. Additionally, individuals with severe systemic or infectious conditions—such as cardiac, respiratory, gastrointestinal, neurological, or endocrine disorders, including neoplastic diseases—were excluded, as these conditions can affect disease activity and the functional or psychological status of patients with rheumatic diseases. Finally, participants who lacked knowledge of the Italian language or had other limitations in verbal communication were excluded from the study. All participants provided written informed consent. Following consent, demographic and clinical data were collected, and patients completed self-report outcome measures. Recruitment was carried out sequentially of all patients presented for a routine outpatient visit at the Unit of Rheumatology, Verona, Italy, between March 2016 and February 2017. More study details have been described elsewhere (Pezzato et al., 2021; Tosato et al., 2023). This study received ethical approval from the Ethics Committee of the Provinces of Verona and Rovigo (Ref. CESC15840, 2016). The investigation was conducted in accordance with the latest version of the Declaration of Helsinki (World Medical Association, 2013).

Measurements

Information about disease duration, family history of rheumatologic diseases, body mass index, comorbidity, erosions, radiographic progression, glucocorticoid and non-steroidal anti-inflammatory drugs (NSAIDs), and antidepressants were collected. The rheumatological treatment was categorized as first-line therapy [conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and/or anti-TNF (anti–tumor necrosis factor drugs)] and second-line therapy [biological disease-modifying antirheumatic drugs (bDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) with or without csDMARDs] [see Tosato et al. (2022) for details]. Disease activity was measured with the Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein (ASDAS-CRP) for axSpA and the Disease Activity in PSoriatic Arthritis (DAPSA) for PsA (Machado et al., 2011; Smolen et al., 2015).

The Health-Related Quality of Life (HRQoL) was assessed by the Medical Outcome Study 36-item Short Form health survey (SF-36) (internal consistency in the total sample α=0.873; internal consistency (α) for the validation in the Italian sample ranged from 0.770 to 0.930, depending on the specific subscale) (Apolone et al., 1998; Ware et al., 2000). It contains the physical component score (PCS) and the mental component score (MCS). Lower scores indicate worse HRQoL.

The Health Assessment Questionnaire – Disability Index (HAQ-DI) (internal consistency in the total sample α=0.890; internal consistency for the validation in the Italian sample α=0.940) evaluated patients' functional ability to perform everyday activities (Berardi et al., 2022; Bruce et al., 2003). Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) (internal consistency in the total sample α=0.887; internal consistency for the validation in the Italian sample α=0.890) (Iani et al., 2014; Zigmond et al., 1983). The Chalder Fatigue Questionnaire (CFQ) was used to assess fatigue (internal consistency in the total sample α=0.901; internal consistency (α) for the validation in the English sample ranged from 0.880 to 0.900) (Cella et al., 2010; Chalder et al., 1993). The Perceived stress scale (PSS) measured the degree of stress experienced in the preceding month (internal consistency in the total sample α=0.775; internal consistency for the validation in the Italian sample α=0.740) (Mondo et al., 2021; Cohen et al., 1983). The Visual Analogue Scale (VAS) measured the subjective experience of pain intensity (internal consistency in the total sample α=0.946; internal consistency for the validation in the Italian sample α=0.910) (Alacreu-Crespo et al., 1983; Bond et al., 1966). The Coping Orientation to the Problems Experiences-new Italian version (COPE-NVI) (internal consistency in the total sample α=0.893; internal consistency (α) for the validation in the Italian sample ranged from 0.700 to 0.910, depending on the specific subscale) evaluated how often the “problem-focused coping” (active coping, planning, suppression of competing activities, restraint, seeking of instrumental social support), the “emotion-focused coping” (seeking of emotional social support, positive reinterpretation, acceptance, denial, turning to religion), and the “dysfunctional” (focus on and venting of emotions, behavioral disengagement, mental disengagement) were used (Sica et al., 2008).

Statistical analyses

Variables were described by frequencies if categorical and means (standard deviations) if continuous. Females and males were compared using the Fisher's exact test with the Phi effect size for categorical variables and the t-test (independent samples) with the Cohen's d effect size for continuous variables. Factors significantly associated (at $p<0.05$) with physical and mental quality of life in univariate linear regression models were selected to estimate multivariate linear regression models. Key checks for model assumptions were executed after each multivariate model estimation, specifically the Shapiro-Wilk test for Normality of residuals (Shapiro et al., 1965), the Breusch-Pagan test for homoscedasticity (Breusch et al., 1979), and the Variance Inflation Factor VIF (Chatterjee et al., 1986) for multicollinearity. Both independent and dependent variables had complete data. All tests were bilateral at $p<0.05$. Analyses were done by SPSS 28 for Windows.

4.2.3 Results

Socio-demographic and clinical characteristics

Patients with axSpA (n=119) and PsA (n=198) were included in the study (Appendix D1 and D2). Females and males were similar in age (axSpA: mean 47.2 SD 11.1; PsA: mean 56.1 SD 12.0). In both diagnostic groups, more women were unemployed. Regarding clinical characteristics, females with axSpA and PsA had significantly higher disease activity ($p<0.001$; $p=0.003$, respectively). In PsA, men had significantly longer disease duration ($p=0.048$), while women had more radiographic progression ($p=0.008$) and physical disability ($p<0.001$). Females with axSpA were more frequently under second-line therapy ($p=0.043$), glucocorticoid treatment ($p=0.006$), and antidepressants ($p=0.005$).

Psychological characteristics

Considering psychological variables, females had lower scores in PCS both in axSpA ($p=0.004$) and PsA ($p<0.001$), with both differences showing a medium effect size. In contrast, only females affected by PsA had lower MCS ($p=0.042$). Women with axSpA and PsA experience higher fatigue ($p=0.005$; $p=0.027$, respectively), perceive higher stress ($p=0.015$; $p=0.038$, respectively), and have stronger pain ($p<0.001$; $p<0.001$, respectively). Women with PsA experienced more difficulties concerning disability (p<0.001; effect size 0.30). While effect sizes for fatigue and stress were between small and medium, pain showed a large effect size. Female patients had more ineffective coping strategies, such as emotion-focused coping (axSpA: p=0.027; PsA: p=0.021) and dysfunctional coping (axSpA: p<0.001; PsA: p=0.023). Effect sizes were between small and medium, with dysfunctional coping showing a value of 0.68 for axSpA. Moreover, females with axSpA more frequently had moderate or severe anxiety (p=0.013). There was no significant gender difference regarding depression (Table 1).

Table 1 - Psychological characteristics of patients with axial spondyloarthritis and psoriatic arthritis, stratified and compared by gender

	Spondyloarthritis, n=119				**Psoriatic arthritis**, n=198			
Psychological characteristics	**Females** n=54	**Males** n=65	**p-value**	**Effect size**	**Females** n=124	**Males** n=74	**p-value**	**Effect size**
Physical quality of life (PCS), mean (sd)	35.7 (8.9)	41.1 (10.8)	**0.004**[c]	0.55[#]	35.0 (10.3)	40.2 (8.6)	**<0.001**[c]	0.54[#]
Mental quality of life (MCS), mean (sd)	46.3 (10.0)	49.4 (8.9)	0.073[c]	0.33[#]	45.1 (10.5)	48.3 (11.5)	**0.042**[c]	0.30[#]
Fatigue (CFQ), n (%)								
No (<=3)	22 (40.7%)	44 (67.7%)	**0.005**[a]	0.27[§]	54 (43.5%)	45 (60.8%)	**0.027**[a]	0.17[§]
Yes (>=4)	32 (59.3%)	21 (32.3%)			70 (56.5%)	29 (39.2%)		
Stress (PSS), n (%)								
Low (<20)	24 (44.4%)	44 (67.7%)	**0.015**[a]	0.23[§]	47 (37.9%)	40 (54.1%)	**0.038**[a]	0.16[§]
High (>=20)	30 (55.6%)	21 (32.3%)			77 (62.1%)	34 (45.9%)		
Pain (VAS), mean (SD)	6.0 (2.4)	4.2 (2.7)	**<0.001**[c]	0.70[#]	5.8 (2.5)	4.34 (2.2)	**<0.001**[c]	0.61[#]
Depression (HADS-D), n (%)								
Normal or Mild (<=10)	48 (88.9%)	61 (93.8%)	0.509[a]	-	111 (89.5%)	70 (94.6%)	0.297[a]	-
Moderate or Severe (>10)	6 (11.1%)	4 (6.2%)			13 (10.5%)	4 (5.4%)		
Anxiety (HADS-A), n (%)								
Normal or Mild (<=10)	37 (68.5%)	57 (87.7%)	**0.013**[a]	0.23[§]	97 (78.2%)	64 (86.5%)	0.188[a]	-

Moderate or Severe (>10)	17 (31.5%)	8 (12.3%)			27 (21.8%)	10 (13.5%)		
Problem-focused coping, mean, sd	50.1 (9.7)	46.6 (10.0)	0.059[c]	-	48.3 (9.8)	48.5 (12.4)	0.893[c]	-
Emotion-focused coping, mean, sd	45.4 (7.8)	42.0 (8.2)	**0.027**[c]	0.41[#]	46.2 (8.2)	43.2 (9.6)	**0.021**[c]	0.34[#]
Dysfunctional coping, mean, sd	23.1 (5.4)	19.8 (4.5)	**<0.001**[c]	0.68[#]	23.0 (4.8)	21.2 (5.1)	**0.023**[c]	0.34[#]

PCS physical component score, *MCS* mental component score, *CFQ* chalder fatigue questionnaire, *PSS* perceived stress scale, *HADS-D* hospital anxiety and depression scale – depression, *HADS-A* hospital anxiety and depression scale – anxiety.

[a] Fisher's exact test

[b] Chi-square test

[c] *T*-test

[#] Cohen's d

[§] Phi

Determinants of quality of life

By considering axSpA, quality of life was associated with a series of characteristics for all patients, and it was gender-specific in the univariate models (Appendix D3). After estimating the multivariate models, a lower PCS result was associated with higher CFQ and VAS in females and a higher ASDAS-CRP in males (Table 2). A lower MCS was associated with a higher HADS-A in all patients. In contrast, family history of rheumatologic diseases, second-line treatment, higher PSS and CFQ were associated only in females. Moreover, in this group, being employed was associated with a higher MCS.

Table 2 - Multivariate linear regression models by sex in axial spondyloarthritis [each cell contains Beta coefficient (p-value)]

	Dependent variable			
	SF36 Physical		**SF36 Mental**	
Independent variable	**F**	**M**	**F**	**M**
Socio-demographic characteristics				
Marital status		-	-	-
Married/cohabitant	-0.046 (0.741)			
Separated/divorced/widowed	0.009 (0.945)			
High education	-	0.089 (0.372)	-	0.116 (0.338)
Employed	0.037 (0.765)	0.166 (0.125)	0.151 (**0.043**)	-
Age	-0.118 (0.340)	-0.082 (0.422)	-	-
Clinical characteristics				
Family history of rheumatologic diseases	-	-	-0.179 (**0.010**)	-
ASDAS-CRP	0.005 (0.975)	-0.489 (**0.022**)	0.007 (0.954)	-
Erosions	-	-0.087 (0.399)	-	-
Radiographic progression	-	-0.050 (0.643)	-0.075 (0.290)	-
Treatment characteristics				
Rheumatological treatment	-	-		-
Second line therapy[1]			-0.264 (**0.001**)	
Glucocorticoid treatment	-0.141 (0.201)	-	-	-0.116 (0.329)
NSAID treatment[2]	-	-0.098 (0.356)	-	-
Antidepressant therapy	-0.164 (0.214)	-	-0.093 (0.282)	-
Psychological characteristics				
Depression (HADS-D>10)	-	-0.131 (0.207)	-0.119 (0.139)	-0.112 (0.394)
Anxiety (HADS-A>10)	-	-0.101 (0.389)	-0.390 (**<0.001**)	-0.319 (**0.026**)
Stress (PSS$\geq$20)	0.013 (0.934)	-	-0.189 (**0.049**)	-0.071 (0.564)

Fatigue (CFQ≥4)	-0.306 (**0.034**)	-0.148 (0.954)	-0.237 (**0.014**)	-0.097 (0.466)
Disability (HAQ-DI≥1)	-0.210 (0.122)	-0.006 (0.187)	-	-
Pain (VAS)	-0.474 (**0.004**)	0.045 (0.821)	-0.017 (0.865)	-0.066 (0.604)
COPE Dysfunctional	-	0.033 (0.765)	-0.016 (0.865)	-0.081 (0.529)
% Variance explained (Adj-R^2)	**54.5%**	**54.3%**	**81.6%**	**27.4%**

SF-36 Short Form health survey, *ASDAS-CRP* ankylosing spondylitis disease activity score with c-reactive protein, *NSAID treatment* non-steroidal anti-inflammatory drug treatment, *HADS-D* hospital anxiety and depression scale – depression, *HADS-A* hospital anxiety and depression scale – anxiety, *PSS* perceived stress scale, *CFQ* chalder fatigue questionnaire, *HAQ-DI* health assessment questionnaire – disability index, *VAS* visual analogue scale, *COPE* coping orientation to the problems experiences.

[1] anti-IL6 / bDMARDs / tsDMARDs with or without csDMARDs

[2] used in the last ten days

Analogously, also in PsA PCS and MCS results were associated with a series of factors for all patients and were gender-specific in the univariate models (Appendix D4). After estimating the multivariate models, all patients had a lower PCS associated with NSAID treatment and higher CFQ and VAS (Table 3). Males only showed negative associations with age and glucocorticoid treatment. A lower MCS was associated with higher HADS-A and CFQ in all patients, while higher HADS-D and PSS were associated only with the female gender. Finally, being employed was negatively associated with MCS only in males.

Table 3 Multivariate linear regression models by sex in psoriatic arthritis [each cell contains Beta coefficient (p-value)]

	Dependent variable			
	SF36 Physical		**SF36 Mental**	
Independent variable	**F**	**M**	**F**	**M**
Socio-demographic characteristics				
Employed	-	-	-	-0.209 (**0.010**)
Age	-	-0.175 (**0.026**)	-	-
Clinical characteristics				
Comorbidity	-	-0.114 (0.122)	-	-
BMI	-0.105 (0.098)	-		
DAPSA	-0.167 (0.069)	-0.042 (0.668)	0.157 (0.137)	-0.059 (0.594)
Erosions	-0.114 (0.096)	-	-	-
Radiographic progression	0.035 (0.610)	-0.125 (0.106)	-	-
Treatment characteristics				
Rheumatological treatment Second line therapy^1	-0.072 (0.280)	-	-	-
Glucocorticoid treatment	-	-0.156 (**0.036**)	-	-0.091 (0.265)
NSAID treatment^2	-0.135 (**0.040**)	-0.226 (**0.003**)	-	-
Antidepressant therapy	-0.049 (0.447)	-	-	-
Psychological characteristics				
Depression (HADS-D>10)	-0.011 (0.863)	0.065 (0.401)	-0.197 (**0.016**)	-0.075 (0.400)
Anxiety (HADS-A>10)	-	-0.121 (0.125)	-0.180 (0.034)	-0.235 (**0.011**)
Stress (PSS≥20)	-	-	-0.254 (**0.001**)	-0.118 (0.193)
Fatigue (CFQ≥4)	-0.176 (**0.011**)	-0.172 (0.028)	-0.207 (**0.013**)	-0.401 (**<0.001**)
Disability (HAQ-DI≥1)	-0.104 (0.146)	-0.100 (0.184)	-0.125 (0.150)	
Pain (VAS)	-0.391 (**<0.001**)	-0.416 (**<0.001**)	-0.210 (0.054)	-0.088 (0.460)
COPE Dysfunctional	-	-0.035 (0.641)	0.039 (0.624)	-0.145 (0.114)
% Variance explained (Adj-R^2)	**55.0%**	**68.2%**	**34%**	**56.8%**

The key checks for assumptions of multivariate linear regression models estimated in Tables 2 and 3 confirmed the hypothesis of Normality of residuals (p>0.05 Shapiro-Wilk tests), the hypothesis of homoskedasticity (p>0.05 Breusch-Pagan tests), and the absence of multicollinearity problems (no VIF value was greater than 10) (Appendix D5 and D6).

4.2.4 Discussion

In this cross-sectional study, some gender differences are reported. First, female patients had higher scores on most psychological features in both axSpA and PsA. Second, in females affected by axSpA and PsA, impaired physical quality of life is mainly explained by high levels of fatigue and pain, while high levels of fatigue, anxiety and stress explain the poor mental quality of life.

The first main finding is that female patients with axSpA and PsA have significantly higher scores on fatigue, pain, and perceived stress and have more severe anxiety symptoms, as numerous studies have previously shown (Garrido-Cumbrera et al., 2021; Wright et al., 2020; Tarannum et al, 2022; Scriffignano et al., 2024; Toledano et al., 2024; Pilgaard et al., 2019; Eder et al., 2013; Coates et al., 2023). Recent reviews concluded that the impact of axSpA and PsA might be experienced differently for men and women (Stovall et al., 2022; Tarannum et al., 2022). The relation between gender and fatigue in arthritis could be mediated and explained by the number of daily roles (Nikolaus et al., 2010), daily positive events or pain level (Davis et al., 2010). Additionally, women with axSpA have a higher density of pain receptors in the skin and report pain in more body parts (Stovall et al., 2022). Moreover, women reported more chronic and cumulative stress, which could be explained by their greater reactivity to stressful life events or higher demands in their social roles (Germain et al., 2021). Psychological distress leads to poorer disease outcomes by enhancing symptom burden, decreasing treatment adherence, and increasing disability (Garrido-Cumbrera et al., 2021; Walsh et al., 2014). Differently than expected (Garrido-Cumbrera et al., 2021; Tarannum et al., 2022), in the present study, gender differences concerning depressive symptoms did not appear. It might be because of the low overall number of depressed patients (about 8%) or the effectiveness of psychotropic therapy (females with axSpA were more frequently under antidepressants).

A plausible explanation for gender differences in arthritis is that it represents a complex interplay of biological and social factors (Coates et al., 2023; Mauvais-Jarvis et al., 2020). It is well-established that genetic differences between men and women underlie the variations in disease prevalence, manifestation, and treatment responses (Mauvais-Jarvis et al., 2020). Conversely, social role theory suggests that females are encouraged from youth to express their distress and discomfort more openly, while males are foster to embody masculinity by suppressing any signs of weakness (Barsky et al., 2014). Therefore, it cannot be one-sidedly interpreted that a woman's experience of more pain, distress, and functional deterioration reflects only an inherent gender difference in the biology of the disease or that it only represents a different impact of social and cultural aspects toward disease (Braaten et al., 2019; Davis et al., 2010). Consequently, patient-reported outcomes must be interpreted cautiously (Stovall et al., 2022).

Women's poorer psychological outcomes in the current study could further decrease everyday functioning and produce frustration, so the expected result was that quality of life is more severely compromised for the females (Barsky et al., 2001). In details, women with axSpA and PsA had impaired physical quality of life, while only female patients with PsA had worse mental quality of life. Considering axSpA, these results align with previous findings where male patients had a better quality of life over time and PCS was more affected than MCS in both sexes (Webers et al., 2016; Law et al., 2018). Regarding PsA, a previous study found that only PCS was decreased in female patients (Eder et al., 2013). Other studies did not find significant gender differences in quality of life in axSpA and PsA (Enginar et al., 2023; Nas et al., 2017).

Previous research has indicated that coping strategies significantly affect psychological well-being in chronic patients (Walsh et al., 2014; Stojanovich et al., 2008). In the present study, axSpA and PsA female patients predominantly and more frequently than males use emotion-focused and dysfunctional coping strategies. This aligns with sex role theory, which suggests that men tend to be task-oriented, while women are more expressive and focused on feelings and relationships (Hare-Mustin et al., 1988). While a dysfunctional strategy unambiguously negatively impacts the patient's life, the result of an emotion-focused strategy needs to be considered carefully since this strategy may have divergent implications for a person's success in coping (Carver et al., 1989). The second main finding of the present study is a clear pattern of psychological variables that explain physical and mental quality of life, primarily in female patients. Physical quality of life is mainly explained by fatigue and pain in female patients with axSpA and male and female patients with PsA. Previously, it was shown that fatigue and pain significantly negatively impact the quality of life (Sarzi-Puttini et al., 2015), while only fatigue was positively associated with the female gender in multivariate analysis (Tournadre et al., 2013). The relationship between physical quality of life and pain could be explained by the fact that pain undermines a patient's ability to perform everyday activities (Sarzi-Puttini et al., 2015), especially if painful arthritis symptoms remain untreated (Atzeni et al., 2015). In the present study, disease activity was higher in women with axSpA and PsA, while in men with axSpA, disease activity was associated with physical quality of life, as previous studies found (Law et al., 2018; Nam et al., 2021). Additionally, the analyses of the current study revealed that in PsA, PCS is related to NSAID treatment in women and age, glucocorticoid and NSAID treatment in men.

In the present study, mental quality of life is explained by fatigue, anxiety and stress in female patients with axSpA and PsA. At the same time, in male patients, MCS is determined by anxiety and fatigue or only anxiety (in PsA and axSpA, respectively). Thus, anxiety was a steady factor associated with poor MCS in both genders in axSpA and PsA, as demonstrated in previous studies (Tarannum et al., 2022; Kilic et al., 2014). This relationship may be partly attributed to anxiety's tendency to increase patients' complaints related to their condition (Barsky et al., 2001). Depression was related to MCS in females with PsA in the present study. In rheumatoid arthritis, depression and anxiety both correlate with impaired quality of life (Sturgeon et al., 2016). Interestingly, in this study, stress negatively affects mental quality of life, primarily among female patients both in axSpA and PsA. Since women perceived higher stress, it was expected to be found that stress decreases mental well-being in females. In studies with rheumatoid arthritis, considering male and female patients together, lower perceived stress contributed to higher general well-being and increased mental quality of life (Germain et al., 2021; Nicassio et al., 2011). In the current study, fatigue also decreases mental quality of life in both genders with PsA and female patients with axSpA. This result is expected since fatigue is a phenomenon experienced both physically and mentally and is driven by physiological, psychological, behavioural, and sociocultural factors (Davies et al., 2021). Stressing the importance of psychological factors, optimal clinical care in rheumatology should involve treating psychological symptoms related to the disease (Sturgeon et al., 2016). The findings of the current study indicate that women exhibit lower scores on psychological symptoms and, according to social support theory, more actively seek medical assistance, suggesting that a proactive response from medical practitioners could lead to improved health outcomes (Barsky et al., 2001). Still, rheumatologists underestimate patient reports of psychological state probably because their evaluation of the patient's health status severity differs from that of the patients (Hewlett et al., 2003). Also, patients rarely discuss their symptoms of depression during their rheumatologist visits (Sturgeon et al., 2016). Therefore, considering the severity of psychiatric comorbidities is essential and more likely to be achieved if holistic approaches to patient care are adopted (Nikiphorou et al., 2021).

Employment contributes to overall well-being, self-esteem, and financial independence in patients with arthritis (Nikiphorou et al., 2021). In the current study, employment was significantly positively related to mental quality of life in female patients with axSpA, while previously, it was found only in men with axSpA (Nam et al., 2021). The surprising finding of a negative correlation between employment and MCS in male patients with PsA in the present study needs further investigation. In the current study, the pain was not related to mental quality of life; that was unexpected since pain is the critical determinant of long-term quality of life, where its cognitive interpretation can have significant implications for the patient's mental health (Sturgeon et al., 2016).

Male and female patients with axial spondyloarthritis and psoriatic arthritis experience distinct differences in clinical and psychological symptoms and quality of life, which may have important practical implications. Screening for and monitoring anxiety, depression and general psychological distress that impairs daily functioning beyond the limits imposed by the disease should be part of rheumatologic practice. The preferred first-line psychological treatment for anxiety disorder and mild depression is cognitive–behavioural therapy employing a variety of techniques, including cognitive restructuring, exposure and behavioural experiments. Based on the findings of this study, psychological interventions should be gender-sensitive, addressing the distinct ways in which male and female patients experience chronic illness. Another implication of the present study is that medical research should systematically integrate gender differences into clinical trials, with the ultimate aim of developing comprehensive gender-adapted clinical guidelines.

There are some strengths and limitations to the present study. The study's main strength is the numerosity of the sample of patients with axial spondyloarthritis and psoriatic arthritis, with longer disease duration, minimizing the effect of possible acute stress reaction provoked by a diagnosis of arthritis. The second strength is the consideration of the broad scope of self-reported psychological and physical disease outcomes, providing a more comprehensive picture of the current disease state and the impact of the disease on daily life. The study's main limitation is a cross-sectional design that does not allow inferences on the temporal relationship between the analyzed variables, and, consequently, diminishes the strength of the study's conclusions. Further, since there was no follow-up of the patients, we cannot understand whether the difference in the explained variance reflects the difference between genders and diagnoses or the effect of an unrecognized confounding variable. The second limitation is the use of general questionnaires instead of specific instruments constructed for axial spondyloarthritis and psoriatic arthritis, such as the quality of life measures. The third limitation is that, even though comorbidity was included as a variable, a more subtle measure utilizing a comorbidity index (such as the Rheumatoid Arthritis Comorbidity Index) would enhance the overall analysis. Given that gender differences are commonly observed in the prevalence of various diseases (Mauvais et al., 2020), a thorough examination of the impact of comorbidities on gender disparities and quality of life would be beneficial. Future research should address our findings and limitations by conducting a longitudinal study with follow-up assessments and more specific instruments to draw more robust conclusions. The fourth limitation is that the study was conducted at a single center, limiting the results' external validity. Future research on this topic should be international and multicenter in order to draw more global conclusions from diverse populations, gain cross-cultural insights and enhance external validity.

4.2.5 Conclusions

The current study demonstrates that female patients with axial spondyloarthritis and psoriatic arthritis have worse scores in most psychological variables than men, representing worse health disease status. Furthermore, reduced physical and mental quality of life is mainly associated with fatigue, stress, pain, and anxiety. Based on these findings, therapeutic strategies for routine clinical practice should be adapted in order to improve patient well-being. By taking into account the clinical and psychological variables that reflect each patient's unique sex and gender differences, effective and individualized care can be provided.

CHAPTER 5. PROTOCOL ON FATIGUE REDUCTION IN RHEUMATIC DISEASES: EFFICACY EVALUATION (FREE) TRIAL

Branko Ristić conceptualized and authored the protocol. The protocol manuscript is being prepared for submission to the journal *Trials*, pending approval from the Ethics Committee. Additionally, Ristić developed a psychological intervention tailored specifically for the purposes of the present trial (see Appendix E2).

Administrative information

Title	Protocol for the FREE trial: A randomized controlled parallel-group study to compare the effectiveness of psychological intervention, physical exercise program and usual medical care alone in reducing fatigue among patients with rheumatic diseases
Trial registration	
Protocol version	03/03/2025, Version 1.0
Funding	*This research received no specific grant from any funding agency, commercial or not-for-profit sectors.*
Author details	
Name and contact information for the trial sponsor	*The present trial does not have a sponsor.*
Role of sponsor	*The present trial does not have a sponsor.*

5.1 Introduction

5.1.1 Background and rationale

Fatigue is a common and disabling symptom in inflammatory rheumatic diseases, affecting up to 90% of patients (Davies et al., 2021; Durcan et al., 2014). It is characterized as an overwhelming, exhausting, and persistent feeling of tiredness that impairs daily functioning (Chmielewski et al., 2023) and negatively impacts patients' quality of life and disease outcomes (Geenen and Dures, 2019; Ristic et al., 2025). As a subjective experience, fatigue has been reported by individuals with rheumatoid arthritis (RA) as a significant loss of both physical and mental energy, often described as feelings of weariness and a lack of motivation (Chmielewski et al., 2023; Hewlett et al., 2005).

Inflammation is the central pathological feature in rheumatic diseases and is considered a primary initiator of fatigue; however, it is unlikely to be the sole cause (Davies et al., 2021). Other factors independently influencing fatigue in these conditions include anxiety, depression, pain, sleep disturbances, poor mental well-being, impaired physical function and activity, and altered energy balance (Bixio et al., 2024; Geenen & Dures, 2019; Matura et al., 2018). Psychological symptoms in rheumatic diseases remain underdiagnosed, and their management is often inadequate (Pezzato et al., 2021). While optimal pharmacological management of rheumatic disease effectively targets inflammation and reduces disease activity, it appears to provide only small benefits for fatigue (Chauffier et al., 2012; Chmielewski et al., 2023). Moreover, higher levels of fatigue negatively impact medication adherence, as patients may become more concerned about side effects or potential dependence (Tosato et al., 2022). This underscores the importance of approaches that specifically address fatigue, with non-pharmacological interventions potentially offering valuable benefits in managing arthritis-related fatigue (Cramp, 2019). Some researchers advocate for future studies to explore tailored interventions that focus on biopsychosocial factors contributing to the persistence of fatigue (Geenen & Dures, 2019). Ultimately, identifying and thoroughly assessing the subjective aspects of fatigue in individual patients is essential for effective management of this symptom in routine clinical practice (Chmielewski et al., 2023).

The European Alliance of Associations for Rheumatology (EULAR) recently emphasized the importance of recognizing that fatigue in rheumatic diseases is a multifaceted condition influenced by biological, psychological, and social factors and of implementing tailored, structured, and time-limited physical activity and psychoeducational interventions (Dures et al., 2023). Moreover, recent comprehensive reviews confirmed that physical exercise and psychosocial and psychoeducational interventions are efficacious in reducing fatigue related to arthritis (Cramp et al., 2013; Santos et al., 2023). Evidence from research indicates that telephone-delivered cognitive behavioral therapy (CBT) and personalized exercise programs have resulted in clinically significant reductions in both the severity and impact of fatigue and other outcomes in patients with rheumatic diseases (Bachmair et al., 2022). It is unclear which non-pharmacological intervention for fatigue is the most effective and yields the greatest benefits in terms of improving other disease outcomes (Cramp et al., 2013; White et al., 2011).

In studies involving psychological interventions for adults with rheumatoid arthritis, a parallel randomized controlled trial (RCT) demonstrated that a CBT group focused on fatigue self-management improved fatigue impact, coping strategies, perceived severity, and overall well-being (Hewlett et al., 2011), while a multicenter, two-year RCT revealed sustained reductions in fatigue impact through a group CBT program (Hewlett et al., 2019a). Qualitative study capturing patient perspectives on fatigue management interventions (Dures et al., 2012) have indicated that such interventions should extend beyond fatigue management alone, incorporating relevant psychological factors that may contribute to overall well-being and mental health, thereby potentially yielding indirect benefits for psychological outcomes associated with arthritis (Davies et al., 2021; Ristic et al., 2023).

The majority of clinical patients with rheumatoid arthritis are physically inactive (Sokka et al., 2008) and reduced physical activity is a hallmark of fatigue in inflammatory rheumatic disease (Davies et al., 2021). The World Health Organization (WHO) considers safe that adults living with chronic conditions, without contraindications, should engage in regular physical activity, as the benefits generally outweigh the risks (Bull et al., 2020). The American College of

Rheumatology recommend that specific type, frequency, intensity, and duration of exercise should be tailored to each person with rheumatoid arthritis with the assistance of their clinicians, considering the potential burden on and capacity of each person (England et al., 2023). One systematic review summarises that physical activity in rheumatoid arthritis was statistically significantly more effective than the control condition at the end of the intervention period, demonstrating a small beneficial effect on fatigue (Cramp et al., 2013). Specifically, a 12-week exercise program can yield significant and clinically meaningful improvements in fatigue and sleep quality (Durcan et al., 2014). Aerobic exercises in rheumatoid arthritis reduce fatigue directly and indirectly over the meaningful improvement in other symptoms (Kelley et al., 2018). In psoriatic arthritis (PsA), anaerobic exercise positively impacts fatigue, disease activity, quality of life, muscle strength, and partly cardiovascular risk factors (Kessler et al., 2021). Although preliminary evidence suggests that exercise may have anti-inflammatory effects that could help manage inflammation and related comorbidities in patients with chronic inflammatory rheumatic diseases, further research is needed to confirm these benefits (Metsios et al., 2020).

5.1.2 Objectives

The primary aim of the study is to measure and compare the effectiveness of cognitive behavioural therapy plus usual care, personalized exercise program plus usual care, and usual care alone in reducing fatigue.

Secondary aims include examining the effectiveness of non-pharmacological interventions on reducing disease activity, symptoms of depression and anxiety and pain levels and improving physical functioning, overall quality of life and sleep quality among participants. Additionally, the study will investigate the relationship between fatigue and other outcome variables within each non-pharmacological intervention, aiming to identify potential mediators and moderators of arthritis-related fatigue.

5.2 TRIAL DESIGN

The study design will be a randomized, controlled, open-label, parallel-group trial. Participants will be randomized (1:1:1) into one of three conditions: first experimental condition (psychological intervention plus usual care), second experimental condition (physical exercise plus usual care) and control condition (usual care only). The study protocol has been reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Chen et al., 2013).

5.3 METHODS: PARTICIPANTS, INTERVENTIONS AND OUTCOMES

5.3.1 Study setting

Recruitment and clinical evaluations for all the participants will be conducted at the Unit of Rheumatology at the GB Rossi Polyclinic Hospital, Integrated University Hospital of Verona, Italy. The psychological intervention will take place at the Department of Psychosomatics and Medical Psychology, Integrated University Hospital of Verona. The physical activity intervention will be held at the facilities of Integrated University Hospital of Verona.

5.3.2 Eligibility criteria

Eligible participants must: (a) be adults aged 18 years or older, (b) have a diagnosis of rheumatoid arthritis - according to the ACR/EULAR criteria (Kay & Upchurch, 2012), psoriatic arthritis - according to the CASPAR criteria or axial spondyloarthritis - according to the ASAS criteria (Rudwaleit et al., 2010), (c) have clinically stable disease, under adequate control as assessed by the rheumatologist in the last consultation before the trial enrollment, (d) have unchanged rheumatological therapy in the last three months and (e) achieved remission or mild disease activity based on the DAS28-CRP in rheumatoid arthritis (DAS28-CRP$\leq$3.5) and the DAPSA in psoriatic arthritis (DAPSA$\leq$14); inactive, moderate or high disease activity based on the ASDAS-CRPS in axial spondyloarthritis (ASDAS-CRP$\leq$2.1).

Participants will be excluded from the study in case: (a) a diagnosis of any severe systemic diseases or any other condition that demanded active medical attention other than rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis, (b) concomitant uncontrolled diabetes mellitus as measured by Glycated Hb levels ≥7.5 mmol/l or other severe or life-threatening illnesses (not under control by the therapy or not in remission malignancy, liver, heart or renal failure, congenital metabolic disease), (c) currently undergoing psychotherapy, (d) female patients who are pregnant or breastfeeding, (e) patients who are not independently mobile or have any invalidity or have some degree of disability that limits the ability to perform simple physical exercises, (f) patients who cannot understand Italian sufficiently to participate in the intervention and (g) patients who are unable or refuse to provide the written informed consent.

Eligibility criteria for individuals performing the interventions are as follows: for psychological interventions, the professional must be a clinical psychologist/psychiatrist and psychotherapist and for a physical exercise program, a qualified physiotherapist.

Who will take informed consent?

After the routine rheumatology visit, the rheumatologist or trainees will explain the study to potentially eligible patients and invite them to participate. Patients who express interest will receive the informed consent form and will have the opportunity to ask questions and clarify any doubts with a member of the research team to ensure they fully understand the study. Only patients who sign the informed consent will be enrolled in the trial. Informed consent will be obtained before any study procedures are conducted. See the Informed consent in Appendix E1.

Additional consent provisions for collection and use of participant data and biological specimens

Biological specimens from routine blood tests are collected from all rheumatic patients prior to the initiation of the trial. Patients will be asked to provide consent for the use of these results in research. This trial does not involve collecting any other biological specimens for storage, nor does it require additional consent for any other aspects of the study.

Explanation for the choice of comparators

All participants will receive usual medical care. Additionally, each participant will be provided with a booklet covering topics related to fatigue and its significance for arthritis conditions. The booklet is based on previously published booklets on the same topic (Lombardy Association of Rheumatic Patients (ALOMAR) - Living with rheumatoid arthritis; Swiss Association of Polyarthritics (ASP) - Living with rheumatoid arthritis). The key difference between the groups is that two experimental groups will receive an additional intervention, while the control group will not receive any supplementary treatments.

5.3.3 Intervention description

Patients will be randomized into one of two experimental groups (psychological intervention or physical exercise) or into a control group. In experimental groups, the intervention will be delivered in a group format and will include 10 participants per group. It will span six months (24 weeks) and consist of 12 sessions, each lasting one and a half hours, scheduled every two weeks. Between sessions, participants will be given homework/exercise to consolidate the topic/activity discussed/done in the previous week. This approach encourages ongoing engagement with the intervention instead of relying solely on the bi-weekly sessions. Additionally, there will be two booster sessions during the follow-up period of another six months.

Intervention content

Psychological intervention

Previous trials on fatigue interventions in arthritis have tailored their interventions individually, they predominantly employed cognitive-behavioral therapy as a foundational approach (e.g., Duarte et al., 2023; Hewlett et al., 2011). To date, we have not encountered two studies with identical intervention plans. Nevertheless, by considering insights from various studies and the theoretical framework of cognitive-behavioural therapy, we have defined the core topics for our sessions and further created intervention content.

Overall, the psychological intervention will focus, other than on fatigue, on emotional regulation, cognitive restructuring, coping skills, disease acceptance, communication skills, and strategies for managing stress, pain, and sleep. Topic for each session will be: (1) Introduction - psychoeducation, (2) Managing fatigue, (3) Behavioral activation (4) Exploring emotions, (5) Challenging negative thoughts, (6) Understanding cognitive distortions and coping strategies, (7) Self-care and fatigue, (8) Social support and communication strategies, (9) Stress management techniques; Pain and fatigue, (10) Sleep Hygiene and other healthy behaviour, (11) Review of skills and integration and (12) Reflection and future planning.

The sessions will follow a consistent structure while remaining adaptable to the specific needs of the patients. Sessions will feature an introduction, a main part and a general conclusion at the end. In the first session, the intervention program will be presented to the patients, while in the final meeting, both patients and psychotherapist will summarize their insights on fatigue and related topics. In general, each session will start with a recap of the previous homework assignment and invite participants to share their thoughts and experiences related to it. Further, it will introduce a new topic related to fatigue through psychoeducation. The main part will have a cognitive/emotional and behavioural approach where the therapist will engage participants in a discussion about their experiences and perspectives, and participants will conduct skill-building activities that reinforce the concepts discussed. Therapists with participants will summarize the key points of the session, highlighting the main themes and take-home messages. Homework Assignments will be at the end, participants will have the tasks to reinforce learning and consolidation of the topic.

An overview of the psychological intervention is presented in Table 1. Detailed description of the psychological intervention please find in Appendix E2.

Table 1 Psychological intervention overview

Session	**Module**	**Content and learning objectives**
Session 1	Introduction - psychoeducation	Overview: Introduction to the intervention and arthritis-related fatigue Activities: · Introduction to the program: goals, overview, and ground rules (discussion on group norms and confidentiality) · Participant presentations: motivations for participating and expectations regarding the intervention · Psychoeducation on arthritis-related fatigue: defining fatigue, clarifying how it differs from regular tiredness, and exploring potential factors associated with it · Participant's personal experiences of fatigue · Identifying current difficulties in managing fatigue and discussing various strategies for dealing with fatigue in daily life Homework: Diary of self-monitoring fatigue (daily experience with fatigue and its impact on everyday life).
Session 2	Managing fatigue	Overview: Recognize the oscillations of fatigue and understand it Activities: · Psychoeducation: Understanding the energy management (boom and bust cycle). · Current self-management strategies - energy management diaries · Energy conservation and achieving a balance: degree of control over own life experience, self-efficacy and locus of control.

		• Developing effective problem-solving techniques to handle fatigue triggers Homework: Monitoring thought and emotions related to fatigue.
Session 3	Behavioural activation	Overview: Discuss the relationship between behaviour activation and fatigue Activities: • Psychoeducation: Introduce the concept of behavioural activation • Participants list enjoyable or meaningful activities and list of life priorities • A routine of the day, organization and distribution of the energy: Setting realistic goals to combat avoidance behaviour • Disability and ways to cope with it. Solution-focused goal feedback Homework: List of positive activities and activities that provoke the fatigue. List of activities organized in advance.
Session 4	Exploring emotions	Overview: Discuss the impact of emotions on fatigue and vice versa. Activities: • Psychoeducation: explain the concept of emotions. • Explore techniques for identifying and regulating emotions. It's association with fatigue. • Recognizing and addressing difficult emotions. • Psychoeducation: general framework of the relationship among emotions, cognition and behavior in arthritis. Examples from the participants. Homework: Register of the emotions and fatigue in daily life. Differentiating thoughts and emotions.

Session 5	Challenging negative thoughts	Overview: Learn methods to challenge and reframe negative thoughts Activities: • Psychoeducation: Introduction into irrational thoughts and techniques for cognitive restructuring. • Insights into negative self-talk, automatic thoughts and rumination: The best ways of self-sabotage • Challenging negative thoughts related to arthritis and positive action that can be taken Homework: Thought monitoring: common irrational thoughts (both general and related to fatigue) and underlying beliefs. Practice reframing at least three negative thoughts from the previous week.
Session 6	Understanding cognitive distortions and coping strategies	Overview: Cognitive distortions and their role in arthritis-related fatigue • Psychoeducation: Introduce common cognitive distortions • Participants identify automatic thoughts that contribute to fatigue • Energy-draining effect of catastrophizing thoughts. • Psychoeducation: Coping with unhelpful thinking patterns • Participants recognize their own coping strategies related to arthritis. Clarify the effectiveness of current coping strategies for fatigue. • Development of alternative illness perception on fatigue to enhance approach coping. Homework: Identify and track cognitive distortions throughout the week using a thought

		record sheet. Make examples of how to transform negative thinking into helpful thoughts.
Session 7	Self-care and fatigue	Overview: Introduce self-care and its benefits for managing fatigue Activities: · Psychoeducation: Importance of self-care · Participants recognize own self-care and self-destructive behaviour · Psychoeducation: Self-compassion and self-acceptance. · Participants try to gain insight into their own values and weaknesses. Behavioural strategies for enhancing self-esteem. · Psychoeducation: Body image. · Participants draw or describe their own body image. Bringing compassion to the body. Homework: When do I feel respected or less respected.
Session 8	Social support and communication strategies	Overview: Importance of social support and communication about fatigue with healthcare providers and family Activities: - Psychoeducation: Social support - Sense of belonging, feeling not alone in this disease - Strategies for enhancing the quality of social support (realistic expectations) - Participants design a social support network map - Fatigue is often invisible to others - lack of social understanding Psychoeducation: Communication skills and tips for talking with the health care team and family. - Effective communication techniques

		Homework: Reflections on current social relationships (family, friends, colleagues).
Session 9	Stress management techniques; Pain and fatigue	Part I Overview: Explore how stress impacts fatigue and introduce stress management techniques. Activities: - Psychoeducation: Managing stress - Participants make a hierarchical list of personal stressors and of stressful situations in everyday life. - Arthritis-related stress: list of priorities - Relaxation techniques Homework: Practice relaxation techniques daily and note the effects on fatigue levels. Part II Overview: Relationship between pain and arthritis-related fatigue Activities: - Psychoeducation: Understand pain in arthritis - Strategies for facing negative emotions and pain - Participants discuss when the pain appears, how it is related to fatigue and how to face it Homework: Diary on pain and fatigue during the day – find the connection.
Session 10	Sleep Hygiene and other healthy behaviour	Overview: Importance of sleep and its relationship to fatigue. Activities: - Psychoeducation: Introduce sleep hygiene practices. Strategies for improving sleep routines. - Participants express their sleep challenges and strategies - How does sleep quality affect fatigue?

		Homework: Implement at least three sleep hygiene practices and record sleep quality in a sleep log
Session 11	Review of skills and integration	Overview: Review and integrate skills learned throughout the program. Activities: - Review of the intervention and personal highlights from the intervention. - Participants create an individualized fatigue management plan using the skills learned - Strategies for maintaining skills beyond the group Homework: Respect fatigue management plan. Diary: Daily activities and fatigue, emotions and thoughts that follow it.
Session 12	Reflection and future planning	Overview: Reflect on the overall experience in the group. Activities: - Group discussion on challenges and successes using CBT skills. - Life with arthritis - Discuss what they learnt from the program -Feedback on the intervention and progress made attending to the initial expectations - Clarifying future directions. - Open discussion: Hopes and dreams for the future. - Assessment for the end of trial. Homework: - Respect fatigue management plan.
Follow-up after 8 and 16 weeks	Booster session	Overview: Refreshment of the main concepts; evaluate difficulties in the implementation

		Homework: Revise fatigue management plan and continue with diary on daily activities, fatigue, thoughts and emotions.

Physical exercise program

The physiotherapist will have a group meeting with patients and present the weekly exercise plan to them. Participants will receive the same exercise program tailored for arthritis patients, with individual adaptation depending on each patient's specific physical condition and age. Initially, physiotherapists will introduce the stretching and breathing exercises program to help patients incorporate these activities into their daily routines. Additionally, baseline self-assessment questionnaires will enable physiotherapists to gain a better understanding of each patient's individual needs. During interactions with patients, physiotherapists will also gather personal narratives related to their experiences with the disease. Previously, this innovative, integrative approach, combining physical exercises with personal experience related to the disease, demonstrated a positive impact on pain and fatigue in rheumatic patients (Galvani et al., 2019). In relation to the daily activities, every patient will receive a physical activity schedule that includes a full body exercise program (stretching, force and resistance), breathing training and aerobic exercise indications. Week by week, all exercises will have a progressive level of difficulty and resistance. Patients need to exercise at home daily except for aerobic activity, which should be practiced three times per week.

An overview of the physical exercise program is provided in Table 2.

Table 2 Physical exercise program overview

Session	Topic	Description of the intervention
1	Background of the participants	• The history and description of fatigue. • Distribution and completion of the questionnaire specifically developed for this study. • Body awareness in different postures and pain awareness.

		• Breath awareness and breathing exercises.
2	Considerations on individual experience, postural hygiene and aerobic physical activity.	• Sharing of the challenges faced and insights gained. • Body and breath awareness. • Postural hygiene with the introduction of personalized posture adjustments to be incorporated into ADLs. • Guidelines for aerobic physical activity.
3	Considerations on individual experience and first approach to physical exercise.	• Sharing of the challenges faced and insights gained. • Body and breath awareness. • Introduction of postural stretching to be incorporated into ADLs. • Selection and proposal of personalized physical exercise based on the previously completed questionnaire.
4	Considerations on individual experience and self-treatment.	• Sharing of the challenges faced and insights gained. • Body and breath awareness. • Introduction of self-manual therapy.
5	Considerations on individual experience and balance exercises.	• Sharing of the challenges faced and insights gained. • Body and breath awareness. • Introduction of balance exercises.
6	Considerations on individual experience and therapy adjustments.	• Sharing of the challenges faced and insights gained. • Body and breath awareness. • Distribution and completion of the questionnaire specifically developed for this study. • Introducing exercise variations or modifications for independent practice.
7	Considerations on individual experience and therapy adjustments.	• Sharing of the challenges faced and insights gained. • Body and breath awareness. • Introducing exercise variations or modifications for independent practice.
8	Considerations on individual	• Sharing of the challenges faced and insights gained. • Body and breath awareness.

	experience and therapy adjustments.	• Distribution and completion of the questionnaire specifically developed for this study. • Introducing exercise variations or modifications for independent practice.
9	Considerations on individual experience and therapy adjustments.	• Sharing of the challenges faced and insights gained. • Body and breath awareness. • Introducing exercise variations or modifications for independent practice.
10	Considerations on individual experience and therapy adjustments.	• Sharing of the challenges faced and insights gained. • Body and breath awareness. • Distribution and completion of the questionnaire specifically developed for this study. • Introducing exercise variations or modifications for independent practice.
11	Considerations on individual experience and therapy adjustments.	• Sharing of the challenges faced and insights gained. • Body and breath awareness. • Introducing exercise variations or modifications for independent practice.
12	Considerations on individual experience and conclusions.	• Sharing of the challenges faced and insights gained. • Body and breath awareness. • Distribution and completion of the questionnaire specifically developed for this study. • Closing thoughts and conclusions.

Usual care - treatment as usual

Clinical care will continue as usual for all patients, regardless of their assigned group, throughout the study. This will include regular outpatient visits. Medications and supplementary therapies will be documented at baseline and during each follow-up visit.

To minimize potential performance bias, participants in the control group, as well as those in experimental groups, will receive a booklet explaining self-management strategies (including physical activity and psychological techniques) for managing fatigue. This booklet provides comprehensive information on topics relevant to the study, such as physical activity, nutrition, and psychological strategies to help patients cope with the daily challenges of living with arthritis. The booklet will be distributed and explained to all patients during the baseline visit, after obtaining consent and completing initial assessments, but before randomization. This approach ensures that even the control group benefits from the trial, although the booklet will not be considered an intervention. The impact of the booklet won't be accounted for, as it will be provided to all participants across all three groups.

Criteria for discontinuing or modifying allocated interventions

Patients experiencing suboptimal disease control (deterioration of their rheumatological or other medical conditions) will discontinue the trial and be referred to a healthcare professional. Additionally, any participant who begins any form of psychotherapy outside the study during the trial will be withdrawn.

Participants may withdraw from the study at any time without providing an explanation. They also have the right to request the destruction of their data or to prevent their data from being included in the final analysis at any point.

Strategies to improve adherence to interventions

After randomization, participants in the experimental group will receive a complete schedule of sessions, while those in the control group will be provided with the dates for the baseline and end-of-treatment assessments. Participants in the experimental group will also receive reminder calls from the research team member one day before each session. If a participant misses a session, a research team member will contact them by phone within one day to inquire about the reason for their absence.

The adherence to the physical exercise program will be monitored during the intervention period. All the participants (both from the control and experimental groups) must fill out one questionnaire weekly to control these variables across all groups. It is the measure of weekly physical activity (Global Physical Activity Questionnaire (GPAQ; Armstrong et al., 2006). The amount of exercise will be calculated by summing the mean minutes per week of the intervention.

Relevant concomitant care permitted or prohibited during the trial

Patients enrolled in the study are not allowed to undergo any psychotherapeutic treatment during the trial period.

Provisions for post-trial care

In accordance with ethical guidelines, participants assigned to the control group (usual care alone) will be offered the opportunity to receive interventions from the trial afterwards.

5.3.4 Outcomes

Primary outcomes

Difference in the level of fatigue as measured by total score on the Chalder Fatigue Questionnaire (CFQ; Chalder et al., 1993) between psychological intervention plus usual care, physical exercise program plus usual care and usual care alone over time (change from baseline to the end of treatment and 6-month follow-up).

Secondary outcomes

a) Effectiveness

Difference between psychological intervention plus usual care, physical exercise program plus usual care and usual care alone over time (change from baseline to the end of treatment and 6-month follow-up) in the total scores of the following instruments:

- The 28-joint disease activity score – C-reactive protein (DAS28-CRP) for rheumatoid arthritis, Disease Activity in PSoriatic Arthritis (DAPSA) for psoriatic arthritis, Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein (ASDAS-CRP) for axial spondyloarthritis for disease activity;
- The Health Assessment Questionnaire – Disability Index (HAQ-DI) for physical functioning;
- The Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF-MDQ) for fatigue (second measure);

- The Hospital Anxiety and Depression Scale - Depression (HADS-D) and the Patient Health Questionnaire-9 (PHQ-9) for depression;
- The Hospital Anxiety and Depression Scale – Anxiety (HADS-A) and the General Anxiety Disorder scale (GAD-7) for anxiety;
- The Visual Analogue Scale (VAS) for pain;
- The Health-Related Quality of Life – Short Form 36 items (SF-36) for quality of life;
- The Pittsburgh Sleep Quality Index (PSQI) for sleep quality;
- Psychosocial and Environmental Stressors (DSM-IV) for stressful life events;
- PREvencion con DIeta MEDiterranea (PREDIMED) for adherence to Mediterranean diet pattern;
- Three Factor Eating Questionnaire-Revised 18 (TFEQ-R-18) for eating behaviour;
- The Global Physical Activity Questionnaire (GPAQ) for physical activity;
- Behavioural Regulation in Exercise Questionnaire (BREQ-3) for motivation towards physical activity and exercise.

b) Mediation and moderation

Association between arthritis-related fatigue (measured using CFQ and BRAF-MDQ) and clinical, psychological and other factors will be examined across three groups over time (change from baseline to the end of treatment and 6-month follow-up). The factors will be evaluated with the following instruments:

- DAS28-CRP for rheumatoid arthritis, DAPSA for psoriatic arthritis, ASDAS-CRP for axial spondyloarthritis for disease activity;
- HAQ-DI for physical functioning;
- HADS-D and PHQ-9 for depression;
- HADS-A and GAD-7 for anxiety;
- VAS for pain;
- SF-36 for quality of life;
- PSQI for sleep quality;
- The Childhood Trauma Questionnaire-Short Form (CTQ-SF) for childhood trauma;

- Psychosocial and Environmental Stressors for stressful life events;
- PREDIMED for adherence to Mediterranean diet pattern;
- TFEQ-R-18 for eating behaviour;
- GPAQ for physical activity;
- BREQ-3 for motivation towards physical activity and exercise.

5.3.5 Assessment instruments

All of the following instruments, except for the measure of disease activity, are self-assessment tools. Participants will complete them at baseline, at the end of treatment, and after the 6-month follow-up period.

- Fatigue will be assessed with two instruments. The primary outcome will be measured by the Chalder Fatigue Questionnaire (CFQ; Chalder et al., 1993), a self-administered questionnaire for measuring the extent and severity of fatigue in the last month. It consists of 11 items rated on a 4-point scale, resulting in scores that range from 0 to 33, with higher scores indicating greater levels of fatigue. The CFQ showed valid and reliable results for measuring fatigue. The secondary outcome will be assessed using the Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire (BRAF MDQ; Nicklin et al., 2010). It measures domains of physical fatigue, living with fatigue, cognitive fatigue, and emotional fatigue. It has 20 items, providing a total fatigue score.
- Disease activity will be measured by the 28-joint disease activity score – C-reactive protein (DAS28-CRP; van Riel & Renskers, 2016) the Disease Activity in PSoriatic Arthritis (DAPSA; Schoels et al., 2010) and the Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein (ASDAS-CRP; van der Heijde et al., 2009) measure disease activity in daily clinical practice among rheumatoid arthritis, psoriatic arthritis and spondyloarthritis (respectively) in daily clinical practice. Assessments will be done by the patient and by the physician.
- Depression will be assessed by two instruments. The Hospital Anxiety and Depression Scale-Depression (HADS-D; Zigmond & Snaith, 1983) is one self-administered tool validated in a hospital context that allows you to investigate severity of depressive symptoms. The Patient Health Questionnaire-9 (PHQ-9;

Kroenke et al., 2001) is a self-administered instrument to assess the severity of participants' depression symptoms.

- Anxiety will be measured by two instruments. The Hospital Anxiety and Depression Scale-Anxiety (HADS-A; Zigmond & Snaith, 1983) is one self-administered tool validated in a hospital context that allows you to investigate severity of depressive symptoms. The General Anxiety Disorder scale (GAD-7; Spitzer et al., 2006) is a 7-item, 4-point rating scale developed to assess how frequently the patient has experienced seven anxiety symptoms during the last 2 weeks.
- The Health-Related Quality of Life (HRQoL) will be assessed by the Medical Outcome Study 36-item Short Form health survey (SF-36; Ware & Sherbourne, 1992). It contains the physical component score (PCS) and the mental component score (MCS). Lower scores indicate worse HRQoL.
- Pain will be measured by the visual analogue scale (VAS; Delgado et al., 2018). The instrument is a validated, subjective measure of acute and chronic pain. Scores are recorded by making a handwritten mark on a 10-cm line representing a continuum between "no pain" and "worst pain."
- Physical functioning will be assessed using the Health Assessment Questionnaire – Disability Index (HAQ-DI, Ranza et al., 1993), a questionnaire that evaluates how the patients' functional ability to fulfil daily activities is limited by organic disease.
- Sleep quality will be measured by the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989). It is a questionnaire of 19 items that evaluate the quality of perceived sleep. Components evaluated the subjective quality of sleep, sleep latency, sleep duration, habitual sleep effectiveness, sleep disorders, use of hypnotic drugs, and disturbances during the day.
- Childhood trauma will be measured by the Childhood Trauma Questionnaire-Short Form (CTQ-SF) (Bernstein and Fink 1998). It is a screening instrument investigating the history of emotional, physical, and sexual abuse and emotional and physical neglect during childhood (<17 years).

- Stressful life events will be assessed by psychosocial and Environmental Stressors (DSM-IV; Muller and Koch, 2011). It comprising the presence and severity of the nine psychosocial stressors and environmental problems of DSM-IV axis IV.
- Adherence to Mediterranean diet pattern will be evaluated by the PREvencion con DIeta MEDiterranea (PREDIMED; Martínez-González et al., 2012). The 14-item questionnaire primarily measures the adherence of participants to the Mediterranean diet.
- Physical activity will be assessed by the Global Physical Activity Questionnaire (GPAQ; Armstrong et al., 2006). It is a widely used self-reported questionnaire developed by the World Health Organization. It has 16 items, records the activity of three domains: work, transport, and leisure time, and can differentiate between vigorous and moderate physical activity.
- Motivation towards physical activity and exercise will be evaluated by the Behavioural Regulation in Exercise Questionnaire (BREQ-3; Cavicchiolo et al., 2022). The instrument measure different types of regulation in the domain of exercise as multidimensional constructs. The scale comprises 6 subscales: amotivation, external regulation, introjected regulation, identified regulation, integrated regulation and intrinsic motivation.
- Eating behaviour will be measured by the Three Factor Eating Questionnaire-Revised 18 (TFEQ-R-18; Rossi et al., 2024). It assesses three features of eating behaviour: cognitive restraint, uncontrolled eating, and emotional eating.

5.3.6 Participant timeline

See Fig. 1 for the SPIRIT figure with the participant timeline.

	STUDY PERIOD							
	Enrolment	Allocation	Post-Allocation					
Time Point (weeks)	Recruitment (0w)	Allocation (0w)	Baseline (0w)	Weekly (1-23w)	End treatment (24w)	Booster 1 (32w)	Booster 2 (40w)	Follow-up (48w)
ENROLMENT								
In- and exclusion criteria screen	x							
Informed consent	x							
Randomization		x						
INTERVENTION								
Psychological intervention			x	x	x	x	x	
Physical exercise intervention			x	x	x	x	x	
Usual care	x	x	x	x	x	x	x	x
ASSESSMENTS								
Disease activity: DAS28-CRP / DAPSA / ASDAS-CRP	x		x		x			x
Fatigue: CFQ, BRAF-MDQ	x		x x		x x			x x
Depression: HADS-D, PHQ-9	x		x x		x x			x x
Anxiety: HADS-A, GAD-7			x x		x x			x x
Pain: VAS			x		x			x

Quality of life: SF-36			x		x			x
Sleep quality: PSQI			x		x			x
Childhood trauma: CTQ-SF			x		x			x
Stressful life events: Psychosocial and Environmental Stressors			x		x			x
Mediterranean diet: PREDIMED			x		x			x
Eating behaviour: TFEQ-R-18			x		x			x
Physical activity: GPAQ			x	x	x			x
Physical activity-motivation: BREQ-3			x		x			x

Fig. 1 Schedule of enrolment, intervention and assessment of the study.

DAS28-CRP, The 28-joint disease activity score and C-reactive protein; DAPSA, Disease Activity in PSoriatic Arthritis; ASDAS-CRP, Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein; HAQ-DI, Health Assessment Questionnaire – Disability Index; CFQ, CFQ, Chalder Fatigue Questionnaire, BRAF-MDQ, Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire; HADS-D, Hospital Anxiety and Depression Scale – Depression; PHQ-9, Patient Health Questionnaire-9; HADS-A, Hospital Anxiety and Depression Scale – Anxiety; GAD-7, General Anxiety Disorder scale; VAS, Visual Analogue Scale; SF-36, Health-Related Quality of Life – Short Form 36 items; PSQI, Pittsburgh Sleep Quality Index; CTQ-SF, Childhood Trauma

Questionnaire-Short Form; PREDIMED, PREvencion con DIeta MEDiterranea; TFEQ-R-18, Three Factor Eating Questionnaire-Revised 18; GPAQ, Global Physical Activity Questionnaire; BREQ-3, Behavioural Regulation in Exercise Questionnaire;

5.3.7 Sample size

The primary outcome of the study will be the difference in fatigue scores among the three groups at the end of treatment, adjusted for baseline values. Based on the minimum clinically meaningful improvement established for the CFQ score, we anticipate a minimum difference of at least 9.9 points in fatigue scores between the experimental and control groups, with the score range being 0 to 33 (Pouchot et al., 2008).

The GPower 3.1.9.7 software was used to calculate the sample size to achieve a power of 0.80 in a Repeated-measures ANOVA (within-between interaction) on the primary outcome (CFQ total score). The following values were set: 3 groups, 3 measurement occasions, a correlation among repeated measures of 0.50, an effect size (measured by Cohen's f statistic) of 0.10 (small effect size), no violation of the sphericity assumption, and an overall significance level of 0.05. A total sample size of 204 (68 for each arm) was estimated. To account for an expected dropout rate of about 20%, the sample size will be inflated to 240 (80 for each arm). See Fig. 2.

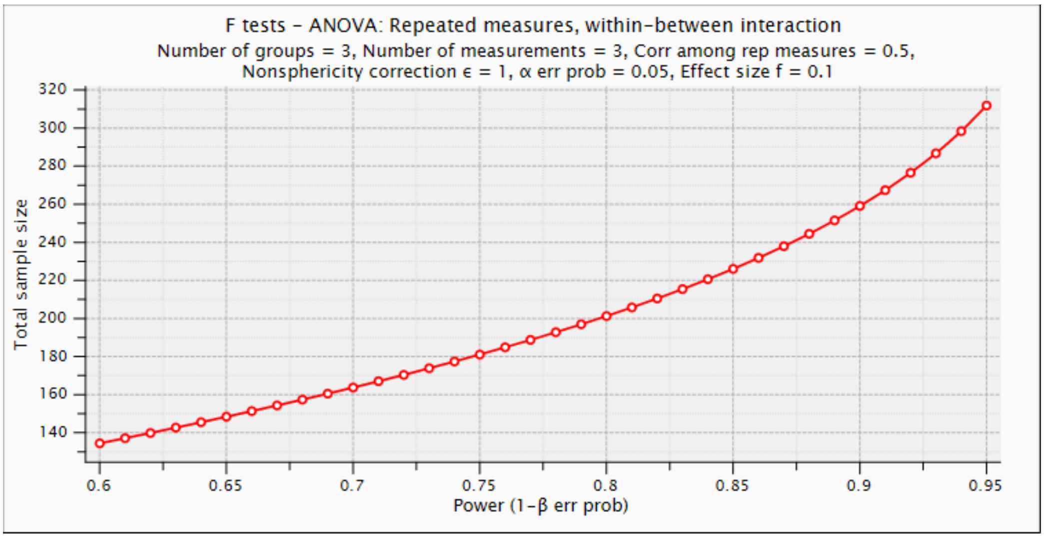


Fig. 2 Power of the study

5.4.1 RECRUITMENT

Patients will be recruited at the Unit of Rheumatology of the University Hospital of Verona, Italy. Recruitment will be done during the regular visits. The rheumatologist or trainees will present the study and invite patients who meet the inclusion and exclusion criteria to participate. Recruitment will last for 6 months, the intervention will extend over 6 months, the follow-up period will last 6 months, and an additional 6 months will be required for data entry, database verification, data analysis, and manuscript preparation. Therefore, the total duration of the study is 24 months. A schematic overview of the study design is presented in the flow diagram shown in Fig. 3.

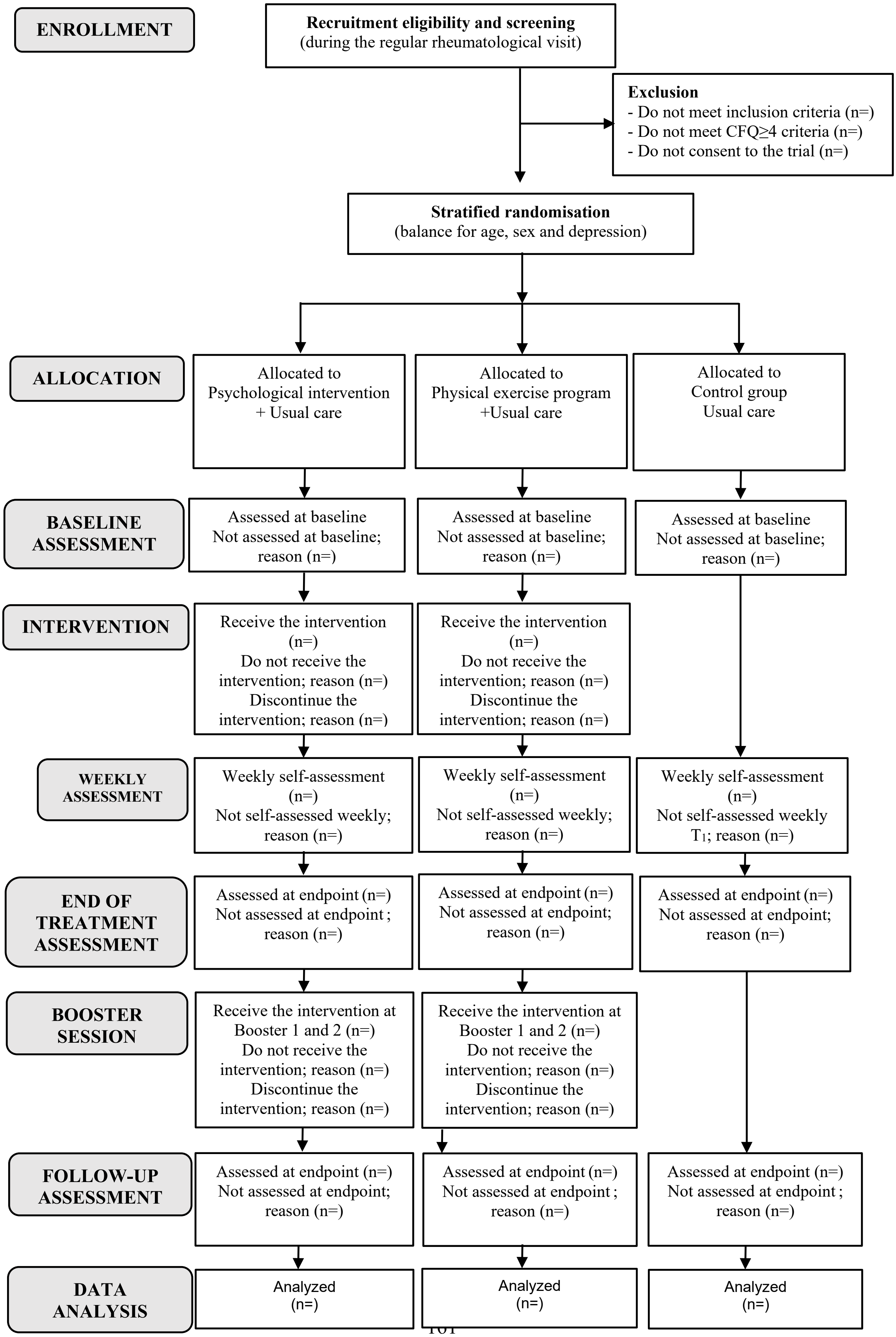

ENROLLMENT
Recruitment eligibility and screening
(during the regular rheumatological visit)
Exclusion
- Do not meet inclusion criteria (n=)
- Do not meet CFQ≥4 criteria (n=)
- Do not consent to the trial (n=)
Stratified randomisation
(balance for age, sex and depression)
ALLOCATION
Allocated to Psychological intervention + Usual care
Allocated to Physical exercise program +Usual care
Allocated to Control group Usual care
BASELINE ASSESSMENT
Assessed at baseline
Not assessed at baseline; reason (n=)
Assessed at baseline
Not assessed at baseline; reason (n=)
Assessed at baseline
Not assessed at baseline; reason (n=)
INTERVENTION
Receive the intervention (n=)
Do not receive the intervention; reason (n=)
Discontinue the intervention; reason (n=)
Receive the intervention (n=)
Do not receive the intervention; reason (n=)
Discontinue the intervention; reason (n=)
WEEKLY ASSESSMENT
Weekly self-assessment (n=)
Not self-assessed weekly; reason (n=)
Weekly self-assessment (n=)
Not self-assessed weekly; reason (n=)
Weekly self-assessment (n=)
Not self-assessed weekly T1; reason (n=)
END OF TREATMENT ASSESSMENT
Assessed at endpoint (n=)
Not assessed at endpoint ; reason (n=)
Assessed at endpoint (n=)
Not assessed at endpoint; reason (n=)
Assessed at endpoint (n=)
Not assessed at endpoint; reason (n=)
BOOSTER SESSION
Receive the intervention at Booster 1 and 2 (n=)
Do not receive the intervention; reason (n=)
Discontinue the intervention; reason (n=)
Receive the intervention at Booster 1 and 2 (n=)
Do not receive the intervention; reason (n=)
Discontinue the intervention; reason (n=)
FOLLOW-UP ASSESSMENT
Assessed at endpoint (n=)
Not assessed at endpoint; reason (n=)
Assessed at endpoint (n=)
Not assessed at endpoint ; reason (n=)
Assessed at endpoint (n=)
Not assessed at endpoint ; reason (n=)
DATA ANALYSIS
Analyzed (n=)
Analyzed (n=)
Analyzed (n=)

Fig. 3 Flowchat of the trial design

The trainees will do the screening after the visit, or they will schedule a new appointment. The screening process is based on the assessment of disease activity [DAS28-CRP for rheumatoid arthritis (van Riel et al., 2016), DAPSA for psoriatic arthritis (Schoels et al., 2010), ASDAS for spondyloarthritis (van der Heijde et al., 2009)] and fatigue [Chalder Fatigue Questionnaire (CFQ; Chalder et al., 1993)] (a level of fatigue above the cutoff of 3 (on the scale of 0-11) as assessed by the Chalder Fatigue Questionnaire (Nordin et al., 2016)). If a participant has been identified as potentially eligible, the trainee asks to sign the informed consent form, and they will explain to her/him that he/she will be informed about the next phase, depending on the randomization. At this point, the trainee will assign a Participant Identification Number (PIN) - a three-digit code based on the order in which patients enter the screening phase. This PIN will be used to maintain the participant's anonymity in questionnaires, and the participant will be instructed to use this number in all assessments without writing their name. The trainee will keep a confidential list linking participant names to their PINs.

5.4.2 Assignment of interventions: allocation

Sequence generation

Using a computer-generated sequence, participants will be allocated into three groups to receive psychological intervention plus usual care (Group 1), a physical exercise program plus usual care (Group 2), and usual care alone (Group 3) (1:1:1 ratio). It will be applied the stratified randomisation method, and groups will be balanced for age [adults (18-64 yrs.), older adults (65 yrs. and above)], sex [male, female] and depression [Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983); not depressed patients (HADS-D score$\leq$8), depressed patients (HADS-D score>8)]. Allocation will be done after the participants pass the screening.

Concealment mechanism

Allocation sequences will be concealed from the research team and staff enrolling participants by using an independent trainee. This ensures that group assignments are not predictable or accessible prior to participant enrollment, minimizing selection bias.

5.4.3 Implementation

After the screening, the statistician will perform the randomization process using participant-specific information for balancing, including gender, age, and HADS-D score, associated with each participant's PIN. The statistician will then disclose only the PIN and the group allocation to the trainee, who knows the corresponding participant name. After the allocation sequence, each patient will be informed by the trainee via telephone about the group to which they have been assigned. The trainee will also provide details regarding the location and time of the first meeting with their group, which will serve as an introduction for the participants, including completing baseline assessments and scheduling follow-up meetings.

5.4.4 Assignment of interventions: Blinding

Who will be blinded

The current trial cannot be blinded for participants, as complete blinding procedures for psychological and physical interventions are impossible due to the nature of these interventions and their outcome measures (Rongen-van Dartel et al., 2015; Baillet et al., 2012; Vadell et al., 2007).

However, two types of blinding will be implemented. First, a blinded assessment will be conducted on researchers responsible for assessing participants, blinding them to participants' allocation and by instructing participants not to discuss their interventions with staff. This approach aims to reduce detection bias. Second, blinded analysis will involve keeping the statistician unaware of participants' group assignments during data analysis.

Procedure for unblinding if needed

Unblinding procedures will not be conducted because of the intervention's nature. After the statistical analysis is completed by the blinded statistician, a member of the research team, who knows which participant corresponds to which groups, will interpret the data.

5.5 DATA COLLECTION AND MANAGEMENT

5.5.1 Plans for assessment and collection of outcomes

Baseline, end-of-treatment, and follow-up assessments will be conducted by the research team. Each of the three groups will undergo the same assessments in terms of content and timing. All data will be collected using paper questionnaires. One part will be collected by the research member and the rest by self-assessment instruments.

Anamnestic evaluations, including sociodemographic information, pathological history, disease activity, and medication history, will be gathered at baseline by a rheumatologist or trainee. Biological measurements such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin (Hb), thyrotropin (TSH), and vitamin D (25-OH-vitD) will be obtained from patients' medical records at baseline, as routine blood tests are performed for all rheumatic patients at the University Hospital of Verona.

Data on disability, psychosocial factors, physical activity, and diet will be collected at baseline, end-of-treatment, and follow-up through self-administered questionnaires. Weekly, the level of physical activity adherence will be assessed throughout the six-month treatment period using self-assessment questionnaires.

Plans to promote participant retention and complete follow-up

After the allocation and the initial session with the experimental groups, the group therapist will contact participants to remind them of the upcoming session and the scheduled assessment at each time point specified in the protocol. Additionally, a member of the research team will be assigned to oversee the accurate and complete collection of all measures throughout the entire trial, from baseline to follow-up.

5.5.2 Data management

All information will be treated in a strictly confidential manner and codified according to the identifiability criterion. This criterion consists of attributing an alphanumeric code to the information packages collected, known only to the operator who manages the pseudonymisation, which operates under the responsibility of the principal investigators of the study. This information management criterion does not preclude the subject from being able to withdraw consent if they so wish.

The immediate attribution of a code for each patient will allow the subject's confidentiality and anonymity to be preserved. The storage of sensitive data will be carried out in both paper and electronic format, both subjected to the coding procedure.

The paper archive will include:

1. a register in which the names of the participants and the related codes assigned will be transcribed;

2. a register in which the different participants will be reported only with their alphanumeric code and with all clinical information (the clinical forms compiled during the study);

3. the collection of informed consent.

Once the study is completed, the anonymized data will be made available for statistical analysis.

All paper documentation will be kept under lock and key in two separate filing cabinets: one containing that relating to points 1 and 3 and the other that relating to point 2. This system guarantees a separation of the registers reporting the clinical and phenotypic characteristics of the donors from the register, allowing us to trace each subject's identity. Access to the register referred to in point 1 is limited only to the operator who manages the data authorised the principal investigators. Access to the information contained in the register referred to in point 2 will be limited to authorised staff members. The data recorded on magnetic media will be kept anonymous by assigning the identification code, and all the computers in which the study data will be stored will be protected by keywords. The rooms where both the cabinets and the computers are kept will be locked and protected by alarm systems if unattended.

Confidentiality

Researchers involved in the study are committed to maintaining the strict confidentiality of all participant information. All source records, including electronic data, will be securely stored within protected systems. No identifiable details about enrolled subjects will be disclosed to unauthorized third parties. Confidentiality will be upheld throughout every stage of publication.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use

Biological measurements, including CRP, ESR, hemoglobin (Hb), TSH, and vitamin D levels, will be extracted from patients' medical records at baseline, as routine blood tests are conducted for all rheumatic patients. No additional biological specimens will be collected or stored as part of this study.

5.5.3 Statistical methods

Statistical methods for primary and secondary outcomes

Descriptive statistics will be presented using frequencies (%) in categorical variables and by means (SD) in continuous variables. All analyses will be conducted using the intention-to-treat approach. Chi-square tests will be used to analyze categorical variables and independent samples t-tests to analyze continuous variables. Effect size will be calculated using Cohen's standardised d. Main effects (group and time) and interactions (group×time) will be estimated using mixed-effects models, which account for correlations between repeated measures and for missing data. To control for potential covariates' effects (including patients' baseline characteristics), models will be estimated with (adjusted models) and without (unadjusted models) them.

Analysis of covariance (ANCOVA) will be used to assess between-group differences in the primary and secondary outcomes at the 6-month follow-up, controlling for baseline values. Potential predictors of fatigue (e.g. disease activity, depression and anxiety, pain) at different time points will be explored through regression analyses.

All tests will be two-tailed with a significance level of 0.05. Statistical analyses will be performed using Stata 18 for Windows.

Interim analyses

No interim analysis of the variables of interest is planned.

Methods for additional analyses (e.g. subgroup analyses)

An exploratory analysis will be performed for each group. Results will be reported according to CONSORT guidelines. A post hoc power analysis will be conducted based on the actual effect size for the CFQ.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Missing data will be addressed using multiple imputation when the data can be assumed to be missing at random.

Plans to give access to the full protocol, participant level-data and statistical code

Not applicable. No access to the full protocol, participant-level data, and statistical code will be given in order to protect participant privacy and confidentiality.

5.6 OVERSIGHT AND MONITORING

Composition of the coordinating centre and trial steering committee

The study will be conducted at a single center, with no coordinating center or trial steering committee. The trial will be directed and overseen by the principal investigators, who will also supervise the research team's work. Regular project meetings with the research team will be held to ensure continuous monitoring of the trial's progress, coordinate activities among team members, provide updates, and address any issues that arise during the study.

Composition of the data monitoring committee, its role and reporting structure

The data monitoring committee (DMC) is not required for the current trial because the interventions involved pose minimal risk to participants. Additionally, as a single-center study with a straightforward operational structure, it can be effectively overseen by the study team.

Adverse event reporting and harms

This is a low-risk study with no anticipated adverse events, but any unforeseen unfavorable events will be evaluated and reported.

Frequency and plans for auditing trial conduct

Monitoring the adherence to the study’s established procedures, ethical standards, and regulatory requirements will be done by the principal investigators. As well, research members will be responsible for conducting the trial in adherence with Good Clinical Practice. Trainees who will be occupied with allocation and assessments will be instructed to report to the principal investigators any issues and concerns about any participant or any problem with the study procedure.

The external auditing process is not planned.

The principal investigators will monitor adherence to the study’s established procedures, ethical standards, and regulatory requirements. Additionally, research team members will be responsible for conducting the trial in accordance with Good Clinical Practice guidelines. Trainees involved in participant allocation and assessments will be instructed to report any issues or concerns regarding participants or study procedures to the principal investigators. An external audit process is not planned.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees)

In case of any protocol amendment, all modifications must be approved by the Ethics Committee of the South-West Veneto Area (CET-ASOV).

Dissemination plans

The results will be disseminated both nationally and internationally through conference presentations and publication of scientific articles in reputable peer-reviewed journals.

5.7 DISCUSSION

The present trial aims to evaluate a non-pharmacological intervention designed to reduce fatigue and other arthritis-related clinical and psychological symptoms, as current standard treatments for rheumatological conditions often do not sufficiently alleviate fatigue. The psychological intervention is a novel approach designed for this trial for targeting fatigue. It incorporates elements and interventions of cognitive-behavioural therapy, and it draws on the structure of previously published psychological interventions for chronic diseases. The physical exercise program is developed based on decades of experience from physiotherapists working with arthritis patients, who are part of a research group. The intervention focuses on tailored activities, posture exercises, and personal narratives to adapt the approach to each individual. The significance of this trial lies not only in assessing the effectiveness of these interventions in reducing fatigue and related symptoms but also in evaluating their implementation, since they are novel and designed for this trial. Additionally, the study aims to analyze the associations between fatigue and various clinical and psychological variables at different time points throughout the trial.

It is expected that participants engaging in psychological interventions or physical exercise program will experience significantly greater reductions in fatigue, depression, and other arthritis-related outcomes compared to the control group (Durcan et al., 2014; Sköldstam et al., 2003; Bachmair et al., 2022; Dures et al., 2023). Both psychological and physical activity interventions are expected to have significant individual effects (Bernard et al., 2018). Psychological interventions should have a beneficial effect on related outcomes such as disability, quality of life, self-efficacy, and sleep (Hewlett et al., 2011; Ayun & Hartini, 2019). Meanwhile, physical exercise alone is likely to improve both physical health and mental well-being (Knapen et al., 2015; Hu et al., 2021). Furthermore, it is expected that across all groups, fatigue will be associated with quality of life, pain, psychological distress, sleep quality, and disease activity (Geenen & Dures, 2019).

The study's importance is to enhance theoretical insights into which non-pharmacological interventions should be prioritized and integrated into standard treatment protocols for arthritis patients experiencing symptoms like fatigue and depression. By assessing outcomes both during and after the intervention, we aim to determine the optimal duration for effectiveness and cost efficiency, potentially reducing untreated symptoms and improving overall disease outcomes. Additionally, we aim to better understand the nature of fatigue and its inflammatory mechanisms that the psychological and physical activity interventions could modify. Our final objective is to integrate effective non-pharmacological interventions into standard arthritis management, enhancing the prevention and treatment of arthritis-related symptoms. Based on our findings, we may advocate for expanding Rheumatology healthcare teams to include psychologists and physiotherapists, highlighting the importance of their interventions on patient symptoms and general well-being.

Once the current study confirms the effectiveness of the non-pharmacological intervention, its implementation could significantly impact the healthcare system in Italy. Rising healthcare costs associated with rheumatic diseases in Italy, largely due to biological treatments, may be alleviated through innovative treatments (Benucci et al., 2016). Furthermore, cognitive behavioural therapy has been shown to be a cost-effective approach to managing rheumatic diseases, demonstrating strong value for its cost relative to the health outcomes it produces (Hewlett et al., 2019b).

The current trial has several strengths. Fatigue is a common and often untreated symptom among patients with rheumatological conditions; therefore, non-pharmacological interventions aimed at addressing it are highly welcome. This study is a randomized controlled trial conducted by a multidisciplinary research team, employing robust methodology that enhances the reliability of evidence regarding the efficacy of the interventions. The six-month duration of the intervention is sufficient to observe meaningful effects. Group interventions offer additional benefits by fostering support and interactive engagement among members who share personal experiences, helping participants feel understood and accepted. The study will include all adult patients, regardless of age, with the physical exercise program tailored to each individual's capabilities. Multiple assessments will be conducted at various time points (from baseline to follow-up) to evaluate both the effectiveness of the interventions and the relationship between fatigue and other arthritis-related conditions.

However, some limitations should be acknowledged. The interventions will be delivered exclusively in group settings, without comparison to individual or online interventions, which may limit the implementation options. Organising consistent in-person group sessions can be challenging. The trial will be conducted at a single center, restricting the applicability of results to other regions within Italy or internationally. Additionally, primary outcome measures, such as fatigue and disease-related outcomes, will rely on self-report questionnaires. While these instruments are standardized and possess good psychometric properties, incorporating clinical evaluations could enhance the robustness of the findings, albeit at the cost of increased time and resources. Finally, biological data will be obtained from patients' medical records at baseline, with no biological sampling during the trial, limiting the ability to assess the intervention's impact on biomarkers.

In conclusion, the FREE trial is based on group, tailored non-pharmacological treatments, such as psychological and physical interventions, aimed at reducing fatigue, disease activity, depression, anxiety, and other disease-related outcomes in rheumatic diseases.

Trial status

FREE, protocol version 1.0, 03/03/2025.

Abbreviations

RA	Rheumatoid arthritis
PsA	Psoriatic arthritis
AxSpA	Axial Spondyloarthritis
RCT	Randomized controlled trial
EULAR	European Alliance of Associations for Rheumatology
ACR	American College of Rheumatology
WHO	World Health Organization
CBT	Cognitive behavioural therapy
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate
Hb	haemoglobin

TSH	thyrotropin
25-OH-vitD	vitamin D
DAS28-CRP	The 28-joint Disease Activity Score and C-reactive protein
DAPSA	Disease Activity in PSoriatic Arthritis
ASDAS-CRP	Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein
HAQ-DI	Health Assessment Questionnaire – Disability Index
CFQ	Chalder Fatigue Questionnaire
BRAF-MDQ	Bristol Rheumatoid Arthritis Fatigue Multi-Dimensional Questionnaire
HADS-D	Hospital Anxiety and Depression Scale – Depression
PHQ-9	Patient Health Questionnaire-9
HADS-A	Hospital Anxiety and Depression Scale – Anxiety
GAD-7	General Anxiety Disorder scale
VAS	Visual Analogue Scale
SF-36	Health-Related Quality of Life – Short Form 36 items
PSQI	Pittsburgh Sleep Quality Index
CTQ-SF	Childhood Trauma Questionnaire-Short Form
PREDIMED	PREvencion con DIeta MEDiterranea
TFEQ-R-18	Three Factor Eating Questionnaire-Revised 18
GPAQ	Global Physical Activity Questionnaire
BREQ-3	Behavioural Regulation in Exercise Questionnaire
SD	Standard deviation
ANCOVA	Analysis of covariance
CONSORT	Consolidated standards of reporting trials
DMC	Data monitoring committee
CET-ASOV	Ethics Committee of the South-West Veneto Area [Comitato etico Territoriale Area Sud-Ovest Veneto]
ALOMAR	Lombardy Association of Rheumatic Patients [Associazione Lombarda Malati Reumatici]
ASP	Swiss Association of Polyarthritics [Associazione Svizzera dei Poliartritici]

Chapter 6. DISCUSSION AND OUTLOOK

6.1 DISCUSSION

The present thesis aimed to analyse the interaction between psychological and clinical variables in order to understand their interplay and dynamics in rheumatic diseases. Based on these findings, it sought to develop an effective non-pharmacological intervention capable of improving disease condition and overall outcomes, which are often less responsive to standard rheumatological treatment procedures.

In the following section, the main findings of each of the four parts of the research are briefly summarized.

6.1.1 Coping with rheumatic disease

The first finding (Chapter 2) is that problem-focused and emotion-focused coping strategies were not associated with fatigue; therefore, further mediation-moderation analyses could not be conducted for these variables. In contrast, dysfunctional coping was significantly associated with fatigue, and depression and anxiety fully mediated this relationship. Moreover, diagnosis moderated the association between dysfunctional coping and fatigue, such that in axial spondyloarthritis, dysfunctional coping was more strongly associated with fatigue than in rheumatoid arthritis and psoriatic arthritis. Sex also moderated the indirect effect of dysfunctional coping on depression, with coping having a stronger depression-reducing effect among females than males. Disease activity and disease duration did not significantly influence these pathways.

Successful adaptation to chronic illness involves several key elements: effective performance of adaptive tasks, maintenance of emotional balance, low levels of negative affect and high levels of positive affect, functional stability, occupational competence, and satisfaction across multiple life domains (de Ridder et al., 2008). Patients who perceive themselves as actively engaged in managing their illness are more likely to believe they are coping effectively (de Ridder et al., 2008; Katz, 1998). Conversely, maladjustment is often linked to emotion regulation styles characterized by avoidance and emotional inhibition. In Western contexts, such avoidant and non-expressive tendencies tend to undermine psychological adjustment and even physical health (de Ridder et al., 2008). Persistent avoidance may become maladaptive, preventing individuals from encountering corrective experiences that could challenge their negative expectations (Nadinda et al., 2024). Our findings presented in Chapter 2 indicate that dysfunctional coping is significantly associated with fatigue, with dysfunctional coping defined as behavioral and cognitive disengagement (Carver et al., 1989). In light of the broader literature, a review on rheumatoid arthritis concluded that the available evidence remains insufficient to establish a consistent relationship between specific coping strategies and long-term outcomes. Nevertheless, avoidance or escape coping emerged as the strategy most consistently associated with adverse outcomes in both cross-sectional and longitudinal analyses (Ramjeet et al., 2008). Recent reviews have concluded that the majority of findings on the relationship between coping and fatigue in RA are based on cross-sectional designs, thereby leaving the causal direction unclear (Matcham et al., 2015).

In our study, neither problem-solving nor emotion-focused coping was found to be associated with fatigue in rheumatic diseases. This finding is consistent with previous research indicating that, in rheumatoid arthritis and axial spondyloarthritis, active coping has not been significantly associated with loss of functional ability. Passive coping, however, remains a stronger predictor of functional limitation, partly because of its association with depressive mood and poor psychological functioning (Brionez et al., 2009; Hinch & Sirois, 2024).

Fatigue may influence coping behavior, just as coping may shape fatigue levels (Ray et al., 1995). Although the mechanisms linking psychosocial factors to fatigue are not fully understood, identifying modifiable factors that can enhance self-management remains critical for effective intervention (Davies et al., 2021). Considering the design and implementation of interventions for fatigue in rheumatic disease, no reference to underlying fatigue mechanisms was presented (Cramp, 2019; Bachmair et al., 2022). The contribution of our study lies in proposing a conceptual model of fatigue, in which the primary influencing factors are psychological and amenable to intervention.

Individuals with chronic illness frequently experience anxiety and depression, and their emotion regulation patterns significantly shape their adjustment. Two broad categories of emotion regulation have been identified: avoidance/inhibition of emotions and expression/acknowledgment of emotions (de Ridder et al., 2008). Regarding our study, the relationship between dysfunctional coping and fatigue in rheumatic diseases was fully mediated by depression and anxiety. Previously Katz (1998) demonstrated that, in rheumatoid arthritis, psychosocial variables, particularly depressive symptoms, are strongly associated with patients' perceptions of both the impact of stressors and their coping efficacy. Those with higher depressive symptoms tend to perceive stressors as more severe and themselves as less capable of managing them. In psoriatic arthritis, negative illness beliefs and behavioral disengagement predict higher levels of depression, and self-blame predicts increased anxiety (Howells et al., 2018). In general, coping strategies such as problem-solving and positive reappraisal enhance emotional well-being, while confrontive and distancing strategies tend to worsen it (Folkman & Lazarus, 1988; Hinch & Sirois, 2024).

Depression is closely linked to fatigue in inflammatory rheumatic diseases (Davies et al., 2021). Although fatigue may contribute to depression through shared mechanisms, they are distinct conditions, and many with fatigue do not experience depression (Davies et al., 2021). Their relationship is complex, as fatigue and mood influence each other: on high-fatigue days, individuals with rheumatoid arthritis report more negative and less positive mood (Sturgeon et al., 2016)

In line with our results is the finding that depression and anxiety remain central mediators in the relationship between physical symptoms and coping and should be given due attention in clinical management (Sempértegui et al., 2017). Beyond pharmacological treatment, early psychological support and structured health care interventions within the first year after diagnosis may facilitate better adjustment (Evers et al., 1997). To promote psychological adaptation, patients are encouraged to remain as active as possible, express and process their emotions, engage in self-management, and focus on potential positive life changes arising from their illness (de Ridder et al., 2008). Tailored education and individualized self-management programs should be designed to optimize coping strategies, reduce disease burden, and minimize the risk of depression stemming from feelings of helplessness (Englbrecht et al., 2013).

Beyond the relationship between coping strategies and emotional distress, the association between coping and quality of life is of critical importance, further underscoring the need to prioritize coping strategies in the care of patients with rheumatic diseases. Problem-focused coping strategies may improve overall coping efficacy and enhance both mental and physical well-being, serving as vital indicators of quality of life in RA (Englbrecht et al., 2012). Coping styles are generally considered relatively stable across time and contexts (Stanisławski, 2019). Yet, in ankylosing spondylitis, behavioral coping strategies appear somewhat variable over time, independent of disease duration or physical functioning. This variability suggests that avoidant coping may be amenable to change and that interventions could foster more adaptive strategies (Boonen et al., 2004). Consistent with this, our findings revealed differences among patients with axial spondyloarthritis compared with those with RA and PsA, in which dysfunctional coping was more strongly associated with fatigue. Flexible use of coping strategies can determine whether symptoms are alleviated or perpetuated, and understanding this interplay may inform therapeutic mechanisms of change. Both cognitive-behavioral therapy and acceptance and commitment therapy have demonstrated potential to improve coping flexibility, enhance quality of life, and reduce psychological distress (Leonidou et al., 2016).

Finally, we found that among females, dysfunctional coping exerted a stronger influence on depression levels. Previous research has shown that coping in RA varies by sex but not by age (Englbrecht et al., 2012).

6.1.2 Health-related quality of life and its determinants in rheumatic disease

The second finding (Chapter 3) revealed that patients with rheumatoid arthritis had worse scores than those with axial spondyloarthritis, while psoriatic arthritis did not significantly differ from the other two diseases. Nevertheless, common factors such as disease activity, depression and anxiety explained a substantial proportion of the variance in HRQoL across rheumatic diseases. Fatigue partially mediated the relationship between disease activity and the physical domains of HRQoL, accounting for up to 40% of the association. Regarding rheumatological treatment, in psoriatic arthritis, first-line therapy had a stronger effect on the association between disease activity and bodily pain, a domain of HRQoL. Sex and comorbidities did not significantly affect these pathways.

Quality-of-life measures are widely recognized as valuable outcome indicators in clinical research, yet they remain underutilized in routine clinical practice. Several barriers impede their integration into everyday care, including concerns regarding cost, feasibility, and clinical utility - QoL instruments must provide data that are directly applicable to patient management. Moreover, conceptual clarity of QoL among medical and health studies is still one of the principal issues. The primary rationale for incorporating QoL assessment into clinical settings lies in its capacity to shift the focus from disease-centered evaluation to a more patient-centered perspective, thereby informing and enhancing clinical decision-making. When effectively applied, QoL measures can become an integral component of the care continuum rather than serving merely as monitoring tools. Nevertheless, they should complement, rather than replace, traditional disease-specific outcome measures (Higginson & Carr, 2001; Haraldstad et al., 2019).

On this rationale, we studied the health-related quality of life (Chapter 3) to obtain an integrative measure encompassing both physical and mental aspects of the complex condition, as rheumatic disease is. In rheumatoid arthritis, impairment typically arises from the complex interplay of multimorbidity within daily rheumatologic care. Health-related quality of life can thus serve as a comprehensive measure of overall disease burden (Gerhold et al., 2015). Similarly, in axial spondyloarthritis, HRQoL assessment should be regarded as a key element in evaluating patients’ health status, offering valuable insights for optimizing disease management and guiding treatment choices (Yang et al., 2016). Moreover, understanding the differences in HRQoL profiles across RA, PsA, and axSpA is essential for interpreting longitudinal changes, setting therapeutic goals, and assessing treatment effects in clinical practice (Landgren et al., 2023).

We found that patients with RA had the lowest scores in health-related quality of life compared with patients with axSpA, particularly in the physical domains of

HRQoL. Patients with PsA, however, did not differ significantly from those with the other two diseases. Longitudinal studies indicate that both RA and PsA patients experience significant improvements in HRQoL over a five-year period, though PsA patients continue to report lower scores in the physical domain. The persistence of impaired HRQoL in PsA remains insufficiently explained (Geijer et al., 2021). Moreover, in PsA, the severity of psoriatic lesions was associated with poor mental quality of life (Salaffi et al., 2009). These variations among rheumatic diseases underscore the need for further investigation into their respective trajectories, correlates, and shared determinants.

Furthermore, our results in Chapter 3 reveal consistent patterns across rheumatic diseases: the physical domain of HRQoL is primarily determined by disease activity, whereas the mental domain is predominantly influenced by depression and anxiety. One study revealed that the physical component was influenced by a high disease activity and comorbidity in RA, PsA and axSpA (Salaffi et al., 2009). In RA, higher disease activity is inversely associated with both physical and mental dimensions of HRQoL, while resilience appears to buffer and partially mediate the relationship between disease activity and mental well-being (Liu et al., 2017). Disease severity, functional disability, depression, and anxiety collectively exert a detrimental influence on QoL in RA (Katchamart et al., 2019). Similarly, in axSpA, increased disease activity predicts poorer physical and mental QoL, whereas fatigue primarily affects mental well-being (Law et al., 2018; Yang et al., 2016). A deeper understanding of both common and disease-specific predictors of HRQoL could guide the development of tailored interventions aimed at improving well-being in these chronic, disabling conditions (Greenfield et al., 2017).

Building on our earlier findings regarding disease activity as the primary determinant of the physical domain of HRQoL, we conducted an analysis showing that fatigue partially mediates this relationship. Fatigue, a common symptom in rheumatoid arthritis, has previously been shown to influence several dimensions of quality of life (Alikari et al., 2017), and evidence suggests that in psoriatic arthritis, the emotional aspects of the disease may be more influential than its inflammatory features (Carneiro et al., 2017). The distinct pathways in our model are consistent with earlier observations by other authors, while we contributed by suggesting a model that explains the association between disease burden, HRQoL, and fatigue more clearly, reflecting the broader framework. Our mediation analysis suggests that interventions targeting fatigue may play a crucial role in understanding, and potentially modifying, the relationship between disease activity and HRQoL. Moreover, the finding that fatigue serves only as a partial mediator aligns with previous research showing that disease activity is only a secondary factor in explaining fatigue in arthritis (Pollard et al., 2006).

Regarding rheumatological therapy, moderation analysis in our study showed that among patients with psoriatic arthritis receiving first-line treatments such as csDMARDs or anti-TNF drugs, disease activity exhibits a stronger positive association with bodily pain (an HRQoL domain) than in patients receiving second-line therapy. Our findings aligns with previous evidence demonstrating that DMARD therapy can significantly improve HRQoL in rheumatoid arthritis, even among individuals with prior treatment resistance (Gerhold et al., 2015). Even though biologics appear to improve all aspects of HRQoL, a greater impact was noted on physical quality of life compared with mental well-being (Kingsley et al., 2011). RA patients achieving persistent or intermittent remission report markedly better HRQoL than those who never achieved remission (Gullick et al., 2019). Over the past decade, randomized controlled trials of novel DMARDs have consistently demonstrated clinically meaningful gains in physical functioning and HRQoL - outcomes that have since been incorporated as key endpoints in the regulatory approval of new therapies (Strand et al., 2009). Nonetheless, evidence suggests that although achieving remission improves HRQoL, it does not fully restore it to normal levels, indicating that treatment strategies should also explicitly target HRQoL enhancement alongside disease control (Scott et al., 2016).

6.1.3 Sex differences in clinical and psychological outcomes

The third finding (Chapter 4) demonstrated that women consistently scored worse across most clinical and psychological variables in both PsA and axSpA, including disease activity, radiographic progression, disability, anxiety, perceived stress, fatigue, HRQoL, and more frequent use of dysfunctional coping strategies.

Moreover, fatigue, perceived stress, anxiety and pain were the main factors explaining both physical and mental HRQoL, particularly among female patients. In a recent review, it was summarized that sex influences PsA outcomes by shaping illness perception, coping mechanisms, health-seeking behaviors, access to care, and treatment approaches. Although men often exhibit more severe psoriasis, women with PsA report a greater negative impact on health-related quality of life, emphasizing the distinct ways sex shapes disease burden (Tarannum et al., 2022). Similarly, in axSpA, women tend to have worse scores across disease-related outcomes, although the factors underlying these poorer outcomes remain insufficiently understood (Marzo-Ortega et al., 2022).

Across studies, women with PsA consistently report worse scores in all patient-reported outcomes, including pain, fatigue, functional ability, work disability, and quality of life (Tarannum et al., 2022; Coates et al., 2023). These differences may stem partly from gendered patterns of unpaid labor (women are more likely to assume caregiving and domestic roles) and from biological differences, including the influence of sex hormones on pain perception (Coates et al., 2023). In axSpA, female sex is strongly associated with fatigue and reduced quality of life, even when inflammatory activity is lower. Women with sacroiliitis report greater fatigue despite lower MRI-detected spinal inflammation and lower CRP levels (Tournadre et al., 2013). Anxiety and depression are also more prevalent in women with axSpA, adding to the overall disease burden (Wright et al., 2020; Nam et al., 2021). Moreover, women are significantly more likely to receive a psychosomatic diagnosis prior to confirmation of axSpA (Wright et al., 2020).

Regarding pain, females in both the PsA and axSpA cohorts reported higher scores. Prior research indicates that pain in axSpA manifests differently between sexes: women more frequently report widespread, pelvic, and heel pain (Wright et al., 2020). Pain processing within the central nervous system is also modulated by sex: women possess a higher density of cutaneous pain receptors and tend to experience pain at more sites, with greater intensity, frequency, and duration than men (Tarannum et al., 2022; Stovall et al., 2022).

Gender norms affect access to healthcare, patterns of help-seeking, and clinician response. Perceptions of gender can influence how symptoms are interpreted and how treatment is offered (Mauvais-Jarvis et al., 2020). Women tend to seek healthcare more frequently and navigate health systems more effectively (Tarannum et al., 2022). They also tend to score higher on composite measures of PsA disease activity, often rating their disease as more active than physicians do (Tarannum et al., 2022). In RA, women with higher stress levels are more likely to use coping strategies such as positive reappraisal, emotional and instrumental support, and denial (Wróbel et al., 2023).

In r-axSpA, both sexes exhibit significantly reduced HRQoL compared with controls, with physical domains being more affected than mental ones (Law et al., 2018). Some studies found no significant sex differences in HRQoL (Nam et al., 2021), whereas others reported that men experience better long-term quality of life regardless of radiographic severity (Webers et al., 2016). Female sex in axSpA has been disproportionately linked to impaired HRQoL, as reflected in multiple instruments including SF-36 MCS (Marzo-Ortega et al., 2022).

When comparing males and females HRQoL across rheumatic diseases, women report lower physical and mental component summary scores for RA, PsA, and axSpA (Landgren et al., 2023). In RA, poorer quality of life among women is often linked to comorbid depression (Krasselt and Baerwald, 2019). In PsA, female patients consistently report impaired quality of life across multiple outcome measures (Eder et al., 2013; Lubrano et al., 2023; Coates et al., 2023). Some authors attribute the better quality of life in men with PsA to less frequent spinal involvement despite similar disease activity (Nas et al., 2021). Others suggest that irreversible joint damage in women contributes to greater functional impairment and lower quality of life (Coates et al., 2023).

Our results in Chapter 4 demonstrated that in both the PsA and axSpA cohorts, fatigue, anxiety, perceived stress, and pain are the main determinants of physical and mental HRQoL, with these relationships being particularly evident in females. Prior research found that higher ASDAS-CRP levels correlate with poorer HRQoL in both sexes, although associations with depression appear stronger in men (Nam et al., 2021). In axSpA, greater disease activity, longer duration, and reduced physical function are associated with lower physical quality of life, while higher fatigue levels predict worse mental outcomes (Law et al., 2018). Our finding that a negative association between employment status and mental HRQoL, which was evident in male PsA patients, was not replicated in the axSpA cohort. This discrepancy is notable, given that prior research on axSpA patients has indicated that employment status mitigates the likelihood of low HRQoL (Nam et al., 2021).

A systematic review concluded that disease-specific measures such as ASQoL show more pronounced sex differences than generic tools, with women consistently reporting worse scores (Stovall et al., 2022).
Sex-based differences in symptoms, outcomes, and treatment efficacy in rheumatic diseases likely reflect anatomical, hormonal, and immunological variations, as well as differences in pain mechanisms (Stovall et al., 2022; Tarannum et al., 2022). Distinguishing true biological disparities from those arising from measurement bias or gender-specific symptom perception remains challenging. Women tend to report more symptoms and lower health scores on questionnaires, whereas men generally seek medical care less frequently (Krasselt and Baerwald, 2019).
A key direction for future research in rheumatology is precision medicine - identifying which patients respond best to specific treatments and tailoring interventions accordingly (Di Matteo et al., 2023). Understanding predictors of treatment response is essential to advance personalized care (Smolen et al., 2016). Since sex is a non-modifiable risk factor for RA, identifying population-specific contributors to disease development could guide preventive strategies for this disabling condition (Finckh et al., 2022). Increasing awareness of sex and gender differences in disease manifestation and treatment efficacy (particularly among women) is vital to improving outcomes (Marzo-Ortega et al., 2022).

6.1.4 Integrative approach to fatigue management and related outcomes

In the Chapter 5 is presented the protocol on the randomized controlled trial, which aimed to evaluate whether, and to what extent, each intervention is effective in reducing fatigue as the primary outcome, as well as in reducing disease activity, symptoms of depression, anxiety and pain levels, and in improving physical functioning, overall quality of life, and sleep quality among participants. Upon confirmation of the interventions' efficacy, their further implementation in clinical settings should be considered to promote a more comprehensive and integrative approach to patient care.

Although remission or low disease activity is the primary therapeutic goal in RA, many patients fail to achieve or maintain this state and continue to rely on medication, indicating the ongoing need for improved therapies (Smolen et al., 2016). Even among patients who achieve remission, health-related quality of life often remains suboptimal, particularly in established disease, despite treatment with cDMARDs, TNF inhibitors, or corticosteroids (Scott et al., 2016). The overarching aim of treatment for chronic diseases should therefore extend beyond symptom suppression to fostering an active and accepting attitude toward illness - integrating both physical and psychological dimensions (Schüssler, 1992).

The observed decline in RA severity over recent decades likely reflects the evolution of treatment paradigms and improvements in disease management. However, newer second-line therapies remain costly and inaccessible in some healthcare systems (Finckh et al., 2022). Given the well-documented influence of psychological factors in RA, there is a clear need to complement pharmacological therapies with psychological and behavioural interventions (Sturgeon et al., 2016). Patients frequently report that fatigue is overlooked or dismissed by clinicians, leading them to believe it is untreatable and must be managed alone (Hewlett et al., 2005). Given the rationale outlined above and the persistent high prevalence of fatigue, even among established patients on adequate therapy, we proceeded to create a non-pharmacological intervention protocol (Chapter 5) and author a psychological intervention manual (Appendix E) focused on fatigue and associated outcomes in arthritis patients.

Comprehensive reviews indicate that physical activity interventions are statistically more effective than control conditions in reducing fatigue, while psychosocial interventions also yield self-reported benefits (Cramp et al., 2013). Evidence quality varies, with the strongest support for physical activity and dietary interventions, and weaker evidence for psychosocial approaches. Ultimately, consensus on optimal fatigue management remains limited (Cramp et al., 2013). Some scoping reviews report inconsistent or minimal effects of non-pharmacological interventions across rheumatic diseases (Beckers et al., 2023). Nevertheless, the World Health Organization (WHO) emphasizes that physical activity is generally safe and beneficial for adults with chronic conditions, provided contraindications are considered (Bull et al., 2020).

The long-term benefits of cognitive-behavioural therapy in RA may reflect not only reduced fatigue severity but also improved coping and a decreased perceived importance of fatigue (Hewlett et al., 2019a). Qualitative studies highlight that psychological interventions enhance self-awareness, emotional regulation, and acceptance of disease, while promoting re-engagement with meaningful activities and relationships (Dures et al., 2012). Fatigue correlates strongly with work impairment, pain, depression, sleep disturbance, and reduced physical function across multiple rheumatic diseases (Esbensen et al., 2020). It is more prevalent among women, those with lower education or income, unemployment, and recent treatment changes (Esbensen et al., 2020). Therefore, clinicians must not only acknowledge the impact of fatigue but also address its interconnections with broader aspects of daily life (Esbensen et al., 2020), as presented in Chapter 5.

Psychological treatments that enhance active coping, reduce emotional distress, strengthen self-efficacy, and build supportive social connections can improve outcomes for RA patients (Sturgeon et al., 2016). Encouraging patients to recognize and process negative emotions associated with chronic illness promotes better adjustment and well-being, which can sometimes even be reflected in objective markers of disease activity (de Ridder et al., 2008). Emotional expression, when integrated into psychological interventions, can positively influence both psychological and physical health, whereas avoidance or denial may hinder adaptation (de Ridder et al., 2008).

Self-management interventions have shown beneficial effects on fatigue coping and perceived severity, as well as improvements in physical functioning, depression, helplessness, and sleep, although effects on disease activity, anxiety, pain and quality of life remain inconsistent (Hewlett et al., 2011; Brown et al., 2023). The authors of the umbrella review concluded that health professional-guided interventions appear more effective and acceptable than self-guided approaches (Brown et al., 2023). In alignment with this finding, our protocol mandates that the intervention be delivered exclusively by qualified professionals, such as psychotherapists and physiotherapists.

Physical fatigue remains the strongest predictor of reduced physical activity in RA (Davies et al., 2021). Evidence supports the safety and benefit of comprehensive physical therapy, though optimal timing and integration into routine care are not well defined. Barriers, such as a fear of symptom exacerbation and uncertainty about safe exercise, persist. Therefore, exercise prescriptions should be individualized-tailored to each patient's capacity and delivered with clinical guidance, ideally involving physical therapists for personalized monitoring and support (England et al., 2022; Thoma et al., 2023). Recent ACR guidelines emphasize interprofessional, team-based care and shared decision-making in developing integrative treatment plans for RA (England et al., 2022). Future research should prioritize identifying causal pathways of fatigue and determining the most effective intervention components in non-pharmacological interventions (Cramp et al., 2013). Notably, among systematic reviews, no studies have assessed emotional well-being, sleep, coping, or physical health as outcome measures in fatigue studies (Santos et al., 2019). Building upon the limitations and suggestions identified in prior studies within this field, we designed our randomized-control trial to address existing knowledge gaps.

6.2 IMPLICATIONS FOR POLICY, CLINICAL PRACTICE, EDUCATION, AND RESEARCH

The findings of our studies underscore the critical role of psychological factors in the management of rheumatic diseases. Accordingly, rheumatology care should adopt a holistic and integrative framework in which psychological assessment and intervention are regarded as essential components of patient management. Screening for psychological distress, maladaptive coping and fatigue should be routine in rheumatology clinics. Comprehensive assessments that include both clinical and psychosocial factors are essential to improve symptom management, emotional well-being, and overall quality of life (Shen et al., 2021; Kojima et al., 2009).

Future clinical models should integrate biomedical and psychosocial dimensions, considering not only disease activity and laboratory findings but also patient beliefs, coping strategies, and social support systems, leading to more effective, person-centered care (Sturgeon et al., 2016; Kojima et al., 2009). Beyond the reduction in disease activity achieved through pharmacological, rheumatological therapies, the active involvement of a multidisciplinary healthcare team can substantially enhance patients' physical quality of life. Furthermore, given that the relationship between disease activity and quality of life is mediated by fatigue, as our study showed (Chapter 3), targeting fatigue represents an additional and meaningful pathway to improving patient well-being. As the enhancement of quality of life is one of the key indirect outcomes of treatment (Di Matteo et al., 2023), the incorporation of structured fatigue management strategies into therapeutic plans may yield significant clinical benefits.

Effective coping also plays a central role in long-term adaptation to chronic illness. Therefore, the development of support programs that strengthen coping and self-management skills is vital, particularly for patients with limited psychological resources (Evers et al., 2011). The presented study (Chapter 2) demonstrated that depression and anxiety mediate the association between dysfunctional coping and fatigue, suggesting that psychological interventions should address these mediating factors in addition to maladaptive coping styles. Collectively, these findings contribute to a deeper understanding of how psychological interventions targeting coping processes and emotional distress can enhance outcomes in rheumatic diseases, particularly in relation to fatigue reduction and quality of life improvement. Evidence indicates that cognitive–behavioural therapy and personalized exercise programs are effective in reducing fatigue, psychological distress, and maladaptive coping, thereby improving long-term functioning (Bachmair et al., 2022; Cramp, 2019). Interventions targeting depression and anxiety - mediators of the link between dysfunctional coping and fatigue - are particularly beneficial (Evers et al., 2011; Hewlett et al., 2019a). To enhance continuity of care, a shift from episodic rehabilitation models toward continuous, multidisciplinary management is recommended, with the ultimate goal of integrating self-management skills into daily lives (Hewlett et al., 2019a; Thoma et al., 2023). This includes periodic booster sessions, telehealth integration, and collaboration among rheumatologists, psychologists and physiotherapists (Thoma et al., 2023). Such approaches not only enhance patient outcomes but also have the potential to reduce healthcare costs, which are increasingly driven by expensive biologic treatments (Michaud et al., 2003; Benucci et al., 2016).

Sex differences in rheumatic diseases such as axial spondyloarthritis and psoriatic arthritis have significant implications for diagnosis, treatment and psychosocial outcomes, as shown in our studies. Sex-sensitive assessment and intervention strategies should therefore be systematically integrated into both clinical practice and research. Screening for anxiety, depression, and psychological distress, while recognizing that men and women experience these conditions differently, should be standard practice (Mease et al., 2021). Psychological interventions, including CBT, should be tailored to sex-specific coping patterns and illness experiences. At the policy level, sex must be treated not merely as a categorical variable but as a dynamic determinant of health that shapes access to care, disease presentation, and treatment outcomes (Connell et al., 2012; Mauvais-Jarvis et al., 2020). This requires revising research frameworks and clinical guidelines to reflect sex differences in pathophysiology, drug safety, and efficacy.

In light of the clinical and psychological factors and the mediation-moderation models explored in this thesis, future research should prioritize the development of holistic, multidimensional models of rheumatic disease management. Such models should integrate biological, psychological, and social determinants of health, providing a comprehensive framework for personalized, evidence-based, and equitable care. Further studies are needed to evaluate the cost-effectiveness and scalability of such integrated care models and to design clinical trials that systematically address sex disparities in disease progression and treatment outcomes.

Medical education remains limited in its attention to sex differences, with most curricula based on male physiological models. Integrating sex-specific medicine into training programs is critical to improve diagnostic accuracy, treatment effectiveness, and patient-centered care (Mauvais-Jarvis et al., 2020). Likewise, education for healthcare professionals should emphasize the ability to identify and manage emotional and cognitive aspects of chronic illness, to foster more empathetic and effective clinical interactions.

From a policy perspective, embedding psychological and gender-sensitive care within rheumatology services aligns with the broader goals of equitable and cost-effective healthcare delivery. Policymakers should support the inclusion of psychologists and physiotherapists within rheumatology teams and promote funding for non-pharmacological interventions that complement traditional biomedical approaches. Ultimately, incorporating psychosocial and sex considerations into rheumatology practice will improve patient quality of life, promote equity in healthcare, and support sustainable, evidence-based healthcare systems.

6.3 FUTURE RESEARCH DIRECTIONS

Results from our studies, in addition to revealing new findings and conclusions in the field, have opened several questions and uncertainties that require further investigation to achieve a more comprehensive understanding. Future research could use our results as an initial foundation for novel and original studies.

Considering that the present study employed a cross-sectional design, with its inherent limitations, future research should adopt a longitudinal design to enable more robust and reliable inferences. A longitudinal cohort study following a large population over time would make it possible to evaluate the trajectory of symptoms from their early subclinical manifestations to established disease. Such an approach would allow for the development of a complex network of symptom analysis and the testing of different mediators and moderators. This, in turn, would clarify and strengthen the identification of predictors of specific conditions and symptoms, thereby contributing to the construction of underlying models that explain the dynamic interactions between clinical and psychological determinants in rheumatic diseases (Eder et al., 2013; Salaffi et al., 2009). Furthermore, future studies should include patient-reported outcome measures and assessments of social support, both family and peer, to capture patients' disease symptoms and outcomes from family members and peers' perspectives.

Regarding health-related quality of life, our findings demonstrated its comprehensive utility in reflecting various aspects of disease burden and outcomes. However, two dimensions warrant further investigation. The first is the positive aspect of illness, including patients' competencies and capacities, which may form the foundation of their baseline quality of life and represent resources to be strengthened (de Ridder et al., 2008). The second is the integration of HRQoL measures into routine clinical practice, using them as standard tools for both screening and follow-up of disease-related conditions. Although HRQoL is widely used as an outcome measure in rheumatology research, it remains underutilized in daily clinical rheumatological settings. Future studies should therefore explore the barriers preventing its implementation and identify strategies to promote its regular use (Matcham et al., 2014; Carr & Higginson, 2001).

In terms of treatment and intervention, future research must deepen the understanding of how to help patients adopt non-pharmacological interventions, such as physiotherapy or psychological intervention, as part of their everyday routines. For these approaches to be effective, patients must internalize and maintain them as part of their self-care management (Cramp, 2019). To this end, involving patients in the co-creation of interventions will be essential. Collaborating with patients to identify which aspects of the intervention and overall approach are most meaningful to them can enhance adherence and long-term benefit. Future intervention studies should aim not only to reduce symptoms but also to identify and strengthen patients' positive attributes and adaptive capacities. Moreover, research should clarify whether online interventions offer greater advantages compared to in-person approaches and determine which modality should be prioritized for institutional investment (Bachmair et al., 2022; White et al., 2022).

Regarding sex differences in rheumatic diseases, our findings appear consistent across several studies conducted from different perspectives. However, beyond theoretical explanations, a comprehensive biopsychosocial approach, including the longitudinal assessment of biological markers in both males and females, is necessary to reach a deeper understanding of these disparities. Additionally, future research should seek to translate the confirmed evidence that females experience a higher illness burden across most clinical and psychological outcomes into practical applications, improving treatment strategies for both sex and promoting a truly functional model of precision medicine (Mauvais-Jarvis et al., 2020).

Finally, future research should also consider the economic implications of rheumatic disease management. While patient health must remain the primary focus, cost-effectiveness analyses are essential to ensure sustainable healthcare delivery and to identify which components of treatment warrant greater investment. In rheumatology, innovative pharmacological treatments have demonstrated considerable effectiveness; however, both pharmacological and non-pharmacological interventions should be evaluated from a cost-effectiveness perspective to ensure a stable and sustainable long-term approach to patient care (Hewlett et al., 2019b; Benucci et al., 2016; Cramp, 2019).

6.4 STRENGTHS

This study possesses several notable strengths that collectively enhance the robustness and external validity of its findings. Foremost, it was based on a large, epidemiologically representative cohort of patients observed over a one-year period in real-world clinical practice. The inclusion of three common inflammatory rheumatic diseases, rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis, enabled comprehensive cross-disease comparisons, offering a nuanced understanding of the shared and distinct psychological and clinical burdens associated with these conditions. Consecutive patient recruitment minimized selection bias and the inclusion of clinically stable individuals without recent pharmacological changes reduced confounding influences of treatment variability on quality-of-life outcomes.

A further strength lies in the methodological rigor and theoretical innovation of the study. It introduced and empirically validated original mediation–moderation models that explore the role of fatigue in the relationship between disease activity and quality of life, and the role of depression and anxiety in the association between coping strategies and fatigue - approaches not previously applied across multiple rheumatic conditions. Moreover, the models incorporated key clinical variables relevant to everyday practice, which explained a substantial proportion of variance in quality of life, indicating strong model performance. Finally, the consistent use of validated and standardized questionnaires across all assessments ensured conceptual comparability and measurement reliability.

Considering the study protocol on non-pharmacological interventions, there are benefits from its multidimensional scope, which examines both psychological and physical outcomes to provide a holistic picture of the disease's impact. The multidisciplinary design and use of robust statistical models further strengthen the reliability and interpretability of the future findings. Regarding non-pharmacological interventions, the randomized controlled design, six-month duration, follow-up period and group-based format offer additional methodological rigor and practical relevance. Group interventions, in particular, promote peer support and shared understanding among participants, potentially amplifying therapeutic benefits. Finally, the inclusion of patients from routine outpatient settings enhances the ecological validity and generalizability of the results to everyday clinical practice.

6.5 LIMITATIONS

Despite its strengths, several limitations must be acknowledged. The primary limitation concerns the cross-sectional design, which precludes causal inference and limits the ability to determine the temporal directionality of associations between disease activity, fatigue, coping strategies and quality of life. Although mediation–moderation models were applied, these analyses rest on theoretical assumptions of causality that cannot be empirically verified without longitudinal data. Future research should therefore adopt prospective designs to clarify the causal mechanisms underlying these relationships.

Another limitation lies in the sample characteristics. Most participants had long-standing disease duration (averaging over ten years), which may not reflect the experiences or coping processes of individuals with recently diagnosed conditions (Ramjeet et al., 2008). Additionally, although the explained variance in quality-of-life models was considerable, several potentially influential variables - such as sleep quality, trauma history, work productivity, social support and biological markers (e.g., cytokines) - were not assessed. The omission of these biopsychosocial and contextual factors may limit the comprehensiveness of the model and obscure important pathways affecting patient well-being (Ferrans et al., 2014; Nicassio et al., 2012). Similarly, environmental and relational determinants, such as the quality of social support and patient-provider relationships, were not incorporated, despite evidence that these factors substantially influence psychological adjustment and quality of life in rheumatic diseases (Sturgeon et al., 2016).

Methodological limitations also include reliance on self-report measures, which may be affected by response bias and the single-center design, which restricts the generalizability of findings beyond the specific clinical and cultural context. Regarding the study protocol on non-pharmacological interventions, the exclusive use of group-based sessions without comparison to individual or online formats may limit practical applicability and the absence of biological follow-up data prevents exploration of potential physiological mechanisms of change (Bachmair et al., 2022).

CHAPTER 7. CONCLUSIONS

7.1 CONCLUSIONS

Our findings highlight the importance of jointly considering sociodemographic, clinical, and psychological factors in rheumatic diseases to achieve a comprehensive understanding of the illness. Examining the prevalence of a wide range of symptoms and outcomes, their interrelationships and the underlying mechanisms explored through the proposed models has allowed for a deeper reflection on potential intervention strategies. The investigation of non-pharmacological approaches, such as psychological interventions and physiotherapy, represents a crucial step toward establishing multidisciplinary healthcare teams dedicated to improving clinical and psychological well-being of patients with rheumatic diseases. Only by acknowledging patients' subjective experiences and psychological responses to chronic illness, together with the complex and multifaceted burden of the disease, can clinicians better determine how to deliver the most appropriate and effective care for each individual. Collectively, these findings underscore the need for a holistic and integrative model of rheumatology care that bridges biological and psychosocial dimensions, fostering equitable, sex-sensitive, and precision-based healthcare aimed at enhancing overall patient well-being.

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APPENDICES

APPENDIX A

Supplementary material of Chapter 2 - Coping strategies and mental health in rheumatic diseases: understanding the fatigue pathway.

Appendix A1

Moderation effects (interactions) of diagnosis on paths (RA Rheumatoid Arthritis, PA Psoriatic Arthritis, axSpA Axial Spondyloarthritis)

Interaction	**Estimate**	**SE**	**95% CI**
Dysfunction*Diagnosis (PA vs RA) ⇒ Depression	-0.04	0.06	-0.17 to 0.08
Dysfunction*Diagnosis (axSpA vs RA) ⇒ Depression	0.008	0.08	-0.14 to 0.16
Dysfunction*Diagnosis (PA vs RA) ⇒ Anxiety	-0.07	0.17	-0.42 to 0.27
Dysfunction*Diagnosis (axSpA vs RA) ⇒ Anxiety	0.15	0.21	-0.26 to 0.56
Dysfunction*Diagnosis (PA vs RA) ⇒ Fatigue	0.01	0.06	-0.11 to 0.13
Dysfunction*Diagnosis (axSpA vs RA) ⇒ Fatigue	0.18*	0.07	0.03 to 0.33
Depression*Diagnosis (PA vs RA) ⇒ Fatigue	0.12	0.08	-0.05 to 0.29
Depression*Diagnosis (axSpA vs RA) ⇒ Fatigue	-0.01	0.09	-0.20 to 0.17
Anxiety*Diagnosis (PA vs RA) ⇒ Fatigue	-0.01	0.03	-0.08 to 0.04
Anxiety*Diagnosis (axSpA vs RA) ⇒ Fatigue	0.03	0.03	-0.04 to 0.10

*p<0.05; **p<0.01; ***p<0.001; CI 95% Confidence Interval computed with 5000 times bias-corrected bootstrap; SE Standard Error.

Appendix A2

Moderation effects (interactions) of sex on paths (F Female, M Male)

Interaction	Estimate	SE	95% CI
Dysfunction*Sex (M vs F) ⇒ Depression	-0.12*	0.06	-0.24 to -0.006
Dysfunction*Sex (M vs F) ⇒ Anxiety	-0.27	0.15	-0.58 to 0.03
Dysfunction*Sex (M vs F) ⇒ Fatigue	-0.01	0.05	-0.12 to 0.09
Depression*Sex (M vs F) ⇒ Fatigue	0.10	0.07	-0.04 to 0.25
Anxiety*Sex (M vs F) ⇒ Fatigue	0.04	0.02	-0.01 to 0.09

*p<0.05; **p<0.01; ***p<0.001. CI 95%: Confidence Interval computed with 5000 times bias-corrected bootstrap; SE Standard Error.

Appendix A3

Association between dysfunctional coping, fatigue, depression and anxiety and moderator variables

	Dysfunctional coping[1]	**Fatigue**[2]	**Depression**[3]	**Anxiety**[4]
Disease activity, Pearson's r				
Rheumatoid arthritis[5]	0.09*	0.25**	0.23**	0.16**
Psoriatic arthritis[6]	0.17*	0.35**	0.36**	0.19**
Axial Spondyloarthritis[7]	0.35**	0.40**	0.51**	0.48**
Disease duration (yrs.), mean (sd)				
<10 yrs.	22.6 (5.0)[a]	4.5 (4.2)[a]	6.9 (4.3)[a]	40.6 (11.5)[a]
>10 yrs.	22.5 (5.3)[a]	4.2 (4.1)[a]	7.0 (4.5)[a]	40.8 (11.2)[a]
Sex, mean (sd)				
Female	23.2 (5.0)[a]***	4.7 (4.3)[a]***	7.4 (4.6)[a]***	41.7 (11.7)[a]***
Male	20.9 (5.2)[a]***	3.5 (3.9)[a]***	5.7 (3.7)[a]***	38.1 (10.1)[a]***
Diagnosis, mean (sd)				
Rheumatoid arthritis	22.9 (5.2)[b]**	4.4 (4.1)[b]	7.2 (4.6)[b]*	41.2 (11.4)[b]
Psoriatic arthritis	22.3 (5.0)[b]**	4.5 (4.4)[b]	6.7 (3.9)[b]*	40.4 (11.0)[b]
Axial Spondyloarthritis	21.3 (5.1)[b]**	4.0 (4.0)[b]	6.1 (4.3)[b]*	38.9 (11.8)[b]

[a] *t-test*; [b] *ANOVA*. **p<0.05*; ***p<0.01*; ****p<0.001*. [1] COPE-NVI: Coping Orientation to the Problems Experienced - New Italian Version; [2] CFQ: Chalder Fatigue Questionnaire; [3] QIDS: Quick Inventory for Depressive Symptomatology; [4] STAI-X1: State-Trait Anxiety Inventory; [5] DAS28-CRP: Disease Activity Score in 28 joints with C-Reactive Protein; [6] DAPSA: Disease Activity in Psoriatic Arthritis; [7] ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein.

Appendix A4

Conditional mediation for diagnosis

	Rheumatoid Arthritis			**Psoriatic Arthritis**			**Axial Spondyloarthritis**		
Effect	**Estimate**	**SE**	**95% CI**	**Estimate**	**SE**	**95% CI**	**Estimate**	**SE**	**95% CI**
Dysfunction ⇒ Depression ⇒ Fatigue	0.12***	0.01	0.09 to 0.16	0.14***	0.03	0.08 to 0.20	0.12***	0.02	0.06 - 0.18
Dysfunction ⇒ Anxiety ⇒ Fatigue	0.03**	0.01	0.009 to 0.05	0.01	0.01	-0.004 to 0.03	0.06***	0.01	0.02 - 0.10
Dysfunction ⇒ Depression	0.33***	0.03	0.26 to 0.40	0.29***	0.05	0.17 to 0.40	0.34***	0.07	0.20 - 0.48
Depression ⇒ Fatigue	0.37***	0.03	0.30 to 0.45	0.49***	0.03	0.42 to 0.57	0.35***		0.28 - 0.43
Dysfunction ⇒ Anxiety	0.77***	0.09	0.59 to 0.95	0.69***	0.15	0.40 to 0.99	0.92***	0.18	0.55 - 1.29
Anxiety ⇒ Fatigue	0.04**	0.01	0.01 to 0.07	0.02	0.01	-0.003 to 0.05	0.07***	0.01	0.04 - 0.10
Dysfunction ⇒ Fatigue (direct)	0.006	0.03	-0.05 to 0.07	0.01	0.05	-0.08 to 0.11	0.18**	0.06	0.06 - 0.31
Dysfunction ⇒ Fatigue (total)	0.16***	0.03	0.09 to 0.23	0.17**	0.05	0.06 to 0.29	0.37***	0.07	0.23 - 0.52

*p<0.05; **p<0.01; ***p<0.001. CI 95%: Confidence Interval computed with 5000 times bias-corrected bootstrap. SE: Standard Error.

Appendix A5

Conditional mediation for sex

	Female			Male		
	Estimate	**SE**	**95% CI**	**Estimate**	**SE**	**95% CI**
Dysfunction ⇒ Depression ⇒ Fatigue	0.13***	0.01	0.09 to 0.16	0.11***	0.02	0.06 to 0.15
Dysfunction ⇒ Anxiety ⇒ Fatigue	0.02*	0.01	0.002 to 0.05	0.04**	0.01	0.01 to 0.06
Dysfunction ⇒ Depression	0.35***	0.03	0.28 to 0.42	0.23***	0.05	0.13 to 0.32
Depression ⇒ Fatigue	0.37***	0.03	0.30 to 0.45	0.47***	0.03	0.40 to 0.55
Dysfunction ⇒ Anxiety	0.83***	0.08	0.66 to 1.01	0.56***	0.13	0.30 to 0.81
Anxiety ⇒ Fatigue	0.03*	0.01	0.004 to 0.06	0.07***	0.01	0.04 to 0.10
Dysfunction ⇒ Fatigue (direct)	0.03	0.03	-0.02 to 0.09	0.02	0.04	-0.06 to 0.10
Dysfunction ⇒ Fatigue (total)	0.19***	0.03	0.12 to 0.26	0.17***	0.05	0.07 to 0.27

*p<0.05; **p<0.01; ***p<0.001. CI 95%: Confidence Interval computed with 5000 times bias-corrected bootstrap; SE Standard Error.

APPENDIX B

Supplementary material of subchapter 3.1 - Determinants and differences of quality of life in rheumatic diseases.

Appendix B1

SF-36 dimensions and summary measures (n=807)

	RA (n=490)		**PsA (n=198)**		**SpA (n=119)**		**p value**	**Bonferroni's post-hoc comparisons**
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**		
Physical quality of life								
Physical functioning	57.9	27.1	63.3	25.9	67.9	26.2	<0.001	RA< SpA
Role limitations due to physical health	42.5	41.4	44.5	42.6	54.4	39.6	0.020	RA < SpA
Bodily pain	46.9	23.9	45.1	21.2	50.1	23.5	0.180	
General health	42.2	20.1	44.5	21.2	44.8	21.1	0.264	
Mental quality of life								
Vitality	49.6	19.4	49.4	20.6	51.8	20.5	0.518	
Social functioning	65.4	23.7	66.3	24.9	69.8	23.7	0.199	
Role limitations due to emotional problems	58.2	41.2	60.4	42.8	67.5	37.1	0.088	
Mental health	64.3	19.1	65.6	19.6	69.8	17.2	0.018	RA < SpA
Summary measures								
Physical component score	36.0	10.3	36.9	10.0	38.6	10.2	0.037	RA < SpA
Mental component score	46.1	10.1	46.3	10.9	48.0	9.5	0.189	

RA rheumatoid arthritis; PsA psoriatic arthritis; SpA spondyloarthritis.

APPENDIX C

Supplementary material of subchapter 3.2 Fatigue's role in quality of life among rheumatic diseases.

Appendix C1

Association between disease activity (in Rheumatoid Arthritis[1], Psoriatic Arthritis[2], Axial Spondyloarthritis[3]), physical quality of life and fatigue and moderator variables

	Moderator variables					
	Sex			Treatment		
	Male, mean (SD)	Female, mean (SD)	Coeff (p-value)	First-line[4], mean (SD)	Second-line[5], mean (SD)	Coeff (p-value)
Disease activity						
Rheumatoid arthritis[1]	2.59 (0.96)	2.92 (1.03)	4.13 (<0.001)	2.76 (1.01)	3.05 (1.03)	-3.48 (<0.001)
Psoriatic arthritis[2]	12.2 (8.02)	15.6 (8.90)	5.09 (<0.001)	13.94 (8.42)	16.85 (9.63)	-3.97 (<0.001)
Axial Spondyloarthritis[3]	2.32 (1.03)	2.71 (1.01)	4.90 (<0.001)	2.52 (1.02)	2.85 (1.00)	-3.77 (<0.001)
Fatigue	3.54 (3.87)	4.69 (4.27)	3.57 (<0.001)	4.11 (4.11)	5.19 (4.37)	-3.06 (0.002)
Physical quality of life						
Physical Component Summary	40.0 (10.0)	35.3 (10.1)	-6.05 (<0.001)	37.60 (10.27)	33.45 (9.73)	4.84 (<0.001)
Physical Functioning	70.4 (25.3)	56.8 (26.7)	-6.71 (<0.001)	62.60 (26.42)	54.42 (27.92)	3.62 (<0.001)
Role of Physical	55.0 (42.9)	40.6 (40.4)	-4.52 (<0.001)	48.28 (42.12)	32.73 (37.67)	4.48 (<0.001)
Bodily Pain	52.9 (22.1)	44.5 (23.3)	-4.72 (<0.001)	48.96 (23.68)	40.17 (20.47)	4.53 (<0.001)
General Health	48.1 (21.6)	41.2 (19.8)	-4.37 (<0.001)	44.66 (20.46)	38.19 (20.23)	3.76 (<0.001)

*p<0.05; **p<0.01; ***p<0.001; [1] DAS28-CRP Disease Activity Score in 28 joints with C-Reactive Protein; [2] DAPSA Disease Activity in Psoriatic Arthritis; [3] ASDAS-CRP Ankylosing Spondylitis Disease Activity Score with C-Reactive Protein; [4] csDMARDs and/or anti-TNF; [5] anti-IL6 / bDMARDs / tsDMARDs with or without csDMARDs.

APPENDIX D

Supplementary material of subchapter 4.2 Sex differences in psychological features and determinants of quality of life in rheumatic diseases.

APPENDIX D1

Socio-demographic characteristics of patients with axial spondyloarthritis and psoriatic arthritis, stratified and compared by gender

	Spondyloarthritis (n=119)			**Psoriatic arthritis (n=198)**		
Socio-demographic characteristics	**Females (n=54)**	**Males (n=65)**	**p-value**	**Females (n=124)**	**Males (n=74)**	**p-value**
Age(yrs.), mean (sd)	51.1 (12.1)	47.2 (11.1)	0.072[c]	57.3 (11.5)	56.1 (12.0)	0.481[c]
Marital status, n (%)						
Single	9 (16.7%)	17 (26.2%)	0.439[b]	13 (10.5%)	10 (13.5%)	0.234[b]
Married	42 (77.8%)	44 (67.7%)		93 (75.0%)	59 (79.7%)	
Separated/ Divorced/Widowed	3 (5.6%)	4 (6.2%)		18 (14.5%)	5 (6.8%)	
Education, n (%)						
Low	18 (33.3%)	27 (37.8%)	0.448[a]	67 (54.0%)	36 (48.6%)	0.557[a]
High	36 (66.7%)	38 (58.5%)		57 (46.0%)	38 (51.4%)	
Employment, n (%)						
No	21 (38.9%)	8 (12.3%)	0.001[a]	69 (55.6%)	26 (35.1%)	**0.006**[a]
Yes	33 (61.1%)	57 (87.7%)		55 (44.4%)	48 (64.9%)	

[a] Fisher's exact test

[b] Chi-square test

[c] *t*-test

APPENDIX D2

Clinical and treatment characteristics of patients with axial spondyloarthritis and psoriatic arthritis, stratified and compared by gender

	Axial Spondyloarthritis (n=119)			**Psoriatic arthritis (n=198)**		
Clinical characteristics	**Females (n=54)**	**Males (n=65)**	**p-value**	**Females (n=124)**	**Males (n=74)**	**p-value**
Disease activity						
ASDAS-CRP, mean (sd)	2.9 (1.0)	2.2 (1.1)	**<0.001**[c]			
Inactive (<1.3)	6 (11.1%)	15 (23.1%)	**0.012**[b]			
Moderate (>=1.3 and <2.1)	6 (11.1%)	17 (26.2%)				
High (>=2.1 and <=3.5)	26 (48.1%)	25 (38.5%)				
Very high (>3.5)	16 (29.6%)	8 (12.3%)				
DAPSA, mean (sd)				16.6 (9.5)	12.8 (7.0)	**0.003**[c]
Remission (<=4)				7 (5.6%)	5 (6.8%)	**0.033**[b]
Low (>4 and <=14)				47 (37.9%)	42 (56.8%)	
Moderate (>14 and <=28)				55 (44.4%)	24 (32.4%)	
High (>28)				15 (12.1%)	3 (4.1%)	
Disease duration, mean (sd), yrs.	8.6 (7.3)	11.2 (8.8)	0.083[c]	8.1 (7.0)	10.1 (6.7)	**0.048**[c]
Comorbidity, n (%)						
No	6 (11.1%)	14 (21.5%)	0.147[a]	14 (11.3%)	5 (6.8%)	0.331[a]
Yes	48 (88.9%)	51 (78.5%)		110 (88.7%)	69 (93.2%)	
Family history of rheumatologic diseases, n (%)	41 (75.9%)	46 (70.8%)	0.542[a]	79 (63.7%)	53 (71.6%)	0.278[a]
No	13 (24.1%)	19 (29.2%)		45 (36.3%)	21 (28.4%)	
Yes						
BMI, mean (sd)	25.4 (5.7)	26.2 (2.9)	0.301[c]	26.2 (5.0)	27.1 (3.6)	0.200[c]
Erosion, n (%)						
No	48 (88.9%)	61 (93.8%)	0.509[a]	102 (82.3%)	63 (85.1%)	0.695[a]
Yes	6 (11.1%)	4 (6.2%)		22 (17.7%)	11 (14.9%)	
Radiographic progression, n (%)						
No	27 (50.0%)	41 (63.1%)	0.193[a]	58 (46.8%)	49 (66.2%)	**0.008**[a]
Yes	27 (50.0%)	24 (36.9%)		66 (53.2%)	25 (33.8%)	
Disability (HAQ-DI), n (%)						
Normal or Low (<=1)	44 (81.5%)	60 (92.3%)	0.098[a]	86 (69.4%)	70 (94.6%)	**<0.001**[a]
Moderate or High (>1)	10 (18.5%)	5 (7.7%)		38 (30.6%)	4 (5.4%)	
Treatment characteristics						
Rheumatological treatment, n (%)						
First-line therapy[1]	41 (75.9%)	59 (90.8%)	**0.043**[a]	97 (78.2%)	58 (78.4%)	0.564[a]
Second-line therapy[2]	13 (24.1%)	6 (9.2%)		27 (21.8%)	16 (21.6%)	

Glucocorticoid treatment, n (%)						
No	37 (68.5%)	58 (89.2%)	**0.006**[a]	91 (73.4%)	62 (83.8%)	0.115[a]
Yes	17 (31.5%)	7 (10.8%)		33 (26.6%)	12 (16.2%)	
NSAID treatment[3], n (%)						
No	33 (61.1%)	37 (56.9%)	0.710[a]	84 (67.7%)	52 (70.3%)	0.753[a]
Yes	21 (38.9%)	28 (43.1%)		40 (32.3%)	22 (29.7%)	
Antidepressant therapy, n (%)						
No	42 (77.8%)	62 (95.4%)	**0.005**[a]	102 (82.3%)	67 (90.5%)	0.146[a]
Yes	12 (22.2%)	3 (4.6%)		22 (17.7%)	7 (9.5%)	

ASDAS-CRP ankylosing spondylitis disease activity score with c-reactive protein, *DAPSA* disease activity in psoriatic arthritis, *BMI* body mass index, *HAQ-DI* health assessment questionnaire – disability index, *NSAID treatment* non-steroidal anti-inflammatory drug treatment

[a] Fisher's exact test

[b] Chi-square test

[c] *t*-test

[1] csDMARDs and/or anti-TNF

[2] anti-IL6 / bDMARDs / tsDMARDs with or without csDMARDs

[3] used in last ten days

APPENDIX D3

Univariate linear regression models by sex in spondyloarthritis [each cell contains % explained variance (only if the variable is significant at $p<0.05$), Beta coefficient (p-value)]

	SF36 Physical		SF36 Mental	
Independent variable	**F**	**M**	**F**	**M**
Socio-demographic characteristics				
Marital status Married/cohabitant Separated/divorced/widowed	10% -0.356 (**0.019**) -0.343 (**0.023**)	-0.023 (0.867) -0.030 (0.827)	-0.178 (0.254) -0.004 (0.980)	-0.160 (0.234) -0.230 (0.089)
High education	0.158 (0.255)	8.9% 0.322 (**0.009**)	0.141 (0.309)	5.3% 0.261 (**0.036**)
Employment Yes	12.9% 0.381 (**0.004**)	8.9% 0.322 (**0.009**)	12.9% 0.381 (**0.004**)	0.057 (0.650)
Age	6.8% -0.293 (**0.032**)	14.0% -0.392 (**0.001**)	-0.013 (0.925)	-0.233 (0.062)
Clinical characteristics				
Family history of rheumatologic diseases	-0.150 (0.278)	-0.088 (0.486)	10.3% -0.346 (**0.010**)	-0.050 (0.693)
Comorbidity	-0.030 (0.830)	-0.006 (0.960)	-0.038 (0.784)	0.015 (0.905)
BMI	-0.181 (0.189)	-0.145 (0.248)	-0.092 (0.506)	-0.231 (0.064)
ASDAS-CRP	29.9% -0.559 (**<0.001**)	50.1% -0.713 (**<0.001**)	18.2% -0.444 (**<0.001**)	-0.231 (0.065)
Erosions	0.052 (0.710)	8.4% -0.314 (**0.011**)	-0.071 (0.608)	-0.029 (0.817)
Radiographic progression	0.108 (0.438)	10.4% -0.343 (**0.005**)	7.1% -0.297 (**0.029**)	-0.204 (0.103)
Disease duration (years)	-0.222 (0.106)	-0.012 (0.925)	-0.137 (0.322)	0.214 (0.086)
Treatment characteristics				
Rheumatological treatment Second line therapy[1]	-0.010 (0.941)	-0.130 (0.302)	6.4% -0.286 (**0.036**)	-0.033 (0.796)
Glucocorticoid treatment	9.8% -0.340 (**0.012**)	-0.226 (0.070)	-0.105 (0.454)	6.9% -0.290 (**0.019**)
NSAID treatment[2]	-0.027 (0.845)	7.3% -0.296 (**0.017**)	-0.139 (0.317)	-0.214 (0.087)
Antidepressant therapy	17.6% -0.438 (**0.001**)	0.084 (0.506)	11.0% -0.357 (**0.008**)	0.036 (0.778)

Psychological characteristics				
Depression (HADS-D>10)	-0.150 (0.279)	5.5% -0.265 (**0.033**)	26.8% -0.530 (**<0.001**)	12.4% -0.371 (**0.002**)
Anxiety (HADS-A>10)	-0.202 (0.144)	7.7% -0.303 (**0.014**)	56.5% -0.757 (**<0.001**)	26.0% -0.521 (**<0.001**)
Stress (PSS≥20)	10.9% -0.355 (**0.008**)	-0.126 (**0.316**)	34.4% -0.597 (**<0.001**)	7.0% -0.292 (**0.018**)
Fatigue (CFQ≥4)	13.3% -0.386 (**0.004**)	13.2% -0.381 (**0.002**)	40.9% -0.648 (**<0.001**)	10.8% -0.349 (**0.004**)
Disability (HAQ-DI≥1)	23.8% -0.502 (**<0.001**)	19.8% -0.459 (**<0.001**)	5.4% -0.268 (**0.050**)	-0.156 (0.213)
Pain (VAS)	39.8% -0.640 (**<0.001**)	39.2% -0.634 (**<0.001**)	11.2% -0.359 (**0.008**)	7.8% -0.304 (**0.014**)
COPE Problem-focused	-0.242 (0.078)	-0.084 (0.504)	-0.160 (0.249)	0.192 (0.126)
COPE Emotion focused	-0.196 (0.155)	-0.165 (0.189)	-0.191 (0.166)	0.143 (0.256)
COPE Dysfunctional	-0.241 (0.079)	4.6% -0.247 (**0.047**)	26.8% -0.531 (**<0.001**)	9.6% -0.332 (**0.007**)

SF-36 short form health survey, *BMI* body mass index, *ASDAS-CRP* ankylosing spondylitis disease activity score with c-reactive protein, NSAID treatment non-steroidal anti-inflammatory drug treatment, *HADS-D* hospital anxiety and depression scale – depression, *HADS-A* hospital anxiety and depression scale – anxiety, *PSS* perceived stress scale, *CFQ* chalder fatigue questionnaire, *HAQ-DI* health assessment questionnaire – disability index, *VAS* visual analogue scale, *COPE* coping oOrientation to the problems experiences

1 anti-IL6 / bDMARDs / tsDMARDs with or without csDMARDs

2 used in last ten days

APPENDIX D4

Univariate linear regression models by sex in psoriatic arthritis [each cell contains % explained variance (only if the variable is significant at $p<0.05$), Beta coefficient (p-value)]

	SF36 Physical		**SF36 Mental**	
Independent variable	**F**	**M**	**F**	**M**
Socio-demographic characteristics				
Marital status Married/cohabitant Separated/divorced/widowed	0.0% -0.092 (0.477) -0.111 (0.389)	0.0% -0.003 (0.979) -0.004 (0.974)	1.5% -0.045 (0.720) -0.207 (0.107)	1.7% 0.085 (0.537) -0.152 (0.270)
High education	0.8% 0.128 (0.155)	0.0% 0.105 (0.369)	1% 0.137 (0.128)	0.9% -0.151 (0.197)
Employment Yes	0.2% 0.103 (0.256)	0.0% 0.103 (0.378)	0.4% -0.109 (0.228)	5.3% -0.257 (0.027)
Age	0.7% -0.125 (0.165)	4% -0.231 (0.047)	0.0% 0.021 (0.813)	0.0% 0.107 (0.366)
Clinical characteristics				
Family history of rheumatologic diseases	0.0% -0.023 (0.798)	0.0% -0.112 (0.339)	0.0% -0.004 (0.965)	0.1% -0.121 (0.304)
Comorbidity	1.8% -0.162 (0.071)	9.4% -0.326 (0.005)	0.0% 0.051 (0.571)	0.0% -0.034 (0.774)
BMI	3.8% -0.215 (0.017)	0.0% -0.014 (0.979)	0.0% 0.047 (0.601)	0.0% 0.005 (0.964)
DAPSA	36% -0.604 (<0.001)	28.1% -0.540 (<0.001)	2.4% -0.179 (0.047)	6.4% -0.277 (0.017)
Erosions	3.7% -0.213 (0.017)	0.0% -0.108 (0.357)	0.0% -0.061 (0.495)	1.2% -0.159 (0.176)
Radiographic progression	2.3% -0.177 (0.049)	14.9% -0.401 (<0.001)	1.2% -0.140 (0.121)	0.0% -0.080 (0.499)
Disease duration (years)	0.8% -0.015 (0.871)	0.0% -0.000 (0.999)	0.0% 0.037 (0.683)	0.0% 0.103 (0.380)
Treatment characteristics				
Rheumatological treatment Second line therapy[1]	3.4% -0.206 (0.022)	0.8% -0.150 (0.203)	0.0% -0.086 (0.340)	0.0% 0.037 (0.756)
Glucocorticoid treatment	0.3% -0.109 (0.228)	14.8% -0.399 (<0.001)	0.0% -0.055 (0.540)	4.5% -0.241 (0.038)
	6.7%	16.4%	0.0%	0.0%

NSAID treatment[2]	-0.273 (0.002)	-0.419 (<0.001)	-0.058 (0.518)	-0.102 (0.386)
Antidepressant therapy	5.6% -0.252 (0.005)	2.6% -0.199 (0.089)	0.0% -0.043 (0.635)	0.0% -0.016 (0.891)
Psychological characteristics				
Depression (HADS-D>10)	2.6% -0.183 (0.041)	4.2% -0.235 (0.044)	12.3% -0.361 (<0.001)	13.8% -0.387 (0.001)
Anxiety (HADS-A>10)	1.9% -0.163 (0.071)	4% -0.230 (0.049)	15.1% -0.398 (<0.001)	23.4% -0.494 (<0.001)
Stress (PSS≥20)	0.0% 0.002 (0.976)	0.0% -0.081 (0.490)	11.4% -0.348 (<0.001)	14.4% -0.394 (0.001)
Fatigue (CFQ≥4)	18% -0.432 (<0.001)	14.5% -0.396 (<0.001)	14% -0.384 (<0.001)	38.1% -0.624 (<0.001)
Disability (HAQ-DI≥1)	15.7% -0.405 (<0.001)	9.9% -0.333 (0.004)	12.4% -0.361 (<0.001)	3.9% -0.229 (0.050)
Pain (VAS)	44.9% -0.673 (<0.001)	50.9% -0.718 (<0.001)	8.2% -0.299 (0.001)	11.5% -0.356 (0.002)
COPE Problem-focused	0.7% 0.121 (0.179)	3.7% -0.225 (0.054)	0.0% 0.089 (0.325)	0.4% -0.131 (0.265)
COPE Emotion focused	1.6% -0.156 (0.083)	0.0% -0.096 (0.417)	0.7% 0.124 (0.170)	0.0% -0.009 (0.935)
COPE Dysfunctional	0.7% -0.124 (0.169)	11.3% -0.354 (0.002)	3% -0.197 (0.028)	13.1% -0.378 (0.001)

SF-36 short form health survey, *BMI* body mass index, *DAPSA* disease activity in psoriatic arthritis, *NSAID treatment* non-steroidal anti-inflammatory drug treatment, *HADS-D* hospital anxiety and depression scale – depression, *HADS-A* hospital anxiety and depression scale – anxiety, *PSS* perceived stress scale, *CFQ* chalder fatigue questionnaire, *HAQ-DI* health assessment questionnaire – disability index, *VAS* visual analogue scale, *COPE* coping orientation to the problems experiences

[1] anti-IL6 / bDMARDs / tsDMARDs with or without csDMARDs

[2] used in last ten days

APPENDIX D5

Checks for model assumptions referring to multivariate linear regression models in axial spondyloarthritis (Table 2 in the paper): Shapiro-Wilk test, Breusch-Pagan test, and Variance Inflation Factor (VIF)

	SF36 Physical		**SF36 Mental**	
	F	**M**	**F**	**M**
Shapiro-Wilk test, z (p-value)	-0.82 (0.794)	0.32 (0.374)	-1.15 (0.876)	0.32 (0.374)
Breusch-Pagan test, chi2 (p-value)	1.72 (0.190)	0.48 (0.488)	0.28 (0.599)	0.00 (0.948)
VIF, mean (min-max)	1.92 (1.30-2.88)	2.01 (1.38-4.03)	2.04 (1.26-4.52)	1.39 (1.23-1.69)

SF-36 Short Form health survey

APPENDIX D6

Checks for model assumptions referring to multivariate linear regression models in psoriatic arthritis (Table 3 in the paper): Shapiro-Wilk test, Breusch-Pagan test, and Variance Inflation Factor (VIF)

	SF36 Physical		**SF36 Mental**	
	F	**M**	**F**	**M**
Shapiro-Wilk test, z (p-value)	1.42 (0.078)	0.12 (0.452)	0.42 (0.337)	1.37 (0.085)
Breusch-Pagan test, chi2 (p-value)	0.55 (0.456)	1.76 (0.185)	2.22 (0.136)	0.61 (0.434)
VIF, mean (min-max)	1.41 (1.11-2.28)	1.48 (1.22-2.47)	1.46 (1.13-2.18)	1.48 (1.04-2.37)

SF-36 Short Form health survey

APPENDIX E

Supplementary material of Chapter 5 - Protocol on fatigue reduction in rheumatic diseases: efficacy evaluation (FREE) trial.

APPENDIX E1

Informed consent materials and Consent to the processing of personal data.

INFORMATIVA E MANIFESTAZIONE DEL CONSENSO AL TRATTAMENTO DEI DATI PERSONALI PER FINALITÀ DI RICERCA IN CAMPO MEDICO, BIOMEDICO, EPIDEMIOLOGICO AI SENSI DEL REGOLAMENTO (UE) 2016/679

(art. 13 del Regolamento (UE) 2016/679, regolamento generale sulla protezione dei dati – GDPR)

Titolo completo dello Studio	Intervento psicologico, attività fisica e dieta mediterranea: strategie per ridurre la fatica nelle malattie reumatiche
Codice del protocollo	FREE
Promotore	Prof.ssa Sarah Tosato, Professore Associato di Psichiatria, Dipartimento di Neuroscienze, Biomedicina e Movimento, Sezione Psichiatria, Università di Verona
Centro di Sperimentazione	Azienda Ospedaliera Universitaria Integrata di Verona
Sperimentatore Principale	Dott. Antonio Carletto, UOC di Reumatologia, Dipartimento ad Attività Integrata Medico-Generale, Azienda Ospedaliera Universitaria Integrata di Verona
Contatti dello Sperimentatore Principale	tel 045/8126521; e-mail: antonio.carlett@aovr.veneto.it

Gentile Signora/Egregio Signore,

Le è stato chiesto di partecipare a uno studio di ricerca clinica, che si svolgerà presso l’Unità Operativa Complessa di Reumatologia del Policlinico G.B. Rossi di Verona, in collaborazione con la sezione di Psichiatria del Dipartimento di Neuroscienze, Biomedicina e Movimento dell’Università di Verona. Lo studio ha l'obiettivo di valutare interventi non farmacologici per il miglioramento degli esiti psicologici e clinici nei pazienti affetti da malattie reumatologiche. La partecipazione allo studio, intitolato "*Intervento psicologico, attività fisica e dieta mediterranea come interventi sulla fatica nelle malattie reumatiche*" (di seguito, lo “Studio”), comporterà la raccolta e il trattamento di dati personali, ovvero informazioni che possono identificare o rendere identificabile l’interessato.

Per tale ragione il presente documento Le fornirà le informazioni necessarie per comprendere come avviene il trattamento dei Suoi dati personali o dei dati personali della persona da Lei rappresentata e per poter decidere liberamente e consapevolmente se acconsentire o meno a tale trattamento in relazione allo Studio sopra indicato. In particolare, Le verranno illustrate le finalità e modalità del trattamento dei Suoi dati personali o dei dati personali della persona da Lei rappresentata, nonché i diritti che potranno eventualmente essere esercitati.

1. Titolari del trattamento, rappresentante UE di un titolare

I titolari del trattamento dei Suoi dati personali nell'ambito dello Studio sono il Centro di riferimento presso il quale lo Studio sarà condotto, e il Promotore, come di seguito identificati:

Centro di riferimento	Indirizzo	Recapiti
Azienda Ospedaliera Universitaria Integrata Verona, Ospedale Borgo Roma	*Piazzale L.A. Scuro, 10, 37134 Verona VR*	*tel: 0458121111* *mail: urp@aovr.veneto.it*

Promotore	Indirizzo	Recapiti
Prof.ssa Sarah Tosato	*Piazzale L.A. Scuro, 10, 37134 Verona VR*	*tel:* 045/8124441 mail: sarah.tosato@univr.it

Il Centro e il Promotore che ha commissionato lo Studio, ciascuno per gli ambiti di propria competenza e in accordo alle responsabilità previste dalle Norme di Buona Pratica Clinica, sono **titolari autonomi** delle operazioni di trattamento correlate all'esecuzione dello Studio e tratteranno i Suoi dati personali solo su Suo previo, specifico ed esplicito consenso esclusivamente per la realizzazione dello Studio stesso e soltanto nella misura in cui siano indispensabili in relazione alle sue finalità.

La preghiamo di notare che, per porre domande o esercitare i propri diritti direttamente con il Promotore, dovrà utilizzare il codice di identificazione del paziente che le è stato comunicato al momento della Sua partecipazione allo studio, avendo cura di non rivelare la Sua identità.

2. Responsabile della Protezione dei dati (RPD)

I dati di contatto del Responsabile della protezione dei dati (RPD) individuato dal Centro di riferimento ai sensi degli artt. 37 e ss., GDPR sono:

Indirizzo e-mail	Recapito telefonico
rpd@aovr.veneto.it	045/812 11 11

Il Titolare del trattamento per finalità sanitarie di cura, diagnosi e prevenzione e ai fini dell'esecuzione del presente Studio: UOC Reumatologia, Azienda Ospedaliero Universitaria Verona, P.le Scuro 10 – 37134 Verona.

I dati di contatto del Responsabile della protezione dei dati (RPD) individuato dal Promotore ai sensi degli artt. 37 e ss., GDPR sono:

Indirizzo e-mail	**Recapito telefonico**
reumatologia@aovr.veneto.it	045/812 40 49

3. Categorie di dati oggetto del trattamento

Il trattamento avrà ad oggetto dati identificativi che la riguardano (dati anagrafici e di contatto) e categorie particolari di dati di cui all'art. 9 GDPR, quali i dati relativi alla salute, esclusivamente in funzione della realizzazione dello studio.

4. Finalità del trattamento cui sono destinati i dati personali

I suoi dati personali (qualsiasi informazione relativa alla persona fisica identificata o comunque identificabile, compreso un numero di identificazione personale), i dati relativi allo stato di salute sarà effettuato per le seguenti **finalità**: *partecipazione allo Studio e alle attività connesse*.

5. Base giuridica del trattamento dei dati personali

Il trattamento dei dati personali è indispensabile allo svolgimento dello Studio: il rifiuto di conferirli non Le consentirà di parteciparvi, fermo restando che la partecipazione è assolutamente libera e volontaria, e l'eventuale mancato consenso al trattamento dei dati non avrà alcun riflesso sulla Sua possibilità di accedere alle cure mediche. La informiamo altresì che durante la ricerca potrebbero emergere a Suo carico scoperte inattese che Le saranno comunicate solo dietro Suo esplicito consenso.

I Titolari tratteranno i Suoi dati personali nel rispetto della normativa vigente in materia di protezione dei dati personali (Regolamento (UE) 2016/679 – "GDPR", Decreto Legislativo 196/2003, così come modificato dal Decreto Legislativo 101/2018 – "Codice Privacy", e norme correlate).

La **base giuridica del trattamento** è costituita dal consenso esplicito fornito dall'interessato per le specifiche finalità dello Studio, in conformità con l'art. 6, par. 1, lett. a) e l'art. 9, par. 2 lett. a) del GDPR.

I dati personali in forma pseudonimizzata (e quindi non attribuibili al soggetto interessato senza l'utilizzo di informazioni aggiuntive) possono essere comunicati e verificati dalle Autorità regolatorie all'interno dello Spazio Economico Europeo (“SEE”) al fine di adempiere agli obblighi legali previsti dalle norme di legge e regolamentari nazionali applicabili. La base giuridica di tale trattamento consiste nell’obbligo di legge a cui sono è soggetti i Titolari ai sensi dell’art. 6, par. 1, lett. c) del GDPR.

6. Modalità di trattamento dei dati ed eventuali destinatari o categorie di destinatari dei dati personali

In relazione alle suddette Finalità dello Studio, il trattamento dei dati personali può consistere nelle seguenti attività: raccolta, registrazione, organizzazione, conservazione, consultazione, comunicazione mediante trasmissione o qualsiasi altra forma di messa a disposizione, limitazione, cancellazione e distruzione dei dati.

I dati saranno raccolti, gestiti e custoditi dal Centro di riferimento, con modalità cartacea o elettronica. I dati saranno trattati con modalità tali da garantire la **riservatezza** e la **sicurezza** delle informazioni, ai sensi degli artt. 25 e 32 del GDPR. Tutte le operazioni pertinenti, effettuate solo da membri del personale debitamente formati e autorizzati dai Titolari del trattamento dei dati o dai loro incaricati, avverranno in conformità al segreto professionale, alla riservatezza medico-paziente e ai principi di correttezza, liceità e trasparenza, come previsto dalla normativa vigente.

I Suoi dati personali saranno trasmessi al Promotore in forma pseudonimizzata. Il personale medico e autorizzato del Centro di riferimento provvederà, infatti, a sostituire il Suo nominativo con un codice secondo un processo chiamato “***pseudonimizzazione***”. Soltanto il Medico e il personale autorizzato del Centro possiede il codice (la chiave di decrittazione) che, se necessario, può essere utilizzato per ricollegare i dati pseudonimizzati al Suo nominativo, come in caso di visita di controllo, ispezione o audit.

I Suoi dati raccolti nel corso dello Studio saranno trattati dai Titolari e dal relativo personale autorizzato e istruito, nonché dai seguenti soggetti designati dal Promotore quali responsabili del trattamento ai sensi dell’art. 28 del GDPR nell’ambito dello Studio:

- Prof.ssa Sarah Tosato, monitoraggio e verifica dei dati.

Se necessario, i dati personali raccolti, elaborati e conservati nel contesto dello Studio potranno essere comunicati, eventualmente anche in chiaro, all'Autorità di controllo competente, alle autorità di regolamentazione e vigilanza, al Comitato Etico Territoriale competente, nel rispetto delle disposizioni di legge.

I dati potranno essere diffusi solo in forma rigorosamente anonima, ad esempio attraverso pubblicazioni scientifiche, statistiche e convegni scientifici nell’ambito dello Studio o di altri ad esso associati, senza che si possa ricondurre il dato alla Sua persona.

7. Periodo di conservazione dei dati

I dati personali dell’interessato oggetto del trattamento saranno conservati per un periodo di almeno 7 (sette) anni dalla conclusione dello Studio in conformità a quanto previsto dal protocollo di Studio e comunque per il periodo necessario a soddisfare lo scopo per il quale sono stati raccolti o di eventuali ulteriori esigenze di analisi dei dati, ovvero al manifestarsi di evidenze significative per la sicurezza dei pazienti. Al termine di tale periodo, i dati personali saranno eliminati. In ogni caso, Lei ha il diritto di chiedere, in qualsiasi momento, l'eliminazione dei dati, nel rispetto del RGPD e della legge sulla protezione dei dati applicabile.

In ogni caso, presso i soggetti esterni che eventualmente collaborano con il Promotore per la gestione e l´analisi statistica, i dati vengono conservati per il solo periodo di tempo non superiore a quello necessario a definire il rapporto finale dello Studio o pubblicarne i risultati.

I dati potranno essere conservati anche per l’utilizzo in future attività di studio e di ricerca, nel qual caso gli interessati ne saranno previamente e adeguatamente informati, al fine di poter manifestare un consenso specifico e distinto rispetto a quello rilasciato per lo Studio principale.

8. Trasferimento dei dati ad un Paese terzo e ad organizzazioni internazionali

I dati personali a Lei riferibili ed oggetto dello Studio **non sono** comunicati a **soggetti non operanti nello Spazio Economico Europeo**.

9. Diritti dell’interessato

Lei, in qualità di interessato, potrà esercitare in qualsiasi momento i diritti indicati dagli articoli 15-22 del GDPR, in quanto applicabili, ivi compresi:

- il diritto di **accedere ai dati personali** che La riguardano;
- il diritto di chiedere al titolare del trattamento la **rettifica** dei propri dati qualora questi siano inesatti (si applica in tal caso l’art. 110, comma 2, del Codice);
- il diritto di ottenere dal titolare del trattamento la **cancellazione** dei dati personali che La riguardano qualora ricorra uno dei casi indicati dal paragrafo 1 dell’art. 17 del GDPR e non sussista una delle deroghe di cui al paragrafo 3;
- il diritto di ottenere la **limitazione del trattamento** da parte del titolare nei casi indicati dall’art. 18 del GDPR;
- il diritto di **opporsi al trattamento** dei propri dati personali per motivi connessi alla Sua situazione particolare.

Lei ha altresì il diritto di **revocare il consenso** in qualsiasi momento e senza fornire alcuna giustificazione la Sua partecipazione allo studio. La revoca del consenso non pregiudica la liceità del trattamento basata sul consenso prima della revoca.

Potrà esercitare i diritti di cui sopra rivolgendosi, senza formalità (lettera raccomandata, e-mail, ecc.), direttamente al Centro di Sperimentazione o, per il tramite del medico sperimentatore, al Promotore, ai recapiti sopra indicati.

10. Diritto dell’interessato di presentare reclamo

Lei, in qualità di interessato, ha altresì il diritto di **proporre reclamo e segnalazioni** all’Autorità competente (in Italia, l’Autorità Garante per la protezione dei dati personali, con sede in Roma) ai sensi dell’articolo 77 del GDPR e degli articoli 141-144 del Codice, ove ritenga che il trattamento che La riguarda violi il GDPR o per qualsiasi altra questione relativa al trattamento dei Suoi dati personali. Il reclamo potrà essere fatto secondo le modalità indicate sul sito internet del Garante accessibile all’indirizzo www.garanteprivacy.it. Il reclamo e la segnalazione non pregiudicano ogni altro ricorso amministrativo o giurisdizionale presentato.

Può inoltre contattare ai recapiti sopra indicati il Responsabile della protezione dei dati (RPD) per tutte le questioni relative al trattamento dei Suoi dati personali e all'esercizio dei Suoi diritti derivanti dal GDPR.

DICHIARAZIONE DI CONSENSO AL TRATTAMENTO DEI DATI PERSONALI

Il/la sottoscritto/a __________________________________ nato/a a ___________________
(____) il ____/____/____, per sé,

letta e compresa l'informativa di cui all'art. 13 del Regolamento (UE) 2016/679 fornitami congiuntamente al presente documento e di cui è parte integrante, nonché ricevute tutte le informazioni comprensibili ed esaurienti sugli scopi e i limiti dello Studio per il quale viene rilasciata la presente dichiarazione,

☐ **Acconsento** ☐ **Non acconsento**

al trattamento dei miei dati personali per gli scopi inerenti allo Studio nei limiti e con le modalità indicate nella predetta informativa

☐ **Acconsento** ☐ **Non acconsento**

_____________, ___________

(Luogo e data)

Firma dell'interessato o di chi
ne fa le veci

____

APPENDIX E2

Psychological intervention

Session 1: PSYCHOEDUCATION ON FATIGUE

Session goal
To introduce the intervention and establish fatigue as a significant, common symptom experienced by individuals with arthritis.

The therapist (indicated with the T) introduces himself, briefly outlining their profession and work experience. He/she explains that will conduct all the sessions.

The participants

Ice-breaking activity to promote group cohesion

Now T addresses all patients, asking them to introduce themselves, sharing some information about who they are and about their condition (such as the type of illness, how long they have had it, whether they have other comorbidities), and their reasons for participating, as well as their expectations regarding the intervention.

T makes pleasant and kind comments toward participants to support their introductions. They summarize everyone's presentations (for example: *"A lovely group, very diverse. working together in the coming sessions will be interesting"*).

"Now I will present the structure of the session. It is composed as follows: first, I will provide an introduction to the intervention; then, we will explore psychoeducation about fatigue in rheumatic diseases; afterward, I will share some personal experiences; next, we will open a discussion on the possible interventions, listening to your thoughts and your motivation for change. At the end, we will conduct a general discussion to establish the direction of the change process and conclude the session. After each meeting, homework will be assigned."

Parte 1 - Introduction to the program

Overview of fatigue

Inflammatory rheumatic diseases are a group of multisystemic rheumatic conditions of immune origin, which include rheumatoid arthritis, psoriatic arthritis, and axial spondyloarthritis. Although the clinical manifestations of inflammatory rheumatic diseases vary, fatigue is a widespread, intrusive, and often disabling symptom in many of them. An international study of more than 6,000 patients found that about half were severely affected by fatigue. For this reason, fatigue is a complex phenomenon and a major health concern for many people with chronic inflammatory rheumatic diseases. Fatigue represents a major economic burden on health and an unmet need for both patients and society. It has been recognized that fatigue is among the most difficult symptoms to manage for patients with inflammatory rheumatic diseases and is *associated with poor quality of life. Fatigue is also an important independent predictor of work loss and disability in rheumatic disease patients. Considering the wide personal and economic impact of fatigue, identifying an effective treatment is a priority* (Davies et al., 2021; Geenen & Dures, 2019).

Overview of treatment

"Our previous study conducted at the Rheumatology Unit of the University Hospital of Verona, involving 807 patients with rheumatic diseases, showed that about 50% of patients experienced a significant level of fatigue. The idea of carrying out the intervention arose from the desire to find a way to help patients combat fatigue, including through non-pharmacological interventions. The goal is that, following this intervention, non-pharmacological treatments may be integrated into the standard care of all patients at the Rheumatology Unit of the University Hospital of Verona."

General structure of the treatment

"The therapist conducts 12 group meetings with patients as part of an intervention that will take place over six months, with meetings held every two weeks. Each meeting will last 1.5 hours and will focus not only on fatigue but also on emotion regulation, cognitive restructuring, coping skills, illness acceptance, communication skills, and strategies for managing stress, pain, and sleep. The topics of each session will be: Psychoeducation on fatigue; Fatigue management; Exploring emotions; Challenging negative thoughts; Understanding cognitive distortions and coping strategies; Behavioral activation; Self-care and fatigue; Social support and communication strategies; Stress-management techniques + Pain and fatigue; Sleep hygiene and other healthy behaviors; Review of skills and integration; Reflection and future planning. A follow-up session will be held 3 months after the end of the study. Its aim will be to review the main concepts. Participants will evaluate difficulties in implementing and/or practicing the acquired skills; they will review and consolidate acceptance, compassion, and other exercises carried out during the sessions."

Structure of each session

"Sessions will be structured, including an introduction, a main part, and a general conclusion at the end. In the first session, the intervention program will be presented to patients, whereas in the last session both the patients and the therapist will summarize their insights on fatigue and related topics. Generally, each session (starting from the second meeting) will begin with a review of the homework assigned during the previous session and will invite participants to share thoughts and experiences related to it. Then, a new topic related to fatigue will be introduced through psychoeducation. The main part will adopt a cognitive/emotional and behavioral approach, in which the psychologist will engage participants in a discussion of their experiences and perspectives, and participants will carry out skill-building activities that reinforce the concepts addressed. The therapist, together with participants, will

summarize the key points of the session, highlighting the main themes and take-home messages. Homework will be assigned at the end, with the aim of reinforcing learning and consolidating the topic. During the off-weeks, participants will be assigned tasks in the form of psychological exercises, which psychologists will introduce at the end of each meeting."

"This intervention was developed based on previous studies on the same topic. The approach used is cognitive-behavioral therapy, and the intervention is based on this model. The objective is to assess whether this approach has an impact on fatigue, disease activity, and disability, as well as on pain, depression, anxiety, quality of life, and sleep; if so, it may become an integral part of treatment at the Rheumatology Unit. Another goal is to compare the effectiveness of three interventions: a psychological intervention integrated with usual care, a personalized exercise program combined with a Mediterranean diet associated with usual care, and usual care alone."

Overview of fundamental group rules

"It is important to emphasize the value of group work. A group possesses its own strength and offers support, actively involving all participants. Every group has its own rules: among these, two fundamental ones are benevolence and respect for privacy. Everything shared within the group remains confidential, thus ensuring respect and freedom of expression for each individual.

If deemed important, T may also read all the signed group rules.

Here, I restate the rules that group members must follow to be part of it.

1. ***Punctuality.*** *Punctuality is required at the beginning and end of sessions. Punctuality allows the group to work without disruptions caused by late arrivals or early departures. With punctuality, the meeting begins, and with punctuality, it ends.*
2. ***Session frequency is biweekly.*** *The group must make a difference in the individual's life; it must be something meaningful (produce significance), which is why a certain frequency of sessions is needed. This contributes to building stable relationships and allows group members to develop a stronger sense of belonging. The biweekly frequency allows sufficient stability to motivate patients.*
3. ***Members commit to mutual confidentiality.*** *Participants commit to a strong mutual protection of privacy; the meaning and value of protective behavior are emphasized. This is a fundamental rule.*
4. ***Responsibility and control over one's own behavior.*** *The patient learns to assume responsibility for their functioning within and in relation to the group.*
5. ***Everyone is free to decide when to express their emotions.*** *The therapist maintains a warm and stimulating attitude while also providing people with permission to explore their own difficulties in opening up.*
6. ***All commit to non-judgment during sessions.*** *In our groups, participants are asked to be direct and not filter communication, recognizing that it is impossible for judgments not to emerge. What is continually emphasized is that communication in general and judgmental communication in particular is a*

hypothesis proposed by the person expressing it about another's experience (in no way an absolute truth), and that this effort to express something regarding the companion's experience is, regardless of content, a concrete expression of interest in that person. Freeing these compressed parts allows access to greater degrees of freedom in relationships with oneself and others."

Part 2 - Concept of fatigue related to arthritis

"Now I will explain the main aspects of fatigue in rheumatic diseases. My intervention is based on the most recent scientific research. For each aspect of fatigue, we can pause and discuss it together; your comments and examples will be fundamental for identifying the best starting point for each of you."

Introduction

Fatigue is often experienced by healthy individuals; it is usually transient and may be caused by lack of sleep or high stress levels. In the general population, fatigue is a universal symptom, varying in severity and chronicity, with an extreme end in which patients experience persistent fatigue, contributing to a significant impact (Matcham et al., 2015). Fatigue is one of the most common symptoms in rheumatic diseases. However, there is confusion regarding the definition and use of the term fatigue (Ream & Richardson, 1996; Davies et al., 2021). Most people have experienced fatigue during daily life, but there are differences between fatigue associated with chronic illness and "common" or pre-morbid fatigue. The most distinctive features of fatigue related to chronic illness include the perception of fatigue as lacking an apparent explanation, lack of improvement with rest, variability in severity, unpredictability, and its profound or overwhelming nature (Davies et al., 2021).

Here, T asks participants to define fatigue using related terms or by providing descriptions (if participants give lengthy descriptions, T must summarize them). The proposals are written on the board. In the center, "FATIGUE" is written, and around it participants' comments are added. If participants are very passive, T does not insist; they proceed with the text and try to include participants during reading.

Steps toward the definition

"Fatigue has several meanings. One of them is "to exhaust as with running or work, to weary or harass," which describes the concept primarily as effort-related: "physical or mental exhaustion due to exertion." Here, it refers to fatigue as the perception of a complex interplay of both somatic and psychological factors.

Four similarly important characteristics of fatigue:

1. *Fatigue follows exertion;*
2. *Fatigue is associated with tiredness and physical or mental exhaustion;*
3. *Fatigue includes unpleasant, bothersome, or distressing sensations;*

4. *Fatigue causes a decrease in functional capacity, which is often temporary."*

Fatigue is not limited to the simple sensation of tiredness or weakness

T asks patients whether fatigue is a type of tiredness, weakness, or something else, or whether it represents something more.
Fatigue has been classified alongside terms such as tiredness, weariness, faintness, weakness, wasting, lassitude, exhaustion, collapse, and prostration, to name a few. The terms most frequently used as synonyms are tiredness and weakness. However, they should not be used as equivalents of fatigue, as they are distinct characteristics (Ream & Richardson, 1996).

Fatigue in rheumatic diseases is different from the normal feeling of tiredness (Dures et al., 2024). Tiredness is a state in which a person perceives a temporary decline in strength and energy. Although these sensations may be part of fatigue, the latter is a more complex concept with additional characteristics (Ream & Richardson, 1996). Weakness is a symptom produced by neurological impairment and, like fatigue, affects the individual's ability to perform certain activities. However, fatigue has a voluntary aspect: people, through willpower and pacing, can still carry out some activities (Ream & Richardson, 1996).

Attributes of fatigue

Fatigue is a subjective and unpleasant symptom involving whole-body sensations, ranging from feeling tired to extreme tiredness, creating an ongoing, pervasive state that interferes with the individual's ability to function at their normal level (Ream & Richardson, 1996).

Several subtypes of fatigue have been proposed, such as "physical," "mental," and "motivational." However, the main point is that individual differences in how patients interpret and respond to fatigue make the picture complex (Davies et al., 2021).
Fatigue is:

1. *A whole-body sensation and experience, encompassing physical, cognitive, and emotional dimensions;*
2. *An unpleasant and distressing experience;*
3. *A chronic and relentless phenomenon;*
4. *A subjective experience dependent on the individual's perceptions (Ream & Richardson, 1996).*

Chronic aspect

The fatigue that frequently accompanies illness is called chronic fatigue. Chronic fatigue is induced by the pathological process rather than by physical activity. It usually has an insidious onset, is cumulative, and persists over time. This contrasts *with the fatigue most people experience in daily life. Acute fatigue is generally linked to an identifiable form of exertion, appears rapidly, has a short duration, and is relieved by a good night's sleep (Ream & Richardson, 1996). Fatigue is a persistent and significant problem for people with arthritis, including both physical exhaustion and cognitive impairment, with impacts on lifestyle, roles, relationships, and emotions (Hewlett et al., 2019).*

Correlates of fatigue

T asks participants whether there are and what might be the factors related to fatigue. As before, on a new board page, T writes "FATIGUE" at the center. Around it, various related factors are added. T may also draw arrows, asking what influences what.

Fatigue is a phenomenon affecting both physical and mental capacities, with consequences for an individual's daily functioning. Daily activities such as going to work, doing housework, participating in social or recreational activities, and self-care tasks like bathing and dressing may be hindered or even reduced. Fatigue typically triggers affective, behavioral, and cognitive responses. These include irritability, altered thoughts, inability to make decisions, difficulty concentrating on daily tasks, inability to cope, forgetfulness, low motivation, and family conflict. These physical and mental factors influence individuals' overall quality of life. Variables identified as worsening fatigue include, among others, medications and therapies, overexertion, sleep quality and quantity, emotional stress, environmental factors, lack of social support, age, nutritional status, and disease activity (Ream & Richardson, 1996).

Now, for each factor that T reads, they add it to the board if it was not already proposed by participants.

There is a complex relationship between fatigue and disease activity in inflammatory rheumatic diseases. Inflammation likely plays an important role in triggering fatigue responses, particularly in the early stages of the disease and during flare-ups (Davies et al., 2021). Disease activity seems to play a role in the relationship between psychological variables and fatigue (Matcham et al., 2015).

Depression is also strongly linked to fatigue in inflammatory rheumatic diseases. Notably, "marked fatigue" is one of the diagnostic criteria for depression. However, although fatigue may contribute to depression through shared mechanistic pathways and consequences in daily life, depression and fatigue are distinct phenomena, and many patients with fatigue are not depressed. Distinguishing depression from fatigue in clinical practice can be difficult (Davies et al., 2021).

Musculoskeletal pain is often a defining feature of many inflammatory rheumatic diseases and is an important predictor of fatigue. However, fatigue can also increase pain. Pain and fatigue may be two symptoms of a coordinated bodily response to chronic stressors, with shared mechanisms (Davies et al., 2021).

Coping strategies and illness perceptions have been linked to fatigue. Catastrophizing, avoidance, and negative beliefs about illness are associated with fatigue in chronic diseases (Davies et al., 2021).

There is also a significant correlation between fatigue and physical disability, poor mental well-being, sleep disturbances, anxiety, and stress, suggesting partially *independent influences on fatigue and differences between individuals (Davies et al., 2021; Geenen & Dures, 2019; Nikolaus et al., 2013). Moreover, self-efficacy appears to be an important factor in the relationship between fatigue and mood (Matcham et al., 2015).*

No conclusive evidence has been found for an association between personality traits and fatigue, nor between social support and fatigue (Matcham et al., 2015). In conclusion, the real influence between fatigue and the variables mentioned is very likely reciprocal (Geenen & Dures, 2019).

Subjective experience of fatigue

Fatigue is inherently a subjective phenomenon and an internal sensation that does not appear to be the same for everyone. People with rheumatic diseases often explain their fatigue in relation to the significant impact it can have on all aspects of daily life (Davies et al., 2021). They describe fatigue as overwhelming, invasive, distressing, and draining of physical and mental energy. It can make people feel lonely, as they withdraw from social interactions and their lives become increasingly limited (Dures et al., 2024).

The experience of fatigue is incomplete without an individual evaluation of one's own feelings. A patient describes it: "Fatigue means that my whole being is tired. The tiredness penetrates the entire bone structure; you feel it in the very marrow of your bones. It is total physical tiredness, and on top of that you add the mental tiredness. It is like an underground current that undermines your thinking. Your body is wearing out. The weight of fatigue hides in the shadows. If I rest, the fatigue overwhelms me" (Ream & Richardson, 1996).

Intervention 1 - Experience of fatigue

"Now I will hand out the sheets containing comments about common experiences of fatigue from patients with rheumatic diseases. Read them carefully and mark the comments that reflect your experience. Also, feel free to add your own personal comments about your experience of arthritis-related fatigue."

T hands the sheets to the participants, while keeping a separate copy for themself, which is different from the others. This copy also includes explanations for each example, providing brief interpretations of what each testimony refers to.

After participants have finished completing their sheets, those who wish may share which testimony they found particularly interesting, and if they added their own testimony, they may decide to read it.

Subsequently, the other participants are invited to join the discussion. If T has doubts about how to interpret some written testimonies, they may consult their own copy.

Non-pharmacological interventions

Fatigue is not a condition that a person either has or does not have, but a continuum. Therefore, it represents a bio-psycho-physiological state that reflects the body's overall strategy for managing resources (energy). Optimal fatigue management requires a personalized and holistic approach (Davies et al., 2021). It is important to understand the networks of biopsychosocial factors—specific to each individual—that maintain fatigue, and to develop tailored interventions targeting the most relevant contributing factors for that person (Geenen & Dures, 2019). Optimal pharmacological management of arthritis, with disease-modifying antirheumatic drugs and biologic therapies, appears to offer only small benefits for fatigue. These benefits may occur indirectly through reducing inflammation and/or pain. Without improvement in cognitive, behavioral, and personal factors contributing to arthritis-related fatigue, even optimal pharmacological management is unlikely to bring substantial benefits (Cramp, 2019).

Stigma linked to psychological factors in rheumatic diseases may contribute to prioritizing physical over mental aspects of health. In care delivery, the preference for treating physical rather than mental health problems may be adopted by patients, clinicians (e.g., during consultation), and health systems, which may prioritize organizing physical-health services. However, psychological and social factors, emotions, and feelings are no less "real" than the physical aspects of illness. Psychosocial factors in fatigue research and clinical practice deserve more attention but require a multidisciplinary and open approach (Davies et al., 2021).

To address the potentially complex and multifactorial nature of fatigue in arthritis, it is likely best to manage it as a symptom in its own right, using a multidimensional approach that incorporates both pharmacological and non-pharmacological methods. Psychosocial interventions such as self-management programs, cognitive-behavioral approaches, and lifestyle interventions, or activity-based interventions, have all been proposed as potentially beneficial (Cramp, 2019). Cognitive-behavioral therapy approaches have shown effects on arthritis-related fatigue (Cramp, 2019). A recent study showed that the effects on arthritis-related fatigue can be improved for 2 years by rheumatology teams delivering a group program using cognitive-behavioral approaches (Hewlett et al., 2019).

T asks participants to identify current difficulties in managing fatigue and previous attempts to address it. Moreover, T asks what kinds of attempts were made, whether they were psychological in nature, and whether they proved effective.

Intervention 2 - Wheel of Life

"Now we will focus on different aspects of life, evaluating how satisfied you are and what should be changed, and which areas of life need work."

T hands each participant the sheet with Intervention 2, reading the instructions. The Wheel of Life consists of four pages: the first contains instructions, the second contains the Wheel itself, and the last two are dedicated to explaining aspects of life. The patient is invited to focus on the Wheel and complete it; if they do not understand one of the aspects, they may consult the pages with the corresponding description. This prevents wasting time.

After completing the wheel, participants present how they carried out the task and explain the strengths and weaknesses related to the different aspects of life. T provides comments in a fairly neutral manner, offering general advice and suggestions for exploring some aspects further in upcoming sessions, or asking other participants to share possible tips. It is important to emphasize that it is essential to be aware of the strengths and weaknesses present in one's own life wheel, as this awareness can be used to improve one's life.

Intervention 3 (optional) - Advice I would give my best friend

Intervention number three is not a priority, and if time remains, it may be carried out; if not, the participant may take it home along with the second task (it will be optional homework).

Because the psychological group intervention is based on discussing personal problems, in the next activity we will try to identify the main problems and possible solutions.

T reads the instructions: *"Right now, you are going through a difficult moment. Imagine that a friend of yours had to face the same difficulties: what advice would you give them? What would you say or suggest they do? Is the way you speak to your friend different from the way you speak to yourself? Why does this happen?"* T asks participants to offer general comments on this exercise, sharing impressions of the task. After a brief discussion, T informs patients that shortly they will explain a homework assignment connected to what has just been done.

Conclusion

T and the participants summarize the main points of this session and the key ideas to take home. Participants are invited to share their opinions.

Homework

"We have reached the end of this session. It is time to hand out the homework, so that you may take an active role in this intervention, practicing and consolidating what was learned during this session over the next 14 days. At the beginning of the next session, we will discuss your homework. Please bring the completed homework to the next session, as we will use it as material for further exploration of fatigue."

T hands participants the sheets with homework one (mandatory) and two (optional). T explains the tasks by reading the instructions.

Assignment 1

Keep a fatigue diary: monitor fatigue through daily experience and its impact on everyday life.

Assignment 2 (optional)

Reflect on why it is so difficult for me to accept good advice.

Intervention 1: Experience of fatigue (for therapist)

Below are testimonies describing the experience of fatigue among patients with rheumatic diseases. If you identify with any of these experiences, indicate the corresponding one. If you have different examples from those listed, write them as an addition.

Different from normal tiredness (“exhaustion”)

The participant **experienced extreme**, absolute, and exhausting tiredness, which left her unable to continue. At times it had a sudden and dramatic onset: *“Well, my expression is ‘exhaustion’; I call my tiredness my exhaustion days... or my exhaustion moments... Because I really don’t want to do anything other than sleep and I feel completely drained of energy. It was a very sudden and definite blow, as if the energy had drained out of me”* (65-year-old woman).

Fatigue varies in **duration** (minutes, days) and frequency (daily, several times a week, constant), and includes physical elements of tiredness, a feeling of emptiness, and loss of physical energy: *“Just tired, a bit exhausted, fatigued, I don’t know, as if everything had vanished from me”* (63-year-old woman).

Participants also described a loss of **mental energy**, motivation, and cognition: *“Well, you feel as if you don’t want to do anything. You feel like you’re quite content to sit and do nothing. The enthusiasm is gone, you know, you lose interest”* (80-year-old woman).

Participants consider arthritis-related fatigue to be **different from normal tiredness**, such as the tiredness they experienced before diagnosis or that people without rheumatic diseases experience: *“Because, I mean, I have friends who are my age and they’re not at all as tired as I am, and I call them normal”* (62-year-old woman).

Arthritis fatigue is not normal because episodes are often **not preceded by activities** (that is, they are not “earned”): *“I feel really very tired, as if it were an abnormal tiredness, not normal, not ‘I have done something to make myself tired’”* (31-year-old woman).

Arthritis fatigue is variable, mostly **unpredictable**, with sudden onset and no regular pattern over time or days of the week, with variations in duration and intensity: *“I can’t put a time on these [exhaustions]... You cannot know when they will arrive”* (65-year-old woman).

RA fatigue **occurs without a specific reason, often unexpectedly** and without a clear pattern, which makes it frustrating and difficult to manage: *“It’s frustrating, my mind* *is full of energy but my body does not have that energy, it doesn't want to respond, it is simply tired and nothing else, completely exhausted"* (55-year-old woman). *"Before having rheumatoid arthritis, I never felt tired; my energy was limitless"* (71-year-old man).

Having to **work harder and longer** because of disability, and having to spend more energy to make compromised joints move normally, are also considered causes of fatigue: *"Everything seems to take twice or three times as long as before, and all this contributes to making me feel tired"* (64-year-old woman).

Some patients also report sleeping well but **still experiencing unrefreshing sleep**: *"I can have a good sleep... And yet I wake up feeling very, very tired and exhausted, and heavy"* (40-year-old woman).

Consequences permeate every aspect of life

The consequences of fatigue permeate every part of life, to the point that **activities are reduced** to a minimum or "simplified": *"When I get home, I feel as if I had done a week's worth of things, the things I should have done in a week, and we have just gone to get the groceries. I mean, my husband brings them in and puts them away, which I would normally do, and I collapse onto a chair. It's as if, I don't know, everything seemed wrong"* (45-year-old woman).

Fatigue in arthritis patients is recognized by most people within their closest circle of family and friends, through the patient's pallor, a change in the eyes (less bright), reduced concentration, irritability, and mobility problems: *"My wife says I need to lie down because I'm not reacting as expected and I can't find the right words, I lose concentration"* (71-year-old man).

The nature of fatigue **limits the participants' ability to perform their normal family roles**, including playing with their children: *"They limit what I do; if my nine-year-old son runs around, I usually sit and watch... So his father has to do all those things I used to do, like running around"* (40-year-old woman).

Fatigue has an **emotional impact on relationships**, leading to frustration, irritability, and loss of control: *"I feel very limited and restricted in what I can do, so I feel limited and restricted... Um, frustrating... Yes, it's a very negative feeling, as if I had lost control over certain things I can do"* (28-year-old woman).

The consequences of **fatigue reduce self-esteem**, leading to resentment: *"I feel useless, because I have two grandchildren, and I feel I cannot do the things I would like with them because I get too tired"* (45-year-old woman).

Fatigue has the **greatest impact on daily life**, particularly on relationships, leisure time, and emotional aspects: *"Sometimes I cry when I discover that something I used to be able to do is no longer possible for me"* (61-year-old woman).

Self-management varies, professional support is rare ("You don't know what to do")

Participants reported having **tried various self-management strategies**, particularly acceptance: *"But you have to accept it sometimes, and try to work around it, and work with it rather than thinking 'Oh, I will get over this,' because I can make myself more tired and more exhausted"* (28-year-old woman).

Positive attitudes must be adopted*: "And I think it's because I have a positive attitude that I manage to get through it, and I do not always complain. I never tell my son 'Oh, you know, I'm feeling terrible' or 'I am tired.' I always pull myself together"* (64-year-old woman).

Occasionally they choose to **continue anyway and deal with the consequences**: *"Or you go out and do everything in a day. You go crazy and then suffer for about 3 days afterward"* (63-year-old man).

Most interviewees indicated **pacing and rest as the first intervention strategy**, followed by relaxation techniques and acceptance. Strategies are not always effective: *"When I have to clean the house, I have to choose the priority activity of that day and even then I have to proceed in stages"* (46-year-old woman). *"I have to lie down a bit and plan to finish the work later, but then I can't because I'm too tired, and it's frustrating"* (46-year-old woman).

Almost all participants report **managing fatigue on their own**, without discussing it as a specific symptom with the rheumatologist or specialist nurse. Professional support is not always tailored and therefore not always suitable for some: *"My doctor told me to slow down, but I didn't listen because it's hard for me to say no when someone asks me for help"* (49-year-old man).

Intervention 1: Experience of fatigue (for patients)

Below are the testimonies regarding the experience of fatigue among patients affected by rheumatic diseases. If you recognize yourself in any experience, indicate the corresponding one. If you have examples different from those listed, write them as an addition.

“Well, my expression is ‘exhaustion’; I call my tiredness my exhaustion days... or my exhaustion moments... Because I really don’t want to do anything other than sleep and I feel completely drained of energy. It was a sudden and definite blow, as if the energy had drained out of me” (65-year-old woman).

“Simply tired, a bit exhausted, fatigued, I don’t know, as if everything had vanished from me” (63-year-old woman).

“Well, you feel as if you don’t want to do anything. You feel as though you just want to sit down and do nothing. The enthusiasm is gone, you know, you lose interest” (80-year-old woman).

“Because, I mean, I have friends who are my age and they are not at all as tired as I am, and I call them normal” (62-year-old woman).

“I feel really very tired, as if it were an abnormal tiredness, not normal, I haven’t done anything to be this tired” (31-year-old woman).

“I can’t put a time on these [exhaustion episodes]... You cannot know when they will arrive” (65-year-old woman).

“It is frustrating, my mind is full of energy but my body does not have that energy, it does not want to react, it is simply tired and nothing else, completely exhausted” (55-year-old woman).

“Before having rheumatoid arthritis, I never felt tired, my energy was limitless” (71-year-old man).

“Everything seems to take twice or three times as long as before, and all this contributes to making me feel tired” (64-year-old woman).

“I can have a good sleep... Yet I wake up feeling very, very tired and exhausted, and heavy” (40-year-old woman).

"When I get home, I feel as if I had done everything I should have done in a week, and we have only gone grocery shopping. I mean, my husband brings it in, unpacks it and puts it away, which I would normally do, and I collapse onto a chair. It's as if, I don't know, everything seemed wrong" (45-year-old woman).
"My wife says that I need to lie down because I'm not reacting as expected and I can't find the right words, I lose concentration" (71-year-old man).

"They limit what I do; if my nine-year-old son runs around, I usually sit and watch... So his father has to do all those things I used to do, like running around" (40-year-old woman).

"I feel very limited and restricted in what I can do, so I feel limited and restricted... Um, it's frustrating... Yes, it's a very negative feeling, as if I had lost control of the things I can do" (28-year-old woman).

"I feel useless, because I have two grandchildren, and it seems to me that I cannot do the things I would like with them because I get too tired" (45-year-old woman).

"Sometimes I cry when I discover that something I used to be able to do is no longer possible for me" (61-year-old woman).

"I think it is because I have a positive attitude that I manage to get through it, and I do not always complain. I never tell my son 'Oh, you know, I look terrible' or 'I am tired.' I always pull myself together" (64-year-old woman).

"Or you go out and do everything in a single day. You go crazy and then suffer for about 3 days afterwards" (63-year-old man).

"When I have to clean the house, I have to choose the priority activity for that day and even then I have to proceed in stages" (46-year-old woman).

"I have to lie down a little and plan to finish the work later, but then I can't because I am too tired, and it is frustrating" (46-year-old woman).

"My doctor told me to slow down, but I didn't listen because it is difficult for me to say no when someone asks me for help" (49-year-old man).

An example of your experience regarding arthritis-related fatigue:
____
____
____
____
____
____.

Intervention 2: The Wheel of Life

The Wheel of Life, as a tool, makes it possible to assess instantly and clearly the level of personal satisfaction experienced in the most important macro-areas of our existence:

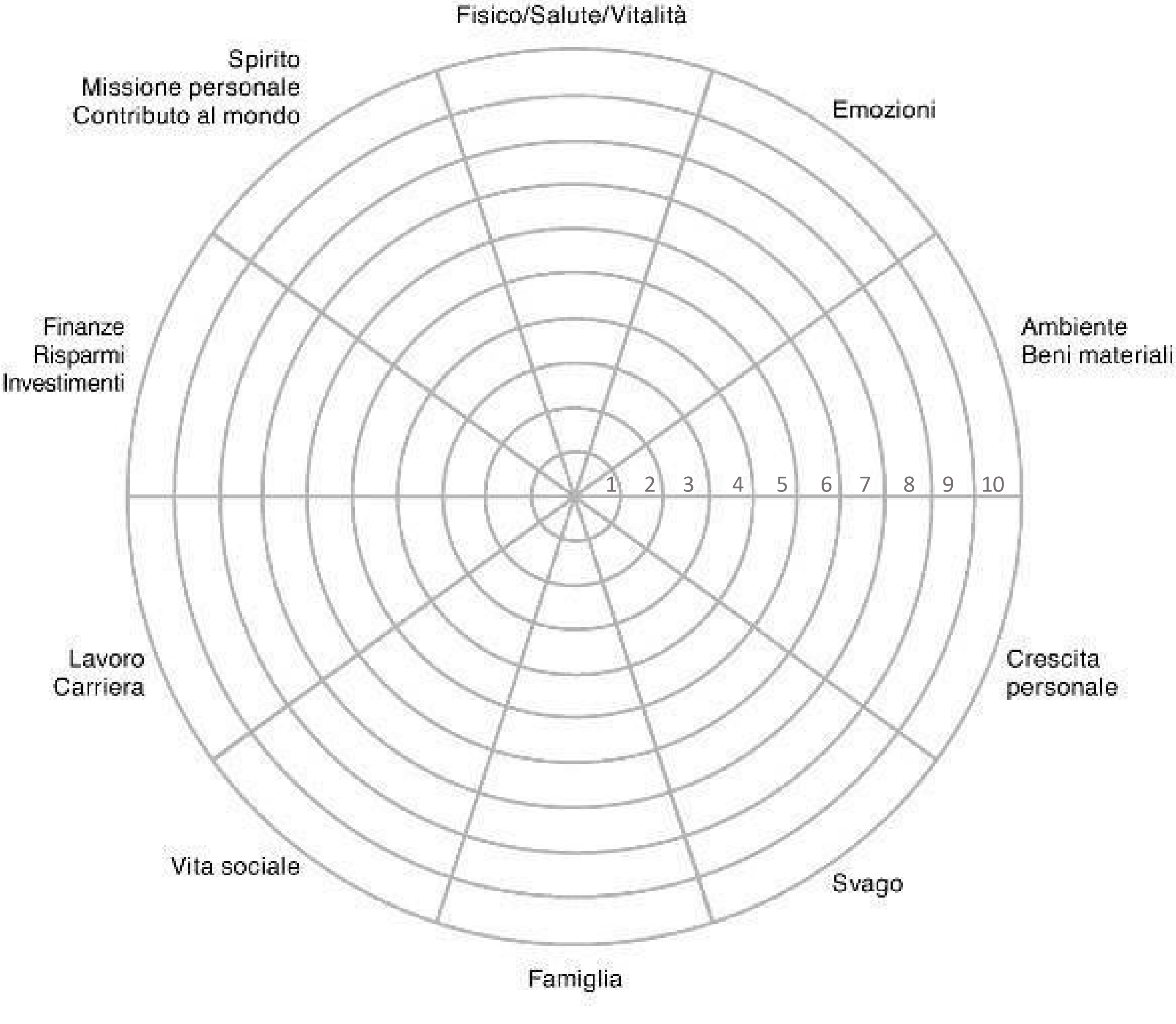
- Physical/Health/Vitality
- Emotions
- Environment/Material Assets
- Personal Growth
- Leisure
- Family
- Social Life
- Work/Career
- Finances/Savings/Investments
- Spirit/Personal Mission/Contribution to the World

The purpose of completing the *Wheel* is to activate a series of reflections on the aspects that constitute our existence and to evaluate the level of satisfaction for each area.

As can be seen on the following page, the *Wheel of Life* is a circle divided into segments, each representing an area of our life.

The level of satisfaction of each area will be assessed, where 1 represents the lowest level and 10 the highest degree of satisfaction. The segments from **1 to 10** will be coloured according to the personal satisfaction associated with each macro-area.

The Wheel of Life



The meaning of the macro-area and its related questions Physical/Health/Vitality The questions to ask oneself to evaluate this area are the following:

Are you satisfied with your body? Do you consider your weight appropriate? Do you like your image in the mirror? Are you in good health? What is your energy level? Do you practise any sport?

Emotions

This area refers to emotional awareness and the ability to manage emotions effectively, namely the capacity to control and express them in the way that best aligns with one's objectives.
What is your usual mood? With what spirit do you begin your day? Are you able to modify your emotional state according to the situation you are experiencing? Are you able to manage your emotions, or are you often overwhelmed by them? Do you find it difficult to communicate your emotional states to others?

Environment/Material Assets

"Environment" refers to the spaces in which we live: the home, the workplace, and all the other environments where we usually spend our time.
Are you satisfied with your home? Do you consider it welcoming and comfortable? Is it located in a place you like? What sensations arise from the images, sounds, and smells you perceive in the place where you carry out your activities? Are there other places where you spend a large part of your time? If so, what emotions do they convey?

Personal Growth

This includes the time dedicated exclusively to our improvement, to the activities we engage in to grow and regenerate ourselves, to everything we do to enrich our lives: from attending a course to reading a book. Personal and professional growth is the greatest tool we possess for achieving a better quality of life.
Do you devote enough time to your personal growth? What kinds of courses do you attend? Do you spend time reading? What types of books and magazines do you prefer? Which topics do you explore, for work or personal interest? Would you like to specialise in a specific field? Are you satisfied with the new things you learn? How do you experience learning?

Leisure

"Leisure" refers to pure enjoyment and rest. Leisure activities have no particular purpose other than the simple pleasure of doing them—of giving yourself moments of joy, cheerfulness, distraction, rest, and tranquillity.

Do you allow yourself enough time for rest and leisure, or do you feel you do not have enough? Do you ever take a vacation? Are you able to carve out some breaks during the year? Do you spend some evenings with friends? How often?

Family

To evaluate this aspect, we must consider our couple life and our relationships with children, parents, etc.
What is your relationship like with your relatives? Does being with them bring you joy and serenity? How do you assess your relationship with your children? Are you able to spend enough time with your family? Do you consider the time you spend with your children to be of quality? How do you manage priorities and time? Is there something you could do differently?

Social Life/Networking

This includes relationships with people we interact with most frequently outside the family, or with whom we engage in activities other than work (neighbours, members of associations, sports teams, clubs, circles, and so on).
How many and which people do you regularly meet outside the professional sphere? Do you keep in contact with the people you know, or do you always wait for them to contact you first? How do you assess the quality of these relationships? Are you satisfied with your social life?

Work/Career

This area concerns our professional position, our level of satisfaction with the activities and tasks we perform, and the degree of responsibility we hold.
What is your level of satisfaction regarding your work? Do you do something you enjoy? Do you think your position aligns with your abilities? Would you like more or fewer responsibilities? Do you find your job stimulating? Do you have a good relationship with your colleagues? Are professional relationships based on collaboration and mutual respect? Are you satisfied with what your colleagues think of you? Do you experience your work with apprehension, or does it stimulate you positively? In what areas would you like to improve?

Finances/Savings/Investments

In this case, self-evaluation concerns our relationship with money, the ability to manage it, save it, and possibly invest it. Naturally, these are entirely subjective considerations, depending on our lifestyle, work, and expectations. The questions to ask oneself to evaluate this area are as follows:
Are you satisfied with your savings? Do you have the habit of saving? Is your relationship with money calm, or does it cause you anxiety? Are your purchases proportionate to your finances?

Personal Mission/Contribution to the World

We must reflect on the coherence with which we live our principles, the things we believe in, and our deepest values. Moreover, we must consider the desire we feel to do something for others and for the world. For example, sponsoring a child at a distance, helping the elderly, or preserving nature are all activities that fully belong to this area—provided they represent important values for us.
Do you live in a way that is consistent with your values? Are you satisfied with your contribution to the lives of others?

Intervention 3: Advice I would give my best friend

Instructions: At this moment, you are going through a difficult time. Imagine that a friend of yours has to face the same difficulties: what advice would you give them? What would you tell them or suggest they do? Is the way you speak to your friend different from the way you speak to yourself? Why does this happen?

Problem I have to face	**Advice I would give a friend**
Why is the advice I would give a friend different from the one I reserve for myself?	

Assignment 1: Self-monitoring of fatigue

Please indicate, for each day, how fatigue has affected your daily life. You may describe physical, behavioral, emotional, cognitive, and social aspects. If you did not experience fatigue, you may write “no fatigue.”

Date	Morning	Afternoon	Evening	Night	Treatment or activity

Assignment 2: Why it is so difficult for me to accept good advice

Instructions: It is often easier to give advice than to accept it. By completing each column, try to examine the reason why it is so difficult for you to accept your own good advice.

Good advice that is difficult to accept	Why it is so difficult for me to accept good advice	Why I should accept good advice

Session 2: RECOGNIZING AND UNDERSTANDING FATIGUE FLUCTUATIONS

Session goal

To help manage fatigue by increasing understanding of its oscillating nature and strengthening the internal locus of control over patient's condition.

Pre-introduction

The therapist (T) begins the session with some classic questions such as: *"How are you?" and "How have the past two weeks been?"* This is done spontaneously, without mentioning each person individually. In this way, the therapist gently enters the second session.

T asks participants how they found the tasks assigned the previous week. The therapist waits for spontaneous comments and responds to them. If there are no comments, T asks typical questions such as: *"Were you able to write the fatigue diary every day? Did you reflect on the writing? What did you notice?"* Together with the group, T tries to summarize the responses, highlighting what is common to everyone and what is different. If the group does not respond much, T gently invites participants to present their diary (if someone brought it), in order to see some examples from at least one participant. In this way, the discussion can continue, with the aim of clarifying to participants that fatigue can vary and depends on the time of day, situations, and activities that provoke it.

Regarding the task related to the difficulty of accepting good advice, since it was optional, T does not focus too much on this aspect. However, the therapist may ask participants for an opinion on the task, while respecting those who chose to complete it. T may also make a general comment, stating that it is easy to give advice but difficult to accept it, and that we must also learn to give and accept good advice to ourselves.

Introduction

T begins with the introduction to today's topic: Today we will talk about how to recognize, understand, and manage fatigue to improve daily well-being. Fatigue can influence our mood, our energy, and the activities we are able to carry out. With a few simple strategies, you can learn to recognize the signs of fatigue and distribute your energy more effectively.

Part 1 - Energy fluctuations

1.Recognizing signs of fatigue

"The first step is learning to recognize the signs that indicate that you are tired. Everyone experiences fatigue differently, but some common signs are":

T asks participants to name the signs and then adds those on the list. If answers do not come immediately, the therapist may say that participants can take time to reflect on their fatigue monitoring task, thinking about their own fatigue signals and using the previously written examples.

- Frequent yawning
- A feeling of heaviness in the eyes or blurred vision
- Difficulty concentrating
- Headaches or muscle and stomach pain
- Irritability or agitation

T invites participants to reflect: *"What are your signs of tiredness? Do you notice changes in thinking, feelings, or behaviors when you are tired? It may also be useful to ask a trusted person if they have noticed anything different in your behavior when you are tired."*

If a brief discussion begins, excellent; otherwise, T does not insist and proceeds. *"Keep in mind that many people discover that they start the day with low energy because they have not fully recovered during the night. Remember that all activities (physical, mental, emotional) consume energy, as if we had a battery: it is important to know how to "recharge" it and not waste it unnecessarily."*

2. Understanding fatigue triggers

T asks: *"Which activities or situations tend to drain my energy the most? And what, on the contrary, helps me recharge? These are the so-called "triggers": factors that increase fatigue or, conversely, activities that promote recovery."*

After listening to participants' responses and having a short discussion, T summarizes everything by saying:
"Some possible triggers are:
- *Doing too much, overloading oneself with commitments*
- *Doing too little, underusing one's energy*
- *Being in crowded or noisy environments*
- *Having a disturbed night of sleep*
- *Experiencing emotionally intense events*

It can be very useful to create a list of your daily activities and, before and after performing them, assign a score from 1 to 10 to indicate how much they tired you. This will help you understand which tasks require more energy and plan accordingly."

3. Observing energy fluctuations

Now T presents one of the main points of the session - the "boom and bust" cycle. *"Many people with fatigue notice that their energy levels fluctuate over time.*

Sometimes they feel more energetic and may think they can do more, but this burst can lead to a subsequent collapse of energy, requiring a long recovery period."

There are two options at this point. First: T presents Images 1 and 2 (from Intervention 1A and B) to the participants. Second: T draws the images on the board while explaining; this option is likely more effective but takes more time and may interrupt the session's rhythm, especially if participants are waiting while T draws.

"This alternating pattern between "boom" (energy peak) and "bust" (drop) is normal, but can become a vicious cycle. The key is finding a sustainable activity rhythm that allows you to maintain a more stable energy level over time.
To do this, it is important to establish a "baseline activity level" that you can maintain without exhausting yourself. Exceeding this limit may lead to worsening symptoms and increased fatigue in the following 24–48 hours."

Intervention 1

T says: *"Now let's try to integrate this experience of fatigue related to arthritis. We have two options for this intervention, related to the two worksheets I just explained. Intervention 1A presents a "Boom and Bust cycle", where for each phase of the cycle you must write your examples of activities.*
Intervention 1B concerns energy fluctuations, with three types of activities that influence fatigue fluctuations in different ways. Try to write your examples. Choose one of the two interventions, whichever you prefer. If something is unclear, I am here to explain it.
The more detailed your observations are, the better: this way you can deepen your understanding of the activities that cause fatigue."

When T sees that participants have almost finished, the discussion begins. *"So, who would like to present their worksheet? What did you notice? Are there similarities among you: are there activities that influence energy in the same way? Or differences: activities that have different effects on fatigue fluctuations?"* T continues the discussion until reaching the conclusion that each participant has their own energy rhythm, but in some way the illness affects everyone in the same way.

4. Practical strategies for managing fatigue

T says: *"Now let us pause and discuss how we can influence the energy rhythm, the fluctuation of fatigue."*

A.Establishing a braking space

"Imagine driving a car: brakes are used to slow down and prevent accidents. In the same way, you must learn to "brake" before fatigue becomes too intense. Do you have any ideas, proposals, or examples to share?"

T waits for a moment: if there are responses, good, T discusses with the group and then proceeds with the text below.
If there are no responses, do not insist; T continues with the text.

"You can proceed as follows:
• Recognize early warning signs of tiredness (for example headache, irritability, difficulty speaking)
• Respond promptly, reducing activity or taking a break
• Set time limits: use alarms or reminders to stop activities before becoming too tired
• Break complex activities into small blocks: for example, reading one page at a time or cleaning one room at a time"

B. Adopting pacing: the right rhythm

T says: *"We are talking about a right and personalized rhythm, with optimal activities based on daily energy levels. Distribute activities throughout the day, alternating moments of work with regular breaks. It is important to take breaks before feeling too tired, so the body can recover and prevent the "boom and bust" cycle.*

Other practical advice:
• Schedule rest breaks during daily activities
• Use a timer to remind yourself to stop and recharge your energy
• Choose relaxing but not overly tiring activities, such as listening to music or practicing relaxation techniques"

Depending on the remaining time in the session (considering that there are other activities to complete), T decides on the spot whether to pause for a moment, saying: *"Now take your assignment from the first session, with the fatigue self-monitoring. Make changes, add any modifications to the dynamics of your daily routine that might help you better control your energy. For example, decide where to insert breaks or relaxing activities, of which type, and make any other necessary changes. In this way, you can better understand how your fatigue fluctuates."*

After a few minutes, T asks participants to share what they have modified, and the entire group discusses how they experienced this activity, whether they found it easy or difficult, and why.

C. Prioritizing and planning

T says: *"Now let us return to the intervention you carried out earlier, related to the Boom and Bust cycle. Now pay attention to this worksheet with your answers: I will give you instructions on how to review them. The main goal is to introduce the necessary changes.*
Evaluate which activities are truly important and need to be done, and which can instead be delegated, modified, or eliminated. Ask yourselves:

- *Is this activity essential?*
- *Does it significantly affect my tiredness?*
- *Can I ask for help or modify it to make it less tiring?"*

Organize your day by planning the most demanding activities in the moments when you feel most energetic, leaving space for rest.

After a few minutes, T asks participants to share what they have modified, and the entire group discusses how they experienced this activity, whether they found it easy or difficult, and why.

5. Summary: Rhythm is the key

T says: *"Now I will summarize this part of the session. If you have doubts or concerns, we can discuss them now, or later, or in the next session, after you have reflected on the fluctuation of fatigue.*

Learning to respect your own energy rhythm is essential. Over time, you will find the level of activity that allows you to maintain a good balance between effort and recovery, thus improving your quality of life.

If it seems difficult to manage everything alone, do not hesitate to seek support from professionals or trusted individuals. Remember: taking care of yourself is the first step toward feeling better."

Part 2 - Degree of control

1. Psychoeducation

T says: *"Now we begin the second part of the session, connected to the first. We will talk about levels of control over daily experience, with a focus on aspects related to the illness. First of all, let us define the main term we will use in this part of the intervention.*

The ***locus of control*** *is the extent to which a person perceives that an outcome depends on their own actions or on external forces, existing along a continuum ranging from a more internalized to a more externalized orientation. Individuals who believe that outcomes depend on their behavior or personal characteristics have an internal locus of control. Conversely, those with an external locus of control believe that life outcomes are determined by forces outside their control (e.g., independent of their actions or due to fate, luck, or chance), depend on powerful others, or are unpredictable due to the complex nature of the social environment (Rotter, 1966; Tyler et al., 2020).*

The concept underlying locus of control *is fairly simple. Our lives are full of actions and outcomes. Each of us attributes a certain locus of control to these outcomes. The theory states that we will place the locus either internally or externally.*

If we place the locus of control externally, we are likely to blame the outcome on fate,

luck, or chance. If instead we place the locus of control internally, we tend to believe that our actions determine the outcome.
Where we place this locus will influence or reinforce or punish our actions. An internal locus of control will lead to reinforcement of that behavior, and the behavior will continue. An external locus of control will cause the behavior to extinguish. Why should we keep trying if the outcome is outside our control?
We should conceive of this as a continuum between external and internal, rather than a binary categorization. In general, healthy adults rarely believe that everything is completely outside our control or completely in our hands. In fact, people who use a combination of both loci, internal and external, in their reasoning report higher levels of happiness.

A person's ability to act intentionally to influence their life and the surrounding environment involves making choices, setting goals, planning, and undertaking actions to achieve them, with a sense of control over outcomes.
Let us ***examine four key aspects****: autonomy and self-determination, intentional action, self-efficacy, and perceived control. At this point, we define them.*
<u>Autonomy and self-determination</u>: you are able to decide what to do and pursue it.
<u>Intentional action</u>: your behavior is guided by goals and plans, not just by habit.
<u>Self-efficacy</u>: confidence in your ability to complete tasks. The belief that you can face and manage daily challenges. Distinction between locus of control and competence: locus of control concerns where we attribute the outcome, whereas self-efficacy is the confidence in our practical ability to act. They can coexist.
<u>Perceived control</u>: the feeling of being able to influence events and outcomes (often linked to whether the locus of control is internal rather than external)."

Now I will give **an example of locus of control** regarding health.
"Marco's doctor tells him that he has the potential to develop type II diabetes. Marco has heard that it is possible to control this outcome through diet, so he decides to eliminate all sugar and try to eat more vegetables.
Anna receives the same diagnosis, but she believes everything is genetic. She comes from a family with a history of diabetes and feels that the outcome is inevitable. She does not try to modify her diet because she thinks it will not make any difference. Different types of locus of control generate different behavioral responses."

T says: *"Think of a recent episode in which something went wrong, any example, as long as it is personal; it may be related to health, but also to work, family, or sports. State two possible attributions: one internal (what you could have done differently) and one external (external factors)."* Then ask: *"Which attribution could lead to concrete action to improve the situation?"*
T briefly discusses the examples with the group and then reflects on the fact that, in different areas of life, a person may also have different loci of control. Some areas may be more controllable than others. The goal is to understand possibilities for gradually increasing internal attributions in areas where one has room for action, without denying external reality.

2. Assessment

T says: *"Now let us assess your locus of control in relation to health. I ask you to complete the present questionnaire (Multidimensional Health Locus of Control Form C; Wallston et al., 1994). As you can see from the instructions, in this questionnaire each statement below expresses what each of you thinks about their medical condition, with which you may agree or disagree. Next to each statement there is a scale ranging from strongly disagree (1) to strongly agree (6). There are 18 statements, and I ask you to respond to each of them. There are no right or wrong answers in the test. If something is unclear, please ask me and I will explain it."*

T waits for them to finish completing the questionnaire and then says:
"Now let us evaluate your responses. The score is obtained by summing the scores of the items that compose the three subscales.
Subscales:
I subscale: Internal (myself, internal control): Reflects the belief that one's own actions influence one's health;
II subscale: Chance (luck/chance): Reflects the belief that chance or luck determine health outcomes;
IIIA subscale: Doctors (powerful people such as doctors): Reflects the belief that powerful figures such as doctors and other healthcare professionals influence health;
IIIB subscale: Other people (powerful people such as healthcare professionals): Reflects the belief that powerful figures such as other healthcare professionals influence health."

Now T asks participants to count the responses corresponding to the numbers indicated below to determine the score of the subscales, according to the table below.

Subscale	**Possible range**	**Items**
Internal	6-36	1, 6, 8, 12, 13, 17
Change	6-36	2, 4, 9, 11, 15, 16
Doctors	3-18	3, 5, 14
Other people	3-18	7, 10, 18

[To give an idea of the expected scores, below are the mean scores and standard deviations of patients with rheumatoid arthritis: Internal: 17.5 (5.9); Chance: 16.6 (6.1); Doctors: 13.4 (3.3); Other people: 7.5 (3.3).]

Now T asks patients to report their scores, and depending on the time left in the session, may choose between two modes:

1. One person read the results and then comment on them;

2. Record the scores of all participants and, together with the participants, observe whether a trend emerges (e.g., the majority attribute the locus of control to the doctor), and then discuss comments with the group. If time permits, the second option is preferable.

T says: *"After this questionnaire and our discussion, you should have a clear understanding of your locus of control related to health. Let us now see what we can do and how to intervene to improve it."*

3. Relationship between locus of control and fatigue

T says: *"When discussing locus of control, it is useful to adopt a broader perspective. People must make concrete choices and act in prosocial ways in order to promote an internal locus of control and take personal responsibility. The goal is to enable people to recognize that their concrete actions (choices, strategies, effort) can improve daily life. The aim is to shift attributions from external to internal explanations, while maintaining realism regarding difficulties and limits."*

Intervention 2

T says: *"To understand whether it is difficult to make changes in the internal/external attribution of events related to the illness, we will now carry out an intervention. Describe three events (if there is not enough time, even one event is sufficient) that are significant and related to the rheumatic illness, preferably also related to fatigue, and write down two attributions: one internal and one external. Indicate which attribution motivated you to act constructively and which was less useful. Finally, describe the limits to changing the attributions."*

After all participants have completed at least one example, T asks the participants to read their examples. Then, together with the group, T comments on whether the example is typical or rare among participants and whether the limits they mentioned are real or whether they can be addressed.

T concludes the intervention by saying: it is important to have a clear idea of how events are attributed and to think about how such attributions may change.

4. Summary

"The locus of control began as an explanation of why certain behaviors thrive and develop, while others never take root. It is now seen as an important element of self-evaluation, a multidimensional construct that also includes self-efficacy, self-esteem, and emotional stability.

When we attribute a life outcome to external forces beyond our control, we may feel powerless to change things. But the truth about our level of control often lies only in our perception of it. Between this real and perceived level of control lies a choice: to believe in ourselves and in our ability to change our destiny.

If we believe in our power to control our lives, we will be more likely to take risks and feel more confident in our autonomy. This belief can be taught from a young age, but it can also be shaped throughout life. Through subtle shifts in mindset, we can begin to feel more in control of our future.

Work on locus of control is context-sensitive: if a person experiences extreme situations beyond their control, it is useful to recognize the limits of immediate autonomy and focus on practical micro-actions and on managing available resources (support, social networks, coping). The goal is always to make the individual more effective in their context, not to blame them for not having control over everything."

Homework

Assignment 1

"For the homework assignment, you must use everything you have learned during these first two sessions. You must create a list of activities you will carry out over the next two weeks, specifying how they influence fatigue, whether you plan to perform relaxation after the activities and of what type, whether the activity is part of your routine, and finally indicate which constructive changes you are making to the activities to reduce the feeling of fatigue.

Since you have two weeks for this assignment, you may make corrections to your answers, provided that you carry out a final review of the activities before submitting it."

Assignment 2

"The second assignment is the "Attribution Diary." It is similar to the second intervention we conducted earlier; however, now you will need to record attributions to events over a period of two weeks. The goal is to slightly increase the proportion of internal attributions in the areas that are controllable.

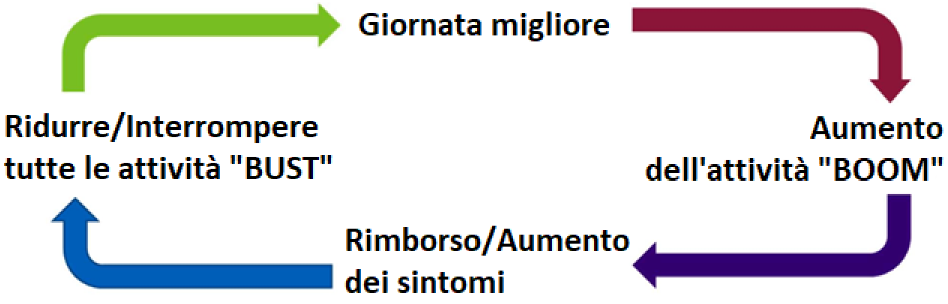
Evaluation of progress: at the end of the week, review what was helpful, which internal attributions guided action, and where the approach may need to be revised. The locus of control represents a potentially meaningful measure of treatment change."

Please bring the completed assignments to the next session, which we will use as material for the next insights on fatigue.

Intervention 1A: Boom and bust cycle

Basic-level activities

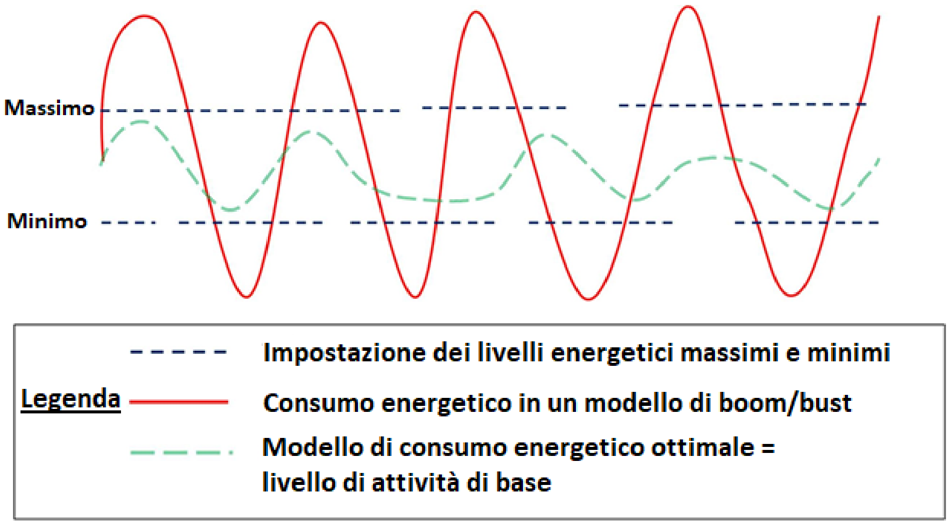
Activities to reduce fatigue



Activities that require an energy expenditure exceeding maximum levels

Symptoms associated with high fatigue

Intervention 1B: Energy fluctuatuions



Basic-level activities	Activities that reach maximum or minimum levels	Activities that require an energy expenditure exceeding maximum levels

Intervention 2: Events and attributions

Describe three significant events related to rheumatic disease, preferably also connected to fatigue, and note two attributions: one internal and one external. Indicate which attribution prompted you to act constructively and which was less useful. Finally, describe the limits to changing the attributions.

	Event description	**INTERNAL ATTRIBUTION**			**EXTERNAL ATTRIBUTION**		
		Attribution description	**Constructive or not**	**Limits to change**	**Attribution description**	**Constructive or not**	**Limits to change**
Event I							
Event II							
Event III							

Assignment 1: Activities and fatigue

List the activities you will carry out in the next two weeks and indicate whether you have started the new activities. For each activity, answer the columns specifying: how they influence fatigue, whether you plan to engage in moments of relaxation after the activity and of what type, whether the activity is part of your routine, and finally which constructive changes you have made to the activities to reduce the sensation of fatigue. Descriptive answers are preferred over brief (yes/no) answers.

CURRENT ACTIVITY	Does it consume or restore energy?	Relaxation afterward?	Part of routine?	Constructive changes?
NEW ACTIVITIES				

Assignment 2: Attribution diary

Describe the significant events related to the rheumatic disease, preferably also connected to fatigue, and note two attributions: one internal and one external. Indicate which attribution prompted you to act constructively and which was less useful. Finally, describe the limits to changing the attributions. Indicate the date of the event.

	Event description	**INTERNAL ATTRIBUTION**			**EXTERNAL ATTRIBUTION**		
		Attribution description	**Constructive or not**	**Limits to change**	**Attribution description**	**Constructive or not**	**Limits to change**
Event I Date:							
Event II Date:							
Event III Date:							

Describe the significant events related to the rheumatic disease, preferably also connected to fatigue, and note two attributions: one internal and one external. Indicate which attribution prompted you to act constructively and which was less useful. Finally, describe the limits to changing the attributions. Indicate the date of the event.

	Event description	**INTERNAL ATTRIBUTION**			**EXTERNAL ATTRIBUTION**		
		Attribution description	**Constructive or not**	**Limits to change**	**Attribution description**	**Constructive or not**	**Limits to change**
Event IV Date:							
Event V Date:							
Event VI Date:							

Session 3: BEHAVIORAL ACTIVATION

Session goal
Utilize behavioral activation principles to help patients reduce fatigue by developing personalized activity plans, setting realistic goals, and increasing engagement in enjoyable or meaningful activities.

Pre-introduction

The therapist (T) begins the session with some standard questions, such as: *"How are you?"* and *"How have the past two weeks been?"*. This is done spontaneously, without addressing each person individually. In this way, T gradually transitions into the third session.

T asks participants how they managed with the assignments given the previous week. T waits for spontaneous comments and responds to them. If no comments arise, T poses typical questions, for example: *"Were you able to write those two diaries on activity and attribution? Did you reflect on the writing? What did you notice?"*. Together with the group, T tries to summarize the answers, highlighting what is common to everyone and what is different. If the group does not respond much, T gently invites participants to present the diary (if someone has brought it), so that at least one example can be reviewed.

T begins with the diary on activities and fatigue and then moves on to the diary on attribution. If, however, participants start with the attribution diary, there is no problem: it is possible to proceed in this order. In any case, the goal of the activity diary is to summarize which constructive changes were observed: participants indicate some of their own changes and T attempts to synthesize and conclude how modifications can be made in order to improve fatigue.

With regard to the attribution diary, the objectives are: a) to summarize with participants whether, over the course of the days, they noticed a greater internal attribution, that is, whether the person assumed responsibility and control; b) to summarize the limits to change, that is, to understand which limits represent true obstacles and which can be modified.

At the end, T concludes this introduction by stating that it is useful to complete these assignments to reach a clear understanding of this intervention, as each day matters and helps to reach the goal of feeling better in various areas of life, despite the illness.

Introduction

T begins introducing today's topic: *"Now we will begin with today's theme. We learned in the previous session that it is not advisable to do too much activity because it can* *cause a drop in energy and considerable fatigue, hindering the return to optimal functioning. On the contrary, energy tends to decrease, and the person with rheumatic disease often experiences fatigue, with a reduction in interest in ordinary activities: activities are reduced, the person interrupts activities previously performed, including daily chores, hobbies, and other activities that provided pleasure. Eventually the person stays at home, away from activities and from people. This new routine leads nowhere: the person leaves behind much of their previous life, convinced they can no longer do anything because they feel ill. Several studies have shown that people with rheumatic diseases need to find an optimal level of activity that also helps the joints and supports functioning on a physiological level, not only a psychological one. Too much activity can lead to exhaustion, whereas a lack of activity compromises various aspects of life and also affects mood and fatigue. This becomes a vicious cycle. The aim of this session is to understand whether each of you, in some aspect of your life, is caught in this cycle and how to break it."*

Part 1 - Psychoeducation

T says: *"There are three behavioral aspects that impact fatigue in daily life:* ***a) Reduction of activities; b) Unhelpful behaviors; c) Avoidance****. Now I will explain each of these aspects."*

1A The vicious cycle of activity reduction

T presents illustration 1 or draws on the board while speaking.
"When we live with the symptoms of a chronic condition (for example, fatigue), these often prevent us from doing things in our daily lives that we enjoy.
Pleasurable activities tend to disappear, while we concentrate only on basic ones: trying to feel better, taking care of children, and doing household chores.
In this way, we risk giving up activities that previously gave us pleasure or a sense of accomplishment."

T asks participants to express their opinion: whether they have had this impression and to provide an example to share with the group. If possible, they are encouraged to focus on fatigue, but other symptoms of rheumatic diseases, such as pain, are also acceptable, provided they are linked to activity reduction.
An important point is that this illustration remains memorable for participants and that it is accepted as a reference during the session.

1B The vicious cycle of unhelpful behaviors

T presents illustration 2 or draws on the board while speaking.

The symptoms of chronic conditions can be a source of discomfort and difficulty.
The way we respond to these symptoms can be either helpful or unhelpful.

Helpful behaviors may include:
- *accepting support from friends and family,*
- *maintaining some activities that give us pleasure and a sense of accomplishment,*
- *learning to pace our energies.*

Sometimes we try to improve how we feel, but unfortunately we may act in ways that are not helpful in the long term.
Less helpful behaviors, which worsen the situation over time, may include:
- *continuously checking symptoms and focusing too much on them,*
- *"all-or-nothing" behaviors (periods of hyperactivity followed by crashes),*
- *taking on too many commitments,*
- *excessively resting.*

T asks participants what they think of this cycle, whether they have any observations to make, and to indicate which unhelpful behaviors they recognize in their daily lives and would like to change.

1C The vicious cycle of avoidance

T presents illustration 3 or draws on the board while speaking.

Sometimes we avoid certain situations because we fear that the symptoms may worsen. Or we stop doing certain things due to the symptoms themselves or the fear that they may appear.
Examples:
- *avoiding physical activities,*
- *not allowing others to help us.*

Avoidance may reduce anxiety or discomfort in the short term, but in the long term it tends to worsen the problem.
The risk is learning that the only way to deal with a difficult situation is to avoid it. In reality, our greatest fears often do not occur and, even when unpleasant things happen, we usually manage them better than we imagine.

T asks participants whether they have found themselves avoiding situations or activities that, as a result, limit their daily life. T also invites them to provide examples.

1D Activities

T says: "*Now let us talk about activities-what is an activity? Activities can be of three main types:* ***1. Cognitive; 2. Social; 3. Physical.***

An activity can be defined as ***anything that stimulates the brain and/or the body****. This includes both mental and more demanding physical activities. Therefore, walking, watching TV, reading, and even eating can be considered "activities.*

Recreational activities are what we might previously have called "moments of relaxation." They are our "stress reducers," such as exercising, watching TV, gardening. These are activities that we generally enjoy and that give us pleasure. Recreational activities are important in daily life and play a significant role in countering depressed mood.

Now let us give examples of activities. T first asks participants to provide examples for each of the three types of activities, and if something is not mentioned, T adds the listed items. *Cognitive: thinking, reading, reflecting, writing emails, watching TV, making decisions. Social: interacting with others in person, communicating online or via messages. Physical: daily activities such as washing and dressing, household chores such as shopping and cooking, physical or sports activities.*

Activities can be classified as high energy and low energy.
Which are high-energy activities?
After participants respond, T adds:
Physical: walking, running, playing sports, showering, combing hair, traveling by car;
Cognitive: watching an interesting TV program, studying, working on the computer, worrying intensely;
Social: chatting with friends, participating in online meetings, playing together.

Which are low-energy activities?
After participants respond, T adds: *watching TV without particular interest; rewatching a film or program seen many times; reading magazines; preparing for creative activities, painting."*

Part 2 - Good Life Model

T says: *"Now let us talk about how to work on activities to improve one's life. Last time we talked about planning and how to prioritize activities. Today, however, we discuss which activities you prefer and which areas of life you consider priorities.*

Today we will work together to reflect on what makes life meaningful and fulfilling, even when there are difficulties related to the illness. The model we will use is called the Good Life Model, and it helps us identify our values and the important activities to maintain them.

The Good Life Model is based on the idea that a good life does not depend solely on the absence of problems, but on cultivating the values that matter to us. Each of us has life areas considered fundamental, such as relationships, sense of competence, creativity, spirituality, health, or contributing to others."

Then T connects this discussion with rheumatic disease by saying: *"The illness may influence some activities, but it does not need to prevent us from living in accordance with our values. We can look for new ways to keep alive what is important to us."*

T begins administering the questionnaire with the following words: *"I invite you to think about the areas of life that are important to you and to ask questions such as: "Why are these areas significant to me?"."*

Intervention 1

T gives participants the sheets with Intervention 1 and reads the instructions: *"Think about the things that give meaning and purpose to your life. The goal is to clarify what matters and to orient yourself toward the goals that are closest to your heart. In the left column we have listed some suggestions, but you may add as many categories or experiences as you wish. In the central column, evaluate how important each item is to you, assigning a score from 0 ("I do not care at all") to 5 ("It is essential"). In the right column, list some things you could do - actions, thoughts, meditation, or anything else - to pursue what is important to you."*

T poses these questions and discusses the answers with the group: *"How many of these aspects do you consider important for your life? How do you manage to keep them active? Does the illness affect them? Are there activities that you no longer carry out that make you sad because you can no longer engage in them? Can you explain this using the circles illustrated earlier? Who would like to describe one of the areas chosen and a small example of an activity that keeps it alive, even if adapted?"*

While participants speak, T identifies common themes and normalizes the difficulty by saying, for example: *"Many of you have chosen relationships as a central value. Even if the illness limits certain things, finding new ways to maintain contact is fundamental for well-being.*
Now think of a small step you can take in the coming days to cultivate one of the values you wrote down. It must be realistic, feasible, and pleasant." T gives examples: *calling a friend, devoting 10 minutes to a hobby, writing a gratitude thought, taking a short walk, listening to favorite music.* T asks participants to share the solution they are thinking and what they intend to do in the coming days. The whole group may then comment.

T concludes this part by saying: *"The Good Life Model reminds us that even with a chronic illness we can live a full and meaningful life if we remain close to our values. The challenge is not to eliminate difficulties, but to find new ways to nurture what truly matters to us."*

Conclusion

T says: *"In the last two sessions we talked about fatigue and activities, with the aim of finding strategies to improve the situation. The idea was to understand which dynamics maintain high fatigue and reduce quality of life, and how it is possible to intervene to improve it.*
From the next session we will move on to the topic of emotions and cognition, because only by integrating these two aspects can we better understand behavior and its connection to fatigue."

Homework

Assignment 1

T says: *"For the assignment I ask you to plan your activities for one week and then check to what extent you manage to follow the program. It is important that the activities reflect the life domains and values that you identified today as significant for you.*
If these aspects do not appear in your weekly schedule, perhaps they are not truly that important: try to reflect on this."

Assignment 2

T says: "*As a second assignment, I propose a long list of pleasant activities. Try to look through it while thinking about what we discussed today: which activities you can still perform despite the illness, and which you had to stop because they were no longer possible. Reflect on what values lie behind the activities you choose. Select all the activities you consider pleasant for you, even if you are not currently practicing them. The main goal is to reflect on these activities and evaluate whether and how you may resume them in the future.*
The following list includes a wide range of activities to choose from. You may freely select those you enjoy or add new ones."

"Please bring the completed assignments to the next session, as we will use them as material for further exploration of fatigue."

Intervention 1: Relevant aspects of my life

Instructions: Think about the things that give meaning and purpose to your life. In the left column, we have listed some suggestions, but you may add as many categories or experiences as you wish. In the central column, evaluate how important each listed element is to you, assigning a score from 0 (“I do not care at all”) to 5 (“It is essential”). In the right column, list some things you could do-actions, thoughts, meditation, or anything else—to pursue what is important to you. The goal is to clarify what matters and to direct yourself toward the aims that are most meaningful to you.

What gives meaning and purpose to my life?	**How important is it to me?**	**Examples of things I can do to achieve it.**
Friendship.		
Love for others.		
Being a good parent, son/daughter, partner.		
Belonging to a community.		
Helping others.		
Being competent in my work.		
Building a career.		
Teamwork.		
Following a healthy lifestyle.		
Engaging in physical exercise and staying active.		
Appreciating what surrounds us and our own life.		
Being grateful.		
Enjoying the beauty of things.		
Feeling connected to something bigger than oneself.		
Justice.		

What gives meaning and purpose to my life?	**How important is it to me?**	**Examples of things I can do to achieve it.**
Making good decisions.		
Working hard and doing things well.		
Being curious and open.		
Having a sense of humor and having fun.		
Increasing one's finances.		
Respecting traditions.		
Engaging in spirituality.		
Learning new things and new skills.		
Being in contact with nature.		
Meditating and praying.		
Learning and growing.		
Venturing and trying new things.		
Expressing oneself.		

Illustration 1

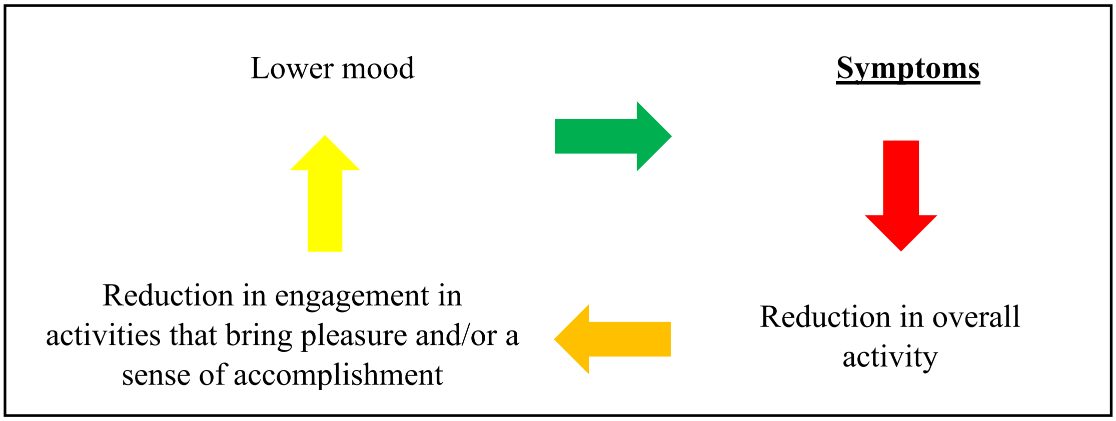


Illustration 2

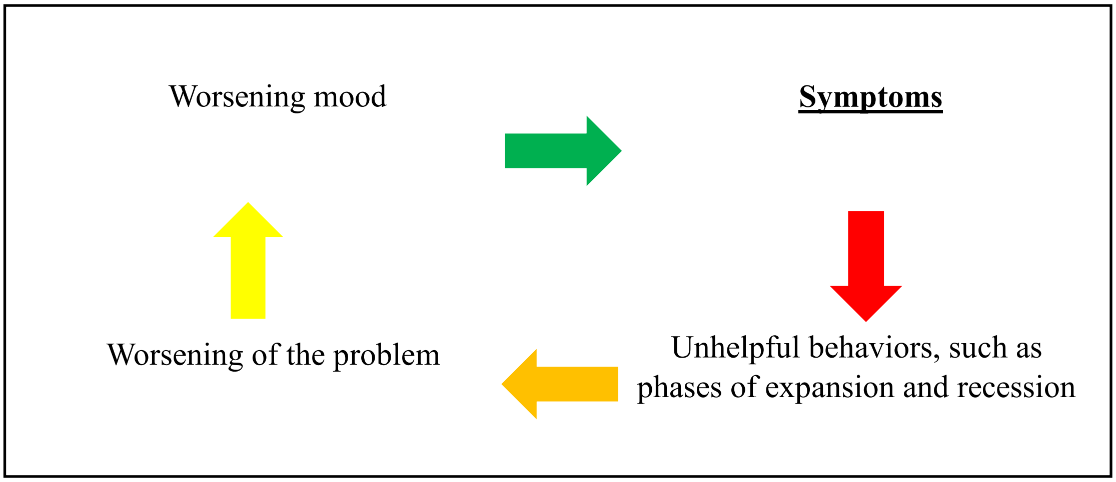
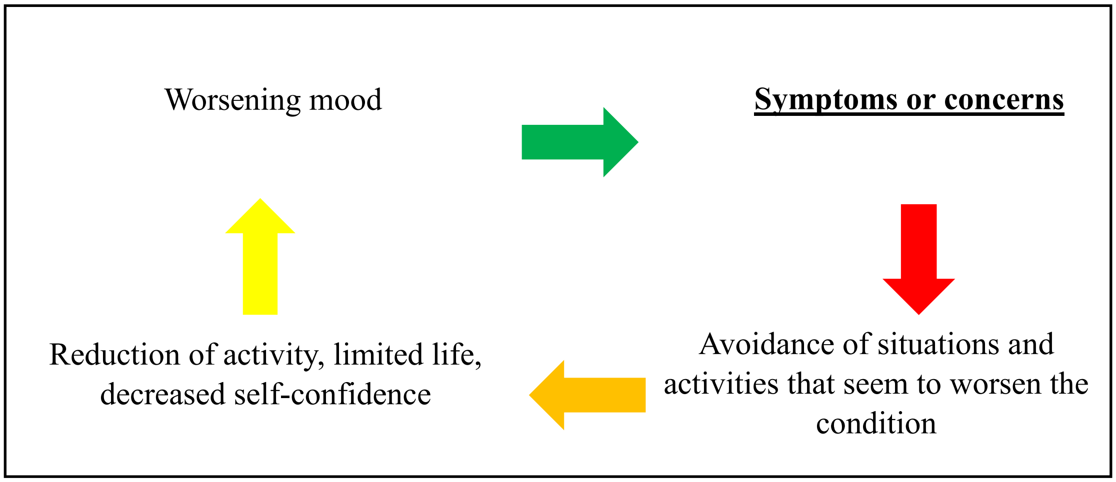


Illustration 3



Assignment 1: Planning ahead

Instructions: You will not be able to do everything you need to do unless you plan it. You can use this activity planning form to identify the most important tasks that you must complete and to decide when to carry them out and how long they will take. Set aside some time for a rewarding activity to be done after completing the others, so that you have a reward waiting for you that motivates you.

Next week, mark which of the scheduled activities you completed.

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday

Assignment 2: List of pleasant activities

The following list includes many activities to choose from. Freely select activities that are pleasant for you or add others.

1. Practicing yoga
2. Attending a parish group
3. Attending recreational clubs
4. Taking a trip to the countryside
5. Talking about sports
6. Meeting new people
7. Playing tennis
8. Going to a rock concert
9. Playing soccer
10. Planning trips or vacations
11. Shopping for myself
12. Going to the seaside
13. Painting
14. Mountaineering
15. Reading sacred scriptures or other religious works
16. Playing golf
17. Participating in military activities
18. Reorganizing and decorating one's room
19. Making a sculpture
20. Going to a sporting event
21. Reading a book or an article on DIY
22. Doing decoupage
23. Going to the races (horses, cars, etc.)
24. Reading novels
25. Going to a bar
26. Attending a club
27. Attending conferences
28. Taking a sports driving course
29. Drawing
30. Listening to a piece of music
31. Meditating
32. Reading short stories
33. Reading poetry
34. Rowing
35. Doing a favor for a friend or family member
36. Restoring antiques, furniture finishes, etc.
37. Watching TV
38. Watching videos
39. Camping
40. Engaging in politics

41. Working on machines (cars, motorcycles, motorbikes, etc.)
42. Playing briscola
43. Playing burraco
44. Playing video games
45. Doing crosswords
46. Attending weddings, baptisms, confirmations, etc.
47. Doing puzzles
48. Lunching with colleagues
49. Lunching with friends
50. Cycling
51. Taking a shower
52. Driving long distances
53. Doing small carpentry jobs
54. Writing stories
55. Being with animals
56. Taking a plane trip
57. Exploring (excursions far from known places, caving, etc.)
58. Writing poems
59. Singing in a choir
60. Doing one's work
61. Going to a party
62. Attending church services
63. Going to social events
64. Learning a foreign language
65. Attending meetings at clubs or associations
66. Attending congresses
67. Traveling in sports cars
68. Playing a musical instrument
69. Preparing snacks
70. Attending an aperitif-dinner
71. Skiing
72. Going to the hairdresser
73. Being with friends
74. Being with relatives
75. Making preserves
76. Producing artistic works
77. Taking a walk downtown
78. Taking a bath
79. Humming to myself
80. Cooking food to sell or give away
81. Playing billiards
82. Being with my grandchildren
83. Playing chess
84. Playing checkers
85. Stringing beads to make necklaces and craft jewelry

86. Doing ceramic work
87. Working leather
88. Sewing clothes
89. Putting on makeup
90. Caring for hair
91. Visiting the sick, hospitalized, or people in difficulty
92. Cheering for my team
93. Bowling
94. Observing wildlife
95. Gardening
96. Reading technical, academic, or specialized publications
97. Going to discos
98. Sitting in the sun
99. Riding a motorcycle
100. Going to a fair
101. Going to the circus
102. Going to the zoo
103. Going to the amusement park
104. Talking about philosophy or religion
105. Planning to organize something
106. Preparing an aperitif at home
107. Riding a motorcycle at high speed
108. Going boating
109. Car racing
110. Listening to the radio
111. Hosting friends at home
112. Participating in a sports competition
113. Giving gifts
114. Attending academic lectures
115. Attending political debates
116. Getting a series of massages
117. Getting a pedicure
118. Getting a manicure
119. Writing letters
120. Writing emails
121. Messaging with friends
122. Talking with friends via Skype
123. Using Facebook
124. Using Twitter
125. Taking a trip to a park
126. Having a barbecue
127. Playing basketball
128. Buying something for one’s family
129. Doing photography
130. Tutoring

131. Reading maps
132. Collecting natural items (leaves, fruit, stones, wood, etc.)
133. Joining a volunteer association
134. Going to the mountains
135. Talking to one’s grandchildren
136. Eating good food
137. Cooking good dishes
138. Starting an exercise program to improve my health
139. Visiting a shopping mall
140. Practicing boxing
141. Playing in a band
142. Hiking in the mountains
143. Going to a museum or exhibition
144. Writing articles, essays, reports
145. Doing well-organized work
146. Fishing
147. Going to the beautician
148. Going to a wellness center
149. Going to a drive-in, to a fast food restaurant
150. Being part of a fraternity
151. Being with my parents
152. Horseback riding
153. Being a political or environmental activist
154. Talking on the phone
155. Collecting leaves, sand, pebbles
156. Walking on meadows
157. Attending school meetings, student assemblies, etc.
158. Going to the cinema
159. Cooking
160. Doing “handyman” tasks at home
161. Attending a family reunion
162. Hosting a party
163. Coaching someone
164. Going out to dinner at a restaurant
165. Admiring flowers and plants
166. Accepting dinner invitations
167. Getting up early in the morning
168. Doing scientific experiments
169. Visiting friends
170. Writing a diary
171. Playing volleyball
172. Praying
173. Practicing massages
174. Doing favors for others
175. Chatting with work colleagues

176. Drinking relaxing herbal teas
177. Playing board games
178. Doing strenuous outdoor work (cutting wood, farming)
179. Reading the newspaper
180. Riding a snowmobile
181. Being part of consciousness-raising groups or groups practicing philosophical reflection
182. Playing table tennis
183. Swimming
184. Walking, fitness, etc.
185. Walking barefoot
186. Playing frisbee
187. Cleaning the house
188. Listening to music
189. Knitting
190. Embroidering
191. Crocheting
192. Downloading a movie
193. Downloading music
194. Hosting guests
195. Reading magazines
196. Sleeping late
197. Having sexual relations
198. Having other sexual satisfactions
199. Going to the library
200. Playing rugby
201. Preparing a new or special food
202. Bird-watching
203. Shopping
204. Selling or bartering
205. Repairing objects
206. Working with others in a team
207. Cycling
208. Giving advice to others
209. Playing board games
210. Talking about one's hobby or interest
211. Playing with sand, grass, etc.
212. Talking to other people
213. Being with one's partner
214. Taking care of houseplants
215. Tending the vegetable garden
216. Having coffee, tea, etc., with friends
217. Sewing
218. Remembering a deceased or loved friend by visiting the cemetery
219. Engaging in activities with children

220. Going to the cinema
221. Eating snacks
222. Staying up late
223. Being with one's children
224. Going to auctions
225. Practicing water-skiing, surfing, scuba diving
226. Fighting for the defense or protection of someone; stopping fraud and abuse
227. Meeting a new friend
228. Talking about one's work or studies
229. Reading comics
230. Taking a group trip
231. Seeing old friends
232. Teaching something to someone
233. Using one's strength
234. Traveling
235. Attending parties organized with colleagues
236. Attending a concert or ballet
237. Playing with pets
238. Participating in a game
239. Training
240. Organizing a vacation
241. Eating out
242. Eating one's favorite food
243. Cooking a healthy meal
244. Having a picnic
245. Sitting in a quiet place
246. Listening to audiobooks
247. Taking a long weekend vacation
248. Playing with video games, computer
249. Surfing the internet
250. Gardening

Other ideas…

Session 4: EXPLORING EMOTIONS

Session goal
Educate patients on the concept and scheme of emotions and their impact on fatigue, while also developing their skills in identifying and regulating various emotions, particularly difficult ones.

Pre-introduction

The therapist (T) opens the session with general questions aimed at re-establishing contact with the group and creating an atmosphere of listening and acceptance: *"How are you? How have the past weeks been?"*

This initial moment serves to reactivate the therapeutic relationship, give space to participants' experiences, and attune to the general emotional state of the group. T then follows with a review of the homework, which represents continuity with the previous session and allows monitoring of the application of the strategies learned. T asks participants to share how they managed the homework, whether they encountered difficulties or gained new insights.

Guiding questions may be: *"Have you noticed changes in your mood or thoughts when you were more or less tired? Were there situations that surprised you or made you reflect?"*

T summarizes the experiences that emerged, offering an empathic and normalizing synthesis: highlighting how physical fatigue and emotions are often closely connected, in a reciprocal cycle in which one fuels the other. From this reflection arises a natural introduction to the day's theme: emotions and their relationship with fatigue.

Introduction

T introduces the session by saying: *"Today we will talk about emotions, how they influence fatigue and how fatigue, in turn, influences emotions. We will learn to recognize them, understand them, and regulate them more effectively."*

T explains that emotions are <u>not positive or negative in an absolute sense</u>: each represents valuable information about our inner state and the way we relate to the world and to others.

<u>Understanding and accepting emotions is an essential step</u> in psychological care, because it allows reducing secondary suffering (that due to judgment or resistance toward one's emotions) and improving quality of life, especially for those living with a chronic illness such as rheumatic diseases.

T asks participants what they think about emotions and how they express them. T also asks for examples. Then T explains that emotions are signals that help us understand what we are experiencing, what we desire, and what we need. Denying or suppressing them can lead to increased internal tension and to a greater perception of fatigue.

Part 1 - Psychoeducation: understanding emotions

T introduces the theoretical part by saying: *"Emotions are complex responses that involve the body, thoughts, and behaviors. Each emotion prepares us to act: for example, anger pushes us to defend ourselves, fear to protect ourselves, joy to seek contact."*

T explains that each emotion has an adaptive function, meaning it serves to maintain balance between oneself and the environment. Through emotions, the body and mind communicate fundamental needs: safety, belonging, autonomy, recognition, protection.

T illustrates the general schema of emotions (presented in an interactive way, pausing on each of the four points, where participants also provide a general or illness-related example):

1. **Activating event**: something happens internally (thought, memory) or externally (situation, interaction).
2. **Cognitive appraisal**: we interpret the event (for example: "it is dangerous", "it is unfair", "it is pleasant").
3. **Physiological response**: the body reacts with changes in heart rate, breathing, muscle tension, or temperature.
4. **Behavior/action**: we act accordingly, for example with attack, avoidance, or seeking support.

T may illustrate this on the board (as a vicious cycle; Illustration 1A).

T highlights the circular and dynamic link between emotions, thoughts, and behaviors: each element influences and is influenced by the others. To make the concept more concrete, T may draw three interconnected circles on the board (thoughts - emotions – behaviors; Illustration 1B).

T asks participants for real examples (related to their illness). T may provide an example to begin: *"When I feel frustrated about my fatigue, I think that I will never improve, and so I give up going out."*

T examines how emotions can modify the perception of pain and fatigue. T explains that in rheumatic diseases, it is common to experience emotions such as anger, sadness, and fear, often accompanied by a sense of loss, helplessness, or injustice. Recognizing and accepting them as natural and legitimate responses to the limits imposed by the illness helps reduce self-criticism and mental rumination.

T invites participants to reflect: *"How do you react to your emotions? Do you find yourselves judging yourselves for how you feel? How does all of this affect your daily energy?"*

Part 2 - Recognizing and regulating emotions

T introduces the activity with the questionnaire "Leahy Emotional Schemas Scale" (Leahy, 2002), explaining that the goal is to explore the personal way in which each person understands, interprets, and manages their emotions. T emphasizes that there are no right or wrong answers, only different ways of experiencing one's inner states. After completing the questionnaire, T guides a discussion through several of its questions (Leahy, 2002, pp. 6–7). If time allows, T may explore several dimensions, helping participants recognize areas of greater difficulty in emotional management (for example, tendency toward avoidance, cognitive rigidity, fear of being overwhelmed by emotions).

Using the article (Leahy, 2002), T selectively explains the different emotional dimensions proposed in the model (Comprehensibility, Guilt, Simple view of emotion, Higher values, Control, Numbness, Rational, Duration, Consensus, Acceptance of feelings, Rumination, Expression, Blame), stimulating group reflection and discussion. T's questions promote introspection: *"What have you discovered about how you experience your emotions? Are there emotions that you tend to avoid or that you find more difficult to manage?"*

T normalizes the difficulty of talking about emotions, reminding the group that creating a space of awareness is already an act of care.
This is followed by an exploration of emotional regulation strategies drawn from the cognitive-behavioral model:

- **Recognition**: naming the emotion ("I feel anxious", "I feel frustrated").
- **Validation**: recognizing that the emotion makes sense and has a function.
- **Self-compassion**: treating oneself kindly and respectfully, without judgment.
- **Cognitive restructuring**: examining the validity of the thoughts associated with the emotion.
- **Behavioral regulation**: acting in a constructive way even in the presence of unpleasant emotions.

T provides concrete examples: *"When we feel angry because fatigue limits our activities, we might think: 'It's not worth trying.' But we can tell ourselves: 'I am frustrated because this illness limits me, but I can still choose to do one small thing today to feel better.'"*
This cognitive shift reduces emotional intensity and fosters a sense of self-efficacy. T asks participants to provide personal examples.

Part 3 – Relationship between thoughts and emotions

T introduces the theme by saying: *"Thoughts and emotions are closely linked. Every emotion is preceded or accompanied by a thought."*

T invites participants to share a recent episode in which they experienced a strong emotion, describing the associated thoughts.
On the board, T draws two columns: "Emotions" and "Thoughts."
Possible examples from the group:

- Sadness → "I can't do what I used to do."
- Anger → "It's not fair that this happened to me."
- Fear → "If I push myself, I will get worse."

T highlights how thoughts can intensify or lessen the emotional response and how greater cognitive awareness allows interruption of vicious cycles of suffering. A brief exercise follows in which participants try to reframe the thoughts in a more realistic or functional way, with T's help.

For example: "I can't do everything like before" → "I can do things differently, adapting to my current limitations."

T emphasizes that this reframing does not deny the reality of the illness, but helps reduce emotional suffering and promote psychological resilience.

Part 4 - Difficult emotions and coping strategies

T introduces the topic with sensitivity: *"Some emotions are more difficult to accept, but all have a function. Anger, fear, and sadness are normal responses to the loss of health or ability. Today we will try to recognize how we can face them."*

The group discusses their personal coping strategies used in difficult moments: some isolate themselves, others seek comfort from others, others distract themselves with daily activities.
T values each response, highlighting that there are no absolutely good or bad strategies, but rather that some are more adaptive because they allow recognizing the emotion, accepting it, and acting in a way consistent with one's values.
T proposes a technique of experiential regulation: breathing deeply, naming the emotion, and describing the bodily sensations that accompany it. This simple exercise promotes interoceptive awareness and helps "deactivate" the body's automatic response, creating a space of choice between emotion and action.

Conclusion and summary

T and the participants summarize together the main points that emerged:

1. Emotions influence fatigue and the perception of pain.
2. Recognizing and accepting emotions helps reduce stress and improve quality of life.
3. Thoughts, emotions, and behaviors are interconnected and modifiable through awareness.

T thanks the group for their participation, emphasizing that learning to understand one's emotions does not mean eliminating them, but living them more authentically and with less suffering.
It is a fundamental step in the path toward more balanced management of fatigue, pain, and relationships with oneself and others.

Homework

Assignment 1 - Emotion log

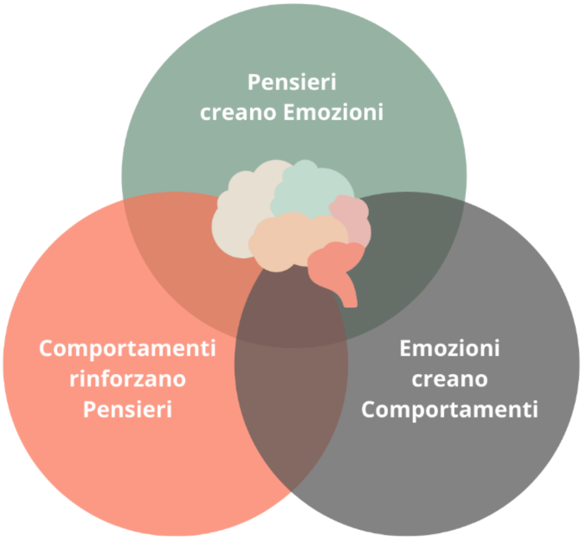
Place an X on the day(s) of the week on which you experienced one or more of the listed emotions. Additional emotions not mentioned may be added. The objective is to increase emotional awareness and recognize recurring patterns related to fatigue or other daily experiences.

Assignment 2 - Differentiating thoughts and emotions

When one feels "upset," thoughts tend to be "upsetting." For example:
• If one feels sad, one may think: "Things will never go right."
• If one feels angry, one may think: "That person is not treating me with respect."
In the left column, describe the situation experienced; in the middle column, the emotions (sadness, anger, anxiety); and in the right column, the corresponding thoughts.
This exercise helps to learn to distinguish what one thinks from what one feels, in order to react in a more balanced and aware way.

Illustration 1A: Vicious cycle

Illustration 1B: Thoughts - emotions - behaviors



Intervention 1: Emotion Log

Instructions: Place an X on the day of the week in which you experienced one or more of the emotions listed in the left column. You may also add others not explicitly mentioned.

Emotions	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**	**Sunday**
Happiness							
Interest							
Excitement							
Care							
Affection							
Love							
Feeling loved							
Compassion							
Gratitude							
Proud							
Trust							
Pain							
Sadness							
Regret							
Irritation							
Anger							
Resentment							
Disgust							
Contempt							
Shame							
Guilt							
Envy							
Jealousy							
Anxiety							
Fear							

Intervention 2: Distinguishing thoughts from emotions

Instructions: when you feel "upset," your thoughts are likely "upsetting." If you feel sad, for example, you might think: "Things will never go right"; when you are angry, you might instead think: "That person is not treating me with the respect I deserve." In the left column describe the situation you are experiencing (what is happening), in the middle column your emotions (for example, sadness, anger, anxiety), and in the right column your thoughts.

Situation Describe what happened, the context in which it occurred, and what triggered it.	**Emotions** Identify your emotions (example: sadness, helplessness, anxiety, displeasure, numbness, despair, anger, jealousy, sense of emptiness, happiness, relief, curiosity).	**Thoughts** What were you thinking?

Session 5: COGNITIVE RESTRUCTURING: RECOGNIZING AND MODIFYING THOUGHTS THAT INFLUENCE FATIGUE

Session goal

Learn concrete techniques to identify, challenge, and restructure negative thoughts (automatic thoughts, self-talk, rumination) that fuel fatigue and limit functioning in individuals with rheumatic diseases. Provide practical tools (acceptance and cognitive restructuring) and connect cognitive work to emotions and behaviors already addressed in previous sessions.

Pre-introduction

The therapist (T) welcomes the participants and opens the session with a few questions: *“How are you today? How have the last two weeks been?”* T does so spontaneously, without calling each participant by name, to create an atmosphere of openness and continuity with the group.

T asks how the homework assigned the previous week went. T waits for spontaneous answers and, if the group is silent, encourages sharing with guiding questions: *“Have you noticed any changes in your emotions?”* or *“Were you able to distinguish thoughts from emotions?”*

After a brief summary of the shared experiences, T introduces the new topic of the session, linking it to previous ones: after learning to observe emotions, today the focus will be on how thoughts can influence them and how to modify them to reduce the impact of fatigue.

Introduction

T introduces the topic of the session by saying:

“Today we will discuss more deeply how our thoughts influence emotions, physical reactions, and the perception of fatigue. We will learn how to recognize thoughts that weaken us and replace them with more realistic and helpful thoughts. This process is called cognitive restructuring, and it serves to modify inaccurate interpretations that maintain fatigue and stress.”

Brief review of definitions:

- ***Automatic thoughts** = short, immediate, often negative phrases (“I won’t make it,” “I have become a burden”), activated automatically and without awareness.*
- ***Self-talk** = the internal dialogue that guides emotions and behaviors.*
- ***Rumination** = mentally repeating the same thoughts, which maintains anxiety and fatigue.*
- ***Dysfunctional cognitive schemas** = deeper, often unconscious beliefs from which inaccurate interpretations of reality arise; they act as “filters” through which the person tends to evaluate themselves, their life, and interpersonal relationships.*

T presents the thought → emotion → behavior diagram (as in previous sessions) to illustrate where cognitive restructuring intervenes.

Part 1 - Identifying thoughts and emotions

In this part, the objective is to help participants understand how thoughts directly influence emotions and, consequently, fatigue, and learn to recognize automatic thoughts that accompany emotions and fatigue.

T says:
"We discussed how many unpleasant emotions, such as anxiety, sadness, guilt, or anger, are often connected to our thoughts. It is not so much what happens that determines how we feel, but the meaning we attribute to what happens."
"Now we will deepen what we discussed in the previous session, with a summary of emotions and the associated thoughts. We will also analyze this today so that you develop stable understanding of this aspect, because it is the basis of our work in the upcoming sessions."

"Many thoughts arise automatically, without our noticing. They are short, immediate phrases activated in difficult situations. They may be thoughts such as 'I won't make it,' 'I am a burden to others,' or 'I will never get better.' These thoughts directly influence emotions and the perception of fatigue. To learn to recognize them well, we will use a guide (T gives participants Intervention 1) that connects emotions and types of thoughts. For example, when we experience fear, we usually think we are in danger; when we experience sadness, we think we have lost something; when we experience anger, we think something is unfair. It is very important to find a way to connect the emotion to the automatic thought, but this is done through questions. You see that there are questions in the middle that help identify the automatic thought underlying each emotion. Do you recognize yourselves in any of the examples? Do you have examples for the other emotions and the related thoughts? I can write your examples on the board, or you can first write them on your sheet, under the examples provided."

T invites the participants to recall a recent episode in which they experienced one of these emotions and describe the thought that accompanied it. Examples connected to illness and fatigue are important.

"Now let us think of alternatives—solutions for automatic thoughts. I will give an example.
Situation: 'I spoke at work and froze' → Automatic thought: 'I will never be good enough' → Question: 'Is this always true? What evidence do I have?' → Alternative thought: 'I froze in one situation, but I performed well in other tasks; I can prepare better next time.'
Our automatic thoughts triggered by a situation lead us into rumination. Instead, we must evaluate the thoughts. This is done with Socratic questions to apply to automatic

thoughts: 'What is the evidence?', 'Am I generalizing?', 'Has something similar already happened? How did it turn out?'"

T invites the group to provide brief personal examples and to proceed together through the process of evaluating automatic thoughts.

Part 2 - Recognizing problematic thinking styles

In this part, the objective is to teach participants to recognize distorted ways of thinking that increase fatigue and suffering.

T says:
"Some recurring thinking patterns can increase stress and fatigue. We call them problematic thinking styles. Let us look at them together."

Main examples:
- ***All-or-nothing** - seeing things in absolute terms ("Either I succeed perfectly or I fail").*
- ***Catastrophizing** - always expecting the worst ("If I do an activity, I will feel unwell for days").*
- ***Should statements** - imposing rigid rules ("I must manage on my own," "I must never complain").*
- ***Overgeneralization** - extending one event to everything ("I failed once, so I will always fail").*
- ***Emotional reasoning** - believing that emotions represent facts ("I feel anxious, therefore something bad will happen").*
- ***Overestimation of risk** - perceiving risks as higher than they really are.*
- ***Self-devaluation** - globally judging oneself or others ("I am a disaster," "I am worthless").*

T asks the group whether they recognize any of these styles in their thinking. Personal examples are discussed and how these thoughts affect motivation and energy management.

Part 3 - Illness-related thoughts; Self-sabotage

T: *"Recognizing typical arthritis-related thoughts, such as: "The illness defines me," "If I rest a bit, then I will not manage anymore," "If I have pain, it means I have done too much and must stop doing everything." These thoughts are often interpretations, not facts: pain does not always equal progressive damage; excessive rest can increase dysfunction."*

T begins guided discussion: *"When do these thoughts appear? What are they connected to (fatigue, anxiety, social events)? What emotions follow (fear, sadness)?"*

It is important that participants identify specific triggers and patterns (e.g., worsening after social activity, after a disturbed night of sleep).

T: "*Let us talk about concrete actions; you must evaluate alternatives to avoid these thoughts (e.g., adapting activities, redistributing energy, gradual behavioral experiments). You need to connect this to pacing strategies and behavioral activation already addressed in previous sessions.*"

T: *"Now let us try to increase awareness of how we self-sabotage. Let us discuss thoughts and behaviors that you often think/do that hinder you. Here are some questions."*

"What thoughts make you give up before even trying?"
"In which situations are you more inclined to ruminate?"
"What behaviors follow a negative thought (avoidance, excessive rest, constant monitoring)?"

T notes emerging themes (common patterns) on the board, normalizing them and linking them to the techniques presented.

Part 4 - Practical exercise (optional, if time remains)

In this part, the objective is to apply cognitive restructuring techniques to concrete situations.

T says: *"Now we will do an exercise to learn how to challenge automatic thoughts. You will form pairs. One person will describe a situation in which they felt fatigue or discouragement, and the other will help examine the accompanying thought using questions such as: 'What evidence do I have that this thought is true?', 'Are there other possible explanations?', 'What would I say to a friend who had the same thought?'"*

After a few minutes, T invites the pairs to share the most interesting insights with the group. Together, the group discusses which alternative thoughts proved more realistic and how these can influence the perception of fatigue.

Conclusion

T concludes the session with a brief summary:
"Today we learned that thoughts directly influence emotions and that we can modify them to better manage fatigue. During the week, try to notice automatic thoughts, the emotions connected to them, and possible alternatives. To consolidate knowledge gained, it is important to practice daily."

Homework

Assignment 1
Complete the automatic thoughts log.

Assignment 2
Reflect on problematic thinking styles: identify which ones you use most often and write practical examples.

Intervention 1: Guide to identifying thoughts from emotions (for patients)

Emotion	Questions to ask yourself	Related thoughts
Fear and anxiety	*"Do I think that something bad might happen to me?"*	Thoughts related to the possibility that something negative might occur. *Examples* • *"I am about to be attacked or harmed."* • *"Something terrible is about to happen."* • *"I am about to be rejected or abandoned."* • • *"I am about to lose control or go crazy."*
Sadness and depression	*"Do I think I have lost hope?"* *"What do I think is missing in me or in my life?"*	Thoughts related to a sense of loss. *Examples* • *"I am worthless."* • *"I have no one to rely on."* • *"Nothing will ever get better."*
Guilt and shame	*"What do I think I have done wrong?"*	Thoughts related to the possibility of having done something wrong. *Examples* • *"I am inadequate."* • *"I am to blame for what happened to me."* • *"I am a terrible person."* • *"I am a failure."*
Anger and irritability	*"What do I think is unfair in this situation?"*	Thoughts related to the possibility of having been treated unjustly. *Examples* • *"I have been treated unfairly."* • *"I have been exploited."* • *"This situation is unpleasant and not right."*

Intervention 1: Guide to identifying thoughts from emotions (for the therapist)

The objective is to help participants understand that certain types of emotions are associated with certain types of thoughts.

T: *What we have just learned is that* ***what we think greatly affects what we feel****. We have also discussed the fact that* ***our previous experiences deeply shape our thinking styles*** *and that, most of the time, these thoughts are so automatic that we are not aware of them. That is, they arise so quickly that we feel the emotion without identifying the thought. Therefore, the first step in cognitive restructuring is to slow down this process and learn to identify thoughts. The* ***"Guide for identifying thoughts from emotions"*** *is a tool that can help you begin to identify your thoughts. In the "Guide" you will find a list of some emotions and the types of thoughts that typically trigger or strengthen these emotions. Now let us look at the "Guide."*

Let us see how this "Guide" can be used. For example, ***when you feel frightened****, you generally think you are in danger and probably think that something bad is going to happen.*
? Does a situation come to mind that you recently experienced in which you felt frightened? What were you thinking?
→ Discuss with participants the moment in which they felt frightened and the thoughts associated with it.

When you feel ***sad****, you are probably thinking about a loss. Do you remember a recent situation in which you felt sad? What were you thinking?*
→ Discuss with participants the moment in which they felt sad and the thoughts associated with it.

If you feel ***guilty or embarrassed****, you are probably thinking about something you did that you perceived as unpleasant, or you may think that you yourself are somehow unpleasant. Tell me about a recent episode in which you felt guilty or embarrassed. What were you thinking?*
→ Discuss with participants the moment in which they felt guilty or embarrassed and the thoughts associated with it.

Finally, ***anger*** *is typically associated with thoughts related to something being wrong or unjust. Do you remember a recent situation in which you became angry?*
→ Discuss with participants the moment in which they became angry and the thoughts associated with it.

You can use the "Guide" whenever you try to understand your thoughts and the emotions connected to them. → Check whether the participant has understood the connection between thoughts and emotions and how to use the "Guide for Identifying Thoughts from Emotions" to identify related thoughts.

Intervention 2: Problematic thinking styles (for patients)

Problematic thinking styles are patterns of thought that people often have in reaction to everyday events. If you can identify a common thinking style, it is very likely that your thinking may be inaccurate. Below are some of the most common problematic thinking styles.

Problematic thinking styles	**Identifying one's own thinking style**
– **All-or-nothing thinking**	When you think that the world is black or white. It is all or nothing, with no middle ground. *Examples* • *"If I am not perfect, I am a failure."* • *"The world is either completely safe or totally dangerous."* **If you think this way, try to find the middle ground.**
– **Overgeneralization**	When you think that a single negative event is something that will repeat endlessly. You think, without evidence, that it will happen again and again. Negative things are "forever" and positive situations will "never" occur. *Examples* • *"Since I was a victim once, I will be again."* • *"Bad things have always happened to me; it will always be like this."* **If you think this way, look for examples of positive things that have happened to you.**
– **Must/should statements, absolute needs**	When you have excessive demands on yourself and on others. *Examples* • *"I should be able to handle this situation."* • *"I absolutely must complete this task."* • *"I can only be happy if I have this."* **If you think this way, try to be more flexible about the rules you impose on yourself and others.**

Problematic thinking styles	**Identifying one's own thinking style**
– **Catastrophizing**	When you imagine extremely negative consequences and expect the worst to always happen. This attitude is often triggered by "what if" thoughts. *Examples* • *"What if I die the next time an earthquake happens?"* • *"I am sure my insurance will not reimburse me for my financial losses and my family will be ruined."* • *"The noise I heard outside my window is caused by a violent criminal trying to break in and harm me and my family."* **If you think this way, try to change your thinking by asking yourself what the most likely outcome in reality would be.**
– **Emotional reasoning**	When you believe that what you feel determines what you think. Although it is important to pay attention to what you feel, emotions can mislead you. If you are constantly anxious, these emotions may lead to incorrect thoughts. *Examples* • *"I am very anxious in this situation, so I think I am going to go crazy and lose control."* • *"I feel panicked, so I think the world is dangerous."* • *"I feel ashamed, so I think I am a despicable person."* • *"I feel guilty, so I think I must have done something wrong."* • *"I feel insecure, so I think I am in danger."* **If you think this way, ask yourself whether there are times when you realize that your emotions may lead you to think inaccurately.**

Problematic thinking styles	**Identifying one's own thinking style**
– **Overestimation of risk**	When you judge that the risk is much greater than the evidence would support. *Examples* • *"I do not intend to go for a walk because I might run into a storm."* • *"I cannot fly because the plane might crash."* • *"I need to take my family out of this region to keep them safe."* • *"I am not going to drive because I might have a car accident."* **If you think this way, try to calculate the actual probability that the feared event will occur.**
– **Guilt and shame**	When you think you are to blame for any negative outcome. People with a strong sense of guilt are not able to accurately assess the responsibility of others. They also tend to attribute all blame to themselves, even in situations where they have no responsibility. *Examples* • *"It is my fault that I was abused."* • *"My wife is angry with me, so I am the one to blame."* **If you think this way, ask yourself whether someone else might also have some responsibility.**
– **Intolerance, unbearability**	When you think you cannot tolerate certain unpleasant events. These thoughts reflect low frustration tolerance and lead you to believe that some objectively unpleasant events cannot be endured. *Examples* • *"I cannot stand being treated this way."* • *"I cannot tolerate this situation going on any longer."* If you think this way, ask yourself whether unpleasant situations could be made more bearable by trying not to give them excessive weight.

Problematic thinking styles	Identifying one’s own thinking style
– **Devaluation of self or others**	When you think that, because you or others have not succeeded in something, the failure is total. If one or more aspects of behavior are negative, then the whole person is negative. *Examples* • *“I am a disaster.”* • *“My coworker is worthless.”* **If you think this way, ask yourself whether it might be better to judge only specific unsuccessful behaviors rather than the entire person, whether it is yourself or others.**

Your examples

Problematic thinking styles	Identifying one’s own thinking style

Intervention 2: Problematic thinking styles (for the therapist)

The objective is to teach participants how to identify problematic thinking styles.

Learning to examine and challenge the thoughts and beliefs that trigger negative emotions is an important skill that will help you deal with your emotions and process your life experiences. Much of the work we will do together will help you achieve this goal. To begin, ***I would like to teach you a useful method to identify when your thinking is leading you to unpleasant emotions and to check whether your thinking is accurate or not****. This method helps you understand which problematic thinking styles, or common unhelpful thinking patterns, often trigger painful, unpleasant emotions.* ***The "problematic thinking styles" are thought patterns that people often develop in response to everyday events.*** *Although they are unhelpful, unnecessary, and contribute to negative emotions, everyone may use them at times. People who have experienced traumatic events may use these types of problematic thinking styles more often than others.*

Now let us examine together some of the most common problematic thinking styles and understand why they are, in some way, inaccurate - that is, why they do not correspond to truth.

Work only on a couple of examples of problematic thinking styles. The others are used as reference if the user asks questions. It would not be possible to finish the session in one hour if all were examined. However, T can be encouraged to read the other styles as homework.

All-or-nothing thinking (or "Black-and-white thinking")
This first problematic thinking style refers to ***seeing a situation in absolute terms; that is, everything is one way or another, with no middle ground****. For example, if you are doing something and you make a small mistake, you may start thinking that you have done a terrible job, becoming discouraged. You may think that when you do something, you either do it excellently or it is as if you did not do it at all, with no middle ground. Another example might be thinking that the world is either completely safe or totally dangerous, whereas in reality, some situations are safer than others. If you discover that you use this thinking style,* ***try to consider a different, more accurate, and more realistic way of looking at things.***

Overgeneralization
Excessive overgeneralization means ***seeing an event as representative of an endless, unchangeable pattern, even when this is not true****. For example, if you were the victim of a crime, you might generalize and say: "Once you are a victim, you are a victim forever. It is easy to take advantage of me," and you would end up feeling bad. If you*

notice that you are overgeneralizing, ***try to find specific situations that do not fit the generalization****, pointing out all the situations in which you were not a victim.*

Must/should statements, absolute needs

Statements such as ***must, should*** *are* ***unwritten rules and expectations about our behavior that are based on myths rather than real facts****. They may lead to thoughts of discouragement, anxiety, fear, sadness, or anger. They represent inflexible rules for your behavior, which you may have learned during your development, or expectations that you think you must meet and live up to. They may also represent a way of thinking that incorrectly leads us to consider indispensable what is actually only desirable, preferable, useful, but something we can live without, even if inconvenient. Some examples of these statements are: "I should be able to handle this situation," or "I absolutely must complete this task," or "I can only be happy if I have this." If you notice that you are using must/should statements,* ***remember to be flexible with these rules.***

Catastrophizing

This type of thinking arises when you ***focus on the most extreme negative consequences of a situation****. This leads to increased fear and anxiety. You always expect a disaster at any moment. Catastrophic thoughts are triggered by questions such as "What if...," "What if there is another disaster?" or "I will never have a home again."*

If you notice you are catastrophizing, ***try to modify the thinking pattern by asking yourself what the most likely outcome would be if the event occurred****. For example, what would really happen if there were another disaster? Another earthquake? Would you die? Would you be injured? Do you know people to whom this happened? Probably not. It would be extremely distressing, but it is highly unlikely that what you imagine in your worst fears would actually happen.*

Emotional reasoning

This thinking style arises when ***what you feel determines what you think****. Although it is important to pay attention to what you feel, your emotions may mislead you. If most of the time you are anxious, your emotions are almost certainly lying. Examples of emotional reasoning include: "I am really anxious in this situation, so I will end up going crazy and losing control," or "I am frightened, so the world must be dangerous." If you use emotional reasoning,* ***ask yourself: "Are there times when my emotions are inaccurate?*** *Could this be one of those times?"*

Overestimation of risk

This is a common problematic thinking style that leads to increased fear and anxiety. ***It happens when we view risk as greater than it actually is****. For example: "I will not go for a walk because I might be attacked," "I cannot enter tall buildings because in case of an earthquake it would be harder to escape," or "I cannot go to the city because the city is a target for terrorist attacks." For example, if you think the city is unsafe* *because it is targeted by terrorists, try to consider the situation realistically: how many times has that city actually been the target of terrorist acts?*

Guilt and shame

This thinking style involves the ***tendency to blame oneself for every negative outcome****. People who tend to blame themselves excessively are not able to accurately assess the responsibilities of others or environmental factors. They tend to attribute all blame to themselves and feel guilty for situations in which they have little or no responsibility. For example: "It is my fault that such a terribly sad event occurred," or "My husband is angry with me, so it is my fault." If you notice that you are blaming yourself,* ***ask yourself whether someone else or something else might be responsible****.*

Intolerance, unbearability

This ***thinking style leads you to believe that you cannot tolerate certain unpleasant events.*** *These thoughts reflect low frustration tolerance and lead you to believe that some objectively unpleasant events cannot be endured. In post-traumatic situations, it is possible that one must face very difficult, unpleasant situations with a high degree of uncertainty. Examples include: "I cannot stand being treated this way," "I cannot tolerate this situation going on any longer." If you notice you are using this thinking style,* ***ask yourself whether unpleasant situations might be made more bearable with a more realistic reframing of the event.***

Devaluation of self or others

This thought consists of believing that, ***if one or more aspects of behavior are negative, then the entire person is negative****. These statements may be directed toward oneself or others. If one has not succeeded at something, one is a total failure, or others are failures. Examples include: "I am a disaster," or "My coworker is worthless." If you think this way,* ***ask yourself whether it might be better to judge only specific unsuccessful behaviors rather than the entire person, whether it is yourself or others.***

Conclusions

Even though these common problematic thinking styles are quite different from each other, they tend to overlap. Therefore, it is understandable that you may use more than one problematic thinking style at the same time. *The important thing to remember is that, when you notice that you are using one of these thinking styles, it is very likely that your thinking is inaccurate and that it is the cause of your suffering. If you can understand when your thinking falls into one of these categories, then you can come up with a more accurate thought, closer to reality. However, in some cases, people believe that their thinking is accurate or corresponds to reality. The next technique you will learn is how to evaluate the accuracy of your thoughts.* ***Remember: just because you think something does not mean it is true.***

Assignment 1 - Automatic thoughts log

Fill out this table whenever you notice a negative or automatic thought. Try to identify the situation, the associated emotions, evidence supporting the thought, evidence contradicting the thought, and attempt to reformulate the thought in a more realistic way.

Date/situation	**Automatic thought**	**Emotion**	**Evidence (Pros)**	**Evidence (Cons)**	**Alternative thought**

Session 6: Understanding cognitive distortions and coping strategies

Session goal
Deepen the understanding of cognitive distortions, explore how these patterns influence fatigue in rheumatic diseases, and introduce coping strategies that promote more adaptive emotional and behavioral responses. The session continues the cognitive-behavioral work developed in previous meetings and prepares participants to adopt more effective perceptions of illness and fatigue.

Pre-introduction

T begins with open questions such as*: "How are you today? How have the past two weeks been for you?"*
T asks how the homework assigned in Session 5 went. If the group is silent, T facilitates sharing with questions such as: *"Did you notice any automatic thoughts more clearly this week?"* or *"Were you able to challenge any unhelpful thoughts?"*
T briefly summarizes what was learned in Session 5 regarding the link between thoughts, emotions, and fatigue. Then introduces today's topic: understanding cognitive distortions more deeply and learning coping strategies to manage dysfunctional thinking.

Introduction

T says: *"Today we will focus on cognitive distortions—habitual ways of thinking that can intensify emotions and drain energy. When these patterns become automatic, they reinforce fatigue and reduce our confidence in managing daily tasks. We will learn to recognize these distortions, understand their role in fatigue, and explore coping strategies that can help you respond more effectively to difficult thoughts."*

Part 1 - Understanding cognitive distortions

The objective is to introduce the most common cognitive distortions and connect them to fatigue.

1. Review of cognitive distortions

T explains: *"As we discussed in the previous session, cognitive distortions are distorted ways of interpreting events. Everyone experiences them, especially under stress or in chronic illness. But when we learn to recognize them, we can reduce their impact on mental and physical fatigue."*

"Now we can review together the common ***cognitive distortions****:*
• All-or-nothing thinking – seeing things in absolute terms.
• Catastrophizing – always expecting the worst.
• "Should" statements – imposing rigid rules on oneself.
• Overgeneralization – extending one event to everything.
• Emotional reasoning – believing that emotions represent facts.
• Overestimation of risk – perceiving risks as higher than they actually are.
• Self-devaluation – globally judging oneself or others."

Open discussion

T asks: *"Which of these thinking patterns do you notice most often? How do these thoughts influence your energy level?"*
T invites examples related to flare-ups of the illness, energy depletion, social activities, or daily functioning.

2. The stages of cognitive restructuring – Psychoeducation

T: *"The objective of the first part is to teach participants how to identify problematic thinking styles and the 5 stages of cognitive restructuring."*

T: *"What do we do with unhelpful beliefs that can be a source of discomfort and suffering? First, we learn what you think in certain situations. You already started doing this in last session's homework. Now evaluate your thought to see if it is accurate and useful for you. Remember, many of the things you think and accept as true appear believable only because you have thought them for a long time. We want to see and evaluate whether what you think in different situations makes sense. If we decide that in certain situations your thoughts are not useful, we will modify them. In general, if you modify an unhelpful thought, you will feel better. This process is called "cognitive restructuring."*

"To judge the accuracy of your thoughts, we must pretend to be scientists, judges in a courtroom, or private investigators, and collect "pro" and "con" evidence when evaluating our thoughts. We must try to be as objective as possible when assessing the evidence for our thoughts. We will work hard to find as much evidence supporting our dysfunctional thoughts as possible and evidence that disconfirms them. In this way, we ensure that our evidence is based on facts and not merely on our emotions.

There are 5 stages of cognitive restructuring:
1. *describe a difficult situation;*
2. *identify the negative emotion;*
3. *identify the underlying thought or belief;*
4. *challenge the thought or belief based on objective evidence;*
5. *develop an action plan, that is, make a decision (Hamblen et al., 2018)."*

3. The stages of cognitive restructuring – Illness-related examples

"Now let us try to do an exercise together" (T gives the Intervention 1: *The 5 stages of cognitive restructuring* to all participants).

In the ***first stage****, write down the unpleasant situation. Let us take common illness-related situations in which you feel uncomfortable. Write your example.*

In the ***second stage****, you must identify the unpleasant emotion you experienced in that situation. Sometimes a person feels more than one emotion in a given situation. This is normal. However, you must focus on the strongest or most unpleasant emotion. There are some questions you might ask yourself to understand what you feel. For example: "What negative outcome do I expect to happen?"*

If the participant feels more than one unpleasant emotion in a given situation, it may be helpful to analyze each of these emotions. It is recommended to consider each emotion separately and work with a different cognitive restructuring worksheet for each emotion. It is best not to try to address more than one emotion with the same worksheet.

In the third stage, you must identify your thoughts about the situation. Remember that it is our thoughts that determine our emotions; to address negative emotions, we must understand more about what we think in different situations. The key to deciphering what you are thinking lies in the unpleasant emotions you are experiencing. What thoughts might be crossing your mind and causing the selected feelings in that situation?
You are likely expecting that something bad might happen. A more specific thought could be. Now let us ask ourselves which problematic thinking style you might have used.
Perhaps emotional reasoning? You think something is likely to happen more than the actual evidence suggests. Write it here.
Remember: if you can identify a problematic thinking style, this indicates that your thought may not be precise or grounded in reality.

Just as participants can identify more than one emotion, they may also identify more than one thought related to the same emotion. When this happens, the participant should work with the most unpleasant thought or the one most closely linked to the strongest emotion in that situation.

The idea is to evaluate whether what you think makes sense and is accurate. If you decide that your thoughts in a particular situation are not useful, you can modify them and, usually, you will find that modifying inadequate thoughts helps you feel better. Sometimes, as soon as you identify your thought, you may recognize it as a common problematic thinking style, such as all-or-nothing thinking or catastrophic thinking.

*In the **fourth stage**, you begin evaluating evidence for and against. What evidence supports that thought? Identify evidence that justifies your thoughts. What evidence challenges what you think? Are you having difficulty generating "against" evidence? Always refer to concrete situations rather than thoughts or emotions, when possible.*

*Cognitive restructuring is a way to help you when dealing with negative emotions by examining your related thoughts and modifying them when they are not accurate or helpful. The **fifth stage**, developing an action plan, may involve modifying the thought, planning how to face the unpleasant situation, or both, combining the two strategies.*

4. The stages of cognitive restructuring - Modifying thoughts

"Now let us move to questions about modifying the chain between situations, thoughts, and emotions."
(T selects some questions to initiate the discussion on modification.)
Is there an alternative way of looking at the situation?
Is there an alternative explanation?
What would someone else think about the situation?
Are your judgments based on how you felt rather than on what you did?

Are you setting for yourself an unachievable and unrealistic standard?
Are you overestimating how much you can control and your responsibility in this situation?
Are you underestimating what you can do to deal with the problem or situation?
What are the advantages of maintaining this belief?
What are the disadvantages of maintaining this belief?

Consider all available evidence and decide whether your thought or belief is accurate or not. Ask yourself whether you could convince someone else that your belief is true. If the evidence does not support your thought, then it is time to develop a new thought—more realistic, more accurate, or more balanced—to replace the old one. This new thought should be supported by the evidence you have. If, instead, the evidence collected supports your thought, then it is time to develop a plan for addressing the situation.

Part 2 - Coping strategies for dysfunctional thoughts

1. Introduction

The objective is to explore coping strategies to manage cognitive distortions related to fatigue.

T: *"Coping with unhelpful thoughts means noticing when a pattern appears and responding skillfully instead of reacting automatically. Coping strategies can reduce emotional activation, help regulate fatigue, and improve decision-making."*

Examples of coping strategies:
- *Cognitive restructuring (challenging distortions)*
- *Self-compassion and supportive self-talk*
- *Behavioral activation and pacing*
- *Attention-shifting and grounding techniques*
- *Problem-solving strategies*

2. Recognizing one's coping strategies related to arthritis

T introduces coping strategies as examples of how to face difficulties in a positive way (Intervention 2: Coping strategies).

Participants list the strategies they currently use when facing thoughts related to fatigue. T asks them to classify them as:
– Helpful
– Neutral
– Unhelpful / Dysfunctional (e.g., avoidance, excessive rest, rumination).
Three columns are drawn on the board and the participants' strategies are written.

Open discussion
T begins a discussion about the strategies suggested: *"Are your current coping strategies effective in reducing fatigue? In which situations do your strategies help, and in which do they worsen fatigue?"*

3. Adopting new coping methods

The objective is to help participants understand why alternative coping strategies are necessary.

T: *"Changing coping strategies does not mean forcing yourself to think positively. It means building a more flexible and realistic way of understanding your illness and fatigue, so that you can make choices that sustain your energy instead of consuming it."*

T introduces the development of alternative illness perceptions:
- *Fatigue does not always equate to danger.*
- *Rest is helpful, but excessive rest increases disability.*
- *Activity can be gradually modulated (pacing) instead of avoided.*
- *Pain can be managed without assuming the worst-case scenario.*

T guides participants in creating a personalized and more balanced interpretation of fatigue, which promotes approach-oriented rather than avoidance-oriented coping.

Part 3 - Problem-solving (structured method)

1. Psychoeducation
T: *"Now we will examine the structured method of problem solving and goal achievement, also known as problem-solving, which can be useful to enhance the action plan of cognitive restructuring, and to address, together with your family members, the concrete problems that may have arisen due to the new situation related to rheumatological illness.*
Here too the method is divided into phases."

First phase: identifying the problem or goal
It is better to express a problem as a goal (for example, social isolation = finding something interesting to do at least two afternoons a week in external environments). It is crucial to define the problem or goal clearly, because this allows focus, reduces the risk of losing direction, and makes it easier to determine whether the problem has been solved or the goal achieved.
To clearly define the problem/goal, the following rules are useful:
- *choose at the beginning a relatively simple problem, one that is not too emotionally charged;*
- *select a very specific, realistic, and achievable goal, measurable, and personally meaningful to the individual rather than decided by others;*
- *consider only one well-defined problem/goal at a time, setting aside other problems, even if important, to address them in the future;*
- *do not jump immediately to the solution but proceed step by step through the next phases.*

T asks participants to present some of their problems related to illness and fatigue on which they can work, going through all the phases together.

Try to identify a simple, concrete fatigue-related problematic situation that can be successfully challenged.

T ensures that the participant appreciates how this technique can be applied and, when used correctly, can lead to effective planning of decisions to solve problems, based on clear and well-defined objectives, possibly with the support of other members of the "resource group."

Second phase: listing possible solutions through brainstorming

Brainstorming, or "free idea generation," is a method to identify as many proposals as possible, in this case, potential solutions.
On the board, all proposed solutions are written down. In turn, participants propose one solution. In the actual brainstorming phase, criticism is not allowed, but only genuine clarifying questions; even a foolish or absurd proposal may be the starting point for reaching original and valid solutions. The process continues until participants cannot propose new solutions or until a dozen different solutions have been listed. Anyone without a proposal may pass.
Brainstorming can be useful not only in the solution-selection phase but also when choosing the problem or goal and in the solution-planning phase.

Third phase: evaluating solutions

This consists of a brief discussion of the advantages and disadvantages of each possible solution. It is neither necessary nor appropriate to dedicate much time to this phase, but it is sufficient to identify the main strengths and weaknesses of the listed solutions.

Fourth phase: choosing the optimal solution

It is almost never easy to choose the solution, because even the seemingly best one almost always has some drawbacks (for example, it may require a lot of time), whereas most solutions also have some positive aspects, such as being more complete or easier to plan.
In many cases it is preferable to choose a solution that is easy and quick to implement, even if not ideal. At least this choice helps to get started immediately, and even if the problem is not fully resolved, partial results may be obtained and valuable lessons learned for a second attempt. Overly ambitious solutions with a high risk of failure should be avoided.
If the goal is too difficult or distant, it is recommended to divide it into smaller, more manageable sub-goals and start with the first one (plan in small steps).

Fifth phase: planning the chosen solution

Because the main cause of failure is insufficient planning of the chosen solution, the plan should be formulated in detail, specifying precisely who must do what, how and when they must do it, and how to verify the plan's implementation. The plan should also include cues and reminders (e.g., someone reminding those responsible of their parts of the plan) and incentives, such as rewards upon reaching the expected result.

Sixth phase: reviewing the plan

The problem-solving process is continuous, as problems or goals are often not fully resolved or achieved on the first attempt. Moreover, it is common to overlook potential obstacles and difficulties during planning, making it necessary to redefine the plan.

At the end of planning, the plan is tested (in our case, a mental test) using the following questions:

What worked?
What did not work?
What could have been done differently?

T discusses with participants the effectiveness and usefulness of this method for their illness-related problems.

Homework

Assignment 1
Describe situations related to your illness and fatigue, analyzing the thoughts connected to the situation.

Assignment 2
Try to practice problem-solving on practical problems.

Assignment 1 - The 5 stages of cognitive restructuring

1. SITUATIONS

Ask yourself: “What happened that is causing me distress?” Write a brief description of the situation.

Situation:____
____
____

2. EMOTIONS

Circle your most intense emotion (if you experience more than one, use a separate sheet for each unpleasant emotion; add any emotions that are not listed).

Fear and anxiety
Guilt and shame
____
Sadness and depression
Anger and irritability
____

3. THOUGHT

Ask yourself: “What am I thinking that is making me feel this way?”
Identify the thought that is most specifically related to the unpleasant emotion circled above. Write your thought below.

Thought:____
____
____

Circle your most common thinking style:
All-or-nothing thinking
Must/Should statements
Emotional reasoning
Guilt
Self- or other-devaluation
Overgeneralisation
Catastrophising
Overestimation of risk
Unbearability/Intolerance

4. CHALLENGE YOUR THOUGHT

Rewrite your thought (as indicated in point 3)
____
____
____

Now ask yourself: “What evidence do I have that this thought is true? Is there an alternative way to view this situation? What would another person think about this situation?”
Write down the answers that support your thought and the answers that do not support your thought.

Evidence supporting my thought:

Evidence that does NOT support my thought:

5. TAKE ACTION!

Now ask yourself: “Is there more evidence supporting my thought or more evidence NOT supporting it?”

__NO, the evidence does not support my thought.

If the evidence does not support your thought, develop a new thought that is more closely connected to reality. These thoughts are usually more balanced and helpful. Write the new and more useful thought you developed in the space below. And remember: if this happens again in the future, replace your automatic and unhelpful thought with the new, more appropriate one.

New thought

In some cases, **even if the evidence does not support your thought** (or only partially supports it), you may still need to develop an action plan. Generally, this involves helping you cope with an unpleasant emotion that persists even after developing a more balanced thought. For example, you may choose to use a breathing technique, ask a friend to accompany you, or develop a systematic plan for facing feared or avoided situations. If you can independently develop an action plan for this situation, write it below. Otherwise, you may engage in problem-solving with your family or friends.

Action plan/Problem-solving

__YES, the evidence supports my thought.

If the evidence supports your thought, decide what needs to be done next in order to deal with the situation. Ask yourself: “Do I need to obtain more information about what to do? Do I need to seek help?”

If you can independently develop an action plan for this situation, write it below. Otherwise, you may engage in problem-solving with your family or friends.

Action plan/Problem-solving

Intervention 2: Coping strategies

Below are additional strategies useful for dealing with negative emotions. Even if you have used some of them at various times in your life, you may not have thought of these responses as “coping skills” or specific “strategies.” You will find that some strategies work better than others. We encourage you to experiment to discover what works best for you.

Coping strategies	
Breathing retraining	Breathing exercises are a quick way to reduce anxiety. Remember to practise often when you are not anxious. Later, when you feel anxious, you will quickly reduce anxiety to a more manageable level.
Scheduling pleasant activities	Remember that one way to feel better is to engage in enjoyable activities. Identify some activities you find pleasant and schedule them in your day. Even if being active is often the last thing you feel like doing when you are depressed, it is actually a very effective way to counter that mood.
Talking to someone	Sometimes it can be helpful to talk with a trusted friend when you feel stressed and distressed. When you are struggling, you may intentionally choose to spend time talking with a friend about other topics, in order to free your mind from stressful thoughts and emotions, even if only for a while.
Giving yourself positive instructions	Remind yourself that you can manage and that you can learn new skills to cope with situations of intense distress. Remember that emotions pass with time. No emotion is permanent.
“Observing” your feelings	Watch painful feelings flowing through you as if they were water running through a stream.
“Observing” your thoughts	For each thought that comes to mind, imagine placing it on a cloud and letting the cloud drift away.
Physical exercise / Diet / Sleep	One way to feel better is to take care of yourself. Sleep, nutrition, and physical exercise are among the first areas affected by stress. Try to establish healthy eating habits and regular exercise. If sleep is a problem for you, you should try to improve its quality.
“Self-soothing”	Taking care of yourself through self-soothing activities - such as spending time with loved ones, engaging in a favourite hobby, taking a bath, setting aside time for yourself (even just 10 minutes), having a massage, reading a book, or taking a walk - can be comforting.
Spirituality and religiosity	If you follow a spiritual or religious practice, engaging in these practices can be helpful during difficult times.
Distraction	This is a coping strategy that can be useful when used in moderation. It can also be helpful in situations where it is not appropriate or possible to fully express your emotions (for example, during a business meeting, at work, etc.). Distraction may include a scheduled pleasant event or something more spontaneous, such as calling someone on the phone, chatting, taking a walk, going shopping, etc.
Challenging your thought	Cognitive restructuring will allow you to challenge your thought to determine whether the distressing emotions are triggered by inaccurate thoughts. If so, you will develop alternative thoughts and action plans.

Assignment 1 - Thought check

Situation 1

What is the situation? You may have thoughts about something that has just happened in the external environment or something that has occurred inside you (for example, an intense emotion, a painful sensation, an image, a fantasy, an intrusive memory, or a stream of thoughts, such as reflections on my future).

What am I thinking or imagining (about the situation)?

What is the cognitive distortion? (optional)

What leads me to believe this thought is true?

What leads me to think that this thought is not true or not entirely true?

What is another way of considering the situation?

If the worst were to happen, what could I do in that moment?

What is the best possible outcome?

What is likely to happen?

What will happen if I continue repeating the same thought to myself?

What might happen if I changed my way of thinking?

What would I say to a friend or family member [think of a specific person] if something similar happened to them?

What would be appropriate to do now?

Situation 2

What is the situation? You may have thoughts about something that has just happened in the external environment or something that has occurred inside you (for example, an intense emotion, a painful sensation, an image, a fantasy, an intrusive memory, or a stream of thoughts, such as reflections on my future).

What am I thinking or imagining (about the situation)?

What is the cognitive distortion? (optional)

What leads me to believe this thought is true?

What leads me to think that this thought is not true or not entirely true?

What is another way of considering the situation?

If the worst were to happen, what could I do in that moment?

What is the best possible outcome?

What is likely to happen?

What will happen if I continue repeating the same thought to myself?

What might happen if I changed my way of thinking?

What would I say to a friend or family member [think of a specific person] if something similar happened to them?

What would be appropriate to do now?

Session 7: Self-care and fatigue

Session goal
Introduce and deepen the concept of self-care, self-awareness, self-compassion and acceptance, with particular attention to their role in managing fatigue in rheumatic diseases.

Pre-introduction
T opens the session with some open questions: *"How are you today? How have the past two weeks been?"* He/she then invites participants to share the homework completed: *"How did the thought-monitoring task go? Did you notice anything new in situations of fatigue?"* T allows space for discussion and facilitates, if necessary: *"Is there a thought or situation that particularly struck you? Would someone like to share an example?"*

Introduction to the topic of the session
T introduces the topic: *"Today we will explore self-care, self-compassion, and the way we welcome both our strong parts and our more fragile parts. Chronic illness often challenges our self-image, our energy, and our self-control: learning to take care of ourselves and to develop kindness toward ourselves is essential for managing fatigue."*

PART 1 - SELF-CARE AND FATIGUE

1. Psychoeducation on self-care
T explains: *"Self-care is not a 'luxury', but an essential physiological and psychological need. In rheumatic diseases, self-care has a direct impact on the level of fatigue. If we take more care of ourselves, we begin to address the causes of tiredness and the possibilities for changing it. The lack of self-care more easily leads to the boom-and-bust cycle, worsening symptoms, and reduced self-efficacy."*

"Some elements we mentioned in previous sessions are also useful in self-care:
- ***Rhythm regulation** (pacing, breaks, limits)*
- ***Emotional care** (recognizing emotions, accepting them, asking for support)*
- ***Body care** (adequate rest, adapted movement, nutrition)*
- ***Self-compassion** (speaking to oneself kindly, reducing self-judgment)*
- ***Protective behaviours toward oneself** (saying NO, asking for help, delegating)."*

After spontaneous discussion with participants, T emphasizes: *"Self-care is not selfishness. It is a therapeutic act. We must focus on doing what is right for ourselves, not just what is comfortable. Order in life and self-control are steps in this direction. Self-care is a process of improvement, a continuous work of deep self-knowledge and readiness for change."*

2. Activity: Recognizing one's self-care behaviours and self-harmful behaviours
T says: *"Now let's talk about self-care behaviours and self-harmful/self-destructive behaviours. In your opinion, how can we define what self-care behaviours are and which ones are self-harmful/self-destructive?"*

T must guide participants toward the following two definitions:

Self-care behaviour: Intentional actions aimed at protecting one's physical, emotional, and mental well-being, such as resting, eating adequately, setting boundaries, asking for help, and adopting healthy habits.
Self-harmful/self-destructive behaviour: Behaviours that harm one's well-being, directly or indirectly, such as neglecting oneself, exposing oneself to unnecessary risks, substance misuse, maintaining harmful habits, or sabotaging one's physical and emotional needs.

If participants do not understand some aspects of the definitions, T stops and explains (for example, "setting boundaries" or "one's emotional needs"). T may explore these aspects in greater depth.

T distributes a sheet with Intervention 1 (*Self-care and self-destructive behaviour*) saying the instruction: *"Write some behaviours you have engaged in over the past week. If a behaviour is self-care, indicate it in the corresponding column and write a strategy to maintain it. If it is self-harmful/self-destructive, write it in the other column and indicate a possible strategy to modify it. Finally, specify whether each behaviour is connected to fatigue and/or the illness."*

T gives participants some time to complete the task and then invites sharing, saying that the rest of the task will be completed at home. T asks participants to share examples, asking questions such as: *"Which self-care behaviour made you feel better? Which self-harmful behaviours do you most often recognize? Why are they so recurrent? What might help you gradually replace them?"*

PART 2 - VALUES AND FRAGILITY

1. Relevant aspects of my life

T says: *"Now let's talk about the relevant aspects of your life, which can also be considered your values and strengths."*

T hands out a sheet with Intervention 2 ("Relevant aspects of my life"), giving the instruction: *"Think about the things that give meaning and purpose to your life. In the left column we have listed some suggestions, but you may add as many categories or experiences as you wish. In the central column, rate how important each item is for you, assigning a score from 0 - I do not care at all; 1 - I care very little; 2 - I care little; 3 - I care moderately; 4 - I care a lot; 5 - It is essential. In the right column, list some things you could do - actions, thoughts, meditation, or anything else - to pursue what is important to you. The goal is to clarify what matters and guide yourself toward the purposes that are closest to your heart."*
After participants have finished, T opens discussion with questions: *"Which aspects did you rate as 4 or 5 and why? What do you generally do to pursue those values? Which personal qualities have helped you during the illness? Which strengths could improve your fatigue management?"*
T concludes by stating that strengths can guide individuals toward a more satisfying life, even with illness, and that sometimes the illness hides strengths but does not erase them.

2. Evaluation by others

T distributes a sheet with Intervention 3 *("Examples of when I feel or do not feel validated"*) saying: *"Now let's focus on how others value your strengths and how this affects your self-esteem. Sometimes we feel understood, supported, and validated by others: describe some specific examples of such situations in the left column. In the right column, instead, list some examples of when you do not feel validated."*

T then initiates discussion, collecting examples and helping identify the main areas in which participants do or do not feel recognized.

T may choose to conduct the interventions even without written materials, in a dialogue-based format.

3. Activity: Writing one's weaknesses
T says: *"After analyzing your values and how others see you, now let's talk about your weaknesses and fragilities."*
T distributes a sheet with Intervention 4 (*"My weaknesses and fragile parts"*) saying: *"Recognizing your fragilities is an act of courage and self-awareness. Write here the traits, behaviours, or emotions that you find difficult (impatience, fear, rigidity, dependence on others, perfectionism…) and how you manage these fragile parts of yourself. Do not judge what you write. Weak parts are not flaws, but areas where care is needed."*
After the task, T opens discussion by asking what the participants' fragile points are and how they can address them. T asks questions such as: *"How do you take care of your fragile parts? Do you tend to judge yourself or support yourself? How would your experience of fatigue change if you were more compassionate with yourself?"*

T normalizes all comments, concluding: *"Weaknesses are not an obstacle to self-care. They are the compass showing where more care and improvement are needed."*

PART 3 - SELF-COMPASSION AND ACCEPTANCE

1. Psychoeducation: Be kind to yourself
T describes concrete examples of everyday self-compassion (selecting only a few).

- **Listening to the body**: allowing oneself breaks when pain increases instead of forcing activities.
- **Speaking to oneself kindly**: saying "I'm doing my best" on days with greater stiffness or fatigue.
- **Adapting activities**: using aids (jar openers, braces, ergonomic chairs) without judging oneself as weak.
- **Accepting the limits of the day**: allowing oneself to change plans when inflammation worsens.
- **Protecting the joints**: asking for help lifting weights or doing difficult manual tasks.
- **Caring for rest**: carving out moments of relaxation or micro-breaks to reduce joint tension.
- **Managing guilt**: remembering that saying "no" is a way to protect one's health.
- **Seeking support**: talking with a family member or friend when emotional fatigue increases, without feeling like a burden.

T opens discussion by asking: *"What strikes you about these examples? Is it easy for you to be kind to yourself? When you feel fatigue or frustration, how do you speak to yourself internally?"*

2. Open discussion: Perceptions influencing self-esteem
T poses group questions: *"Where does the image you have of yourself come from? How much do illness and fatigue influence your self-esteem? How do you perceive your body, and how is this linked to self-esteem? Which beliefs about yourself strengthen your energy, and which ones drain it?"*

T then links what emerged to the cognitive-behavioural framework, explaining how a cycle can maintain or worsen distress: *"When self-devaluing thoughts appear, they generate negative emotions; negative* *emotions often lead to avoiding activities or situations; avoidance further reduces self-esteem and, over time, increases the perception of fatigue."*

Summary

T concludes with the group the main points of the session:
- The concept of self-care as a tool for energy.
- Values, strengths, and fragile parts as guides for daily life.
- The importance of recognizing destructive behaviours and gradually replacing them.
- Self-compassion as an antidote to perfectionism and self-criticism.

Homework

Assignment 1
Self-care and self-destructive behaviour: Continue recording weekly behaviours, distinguishing those of self-care from those that are self-destructive, indicating for each maintenance or modification strategies and whether they are connected to fatigue and/or illness.

Assignment 2
Important aspects of life: Continue reflecting on values and how to keep them active in daily life, in a realistic and gentle way toward oneself.

Intervention 1: Self-care and self-destructive behavior

Instruction: Write the behaviors observed during the week. If a behavior concerns self-care, record it in the corresponding column and indicate a strategy to maintain it. If instead it is a self-destructive behavior, enter it in the appropriate column and describe a strategy to modify it. Finally, specify whether and how each behavior is connected to fatigue and/or illness.

Self-care behavior	Strategy to maintain that behavior	Related to fatigue/illness

Intervention 2: Relevant aspects of my life

Instructions: Think about the things that give meaning and purpose to your life. In the left column, we have listed some suggestions, but you may add as many categories or experiences as you wish. In the central column, evaluate how important each item is to you by assigning a score from 0 - I do not care at all; 1 - I care very little; 2 - I care little; 3 - I care moderately; 4 - I care a lot; 5 - It is essential. In the right column, list some things that I could do - actions, thoughts, meditation, or anything else - to pursue what is important to you. The objective is to clarify what matters and to move toward the goals that are most meaningful to us.

What gives meaning and purpose to my life?	How important is it to me? (0-5)	Examples of things I can do to obtain it.
Friendship.		
Love for others.		
Being a good parent, child, partner.		
Belonging to a community.		
Helping others.		
Being competent in one’s work.		
Building a career.		
Teamwork.		
Following a healthy lifestyle.		

What gives meaning and purpose to my life?	How important is it to me? (0-5)	Examples of things I can do to obtain it.
Engaging in physical exercise and staying active.		
Appreciating what surrounds us and our own life.		
Being grateful.		
Enjoying the beauty of things.		
Feeling connected to something greater than oneself.		
Justice.		
Learning and growing.		
Exploring and trying new things.		
Expressing oneself.		
Making good decisions.		
Working hard and doing things well.		
Being curious and open.		
Having humor and having fun.		
Increasing one's finances.		

What gives meaning and purpose to my life?	How important is it to me? (0-5)	Examples of things I can do to obtain it.
Respecting traditions.		
Engaging in spirituality.		
Learning new things and new skills.		
Courage.		
Wisdom.		
Temperance.		
Being in contact with nature.		
Meditating and praying.		

Intervention 3: Examples of when I feel or do not feel validated

Instructions: Sometimes we feel understood, supported, and validated by others; describe some specific examples of similar situations in the left column. In the right column, instead, list examples of when you do not feel validated.

I feel validated (understood, supported) when…	I do not feel validated (understood, supported) when…

Intervention 4: My weaknesses and fragile parts

Instructions: Recognizing one’s fragilities is an act of courage and self-awareness. Write here the characteristics, behaviors, or emotions that are difficult for you and how you face these fragile parts of yourself.

Examples: fear of disappointing others, difficulty saying no, impulsivity, perfectionism, avoidance.

My weaknesses	How do I face these fragile parts of myself?

Session 8: Social Support and communication strategies

Session goal

To help participants recognize the importance of social support in managing fatigue, improve the quality of relationships, and provide practical and proven tools to communicate effectively with family members, friends, and physicians about their fatigue.

Pre-introduction

T opens the session with some open-ended questions: *"How are you today? How have things been over the past two weeks?"*

T then invites participants to share the work completed at home: *"How did the homework go, both the self-care and self-destructive behaviors and the values connected to self-care? Would anyone like to share their observations? In any way did you link that with fatigue?"*

Introduction

T introduces the theme: *"Today we will explore social support in general and in relation to illness, and ways to improve social relationships through enhanced communication strategies."*

PART 1 - FAMILY

1. Psychoeducation

T explains: *"Chronic illness is not an isolated issue, but part of a broader and interconnected process, influencing the family system's ability to learn and adapt over time. The idea is not to focus solely on the individual, but to consider the illness as an event that involves the entire family unit, examining how illness influences—and is influenced by—relational and communication dynamics within it. For a family to function well, it must be able to balance its resources and vulnerabilities in relation to the psychosocial demands imposed by the illness over time. To help a family cope with the illness, it is necessary to analyze its functioning in terms of beliefs, organization, communication, and power.*

The impact of chronic illness on the family is particularly important because it can trigger processes of developmental blockage that may then have negative, collusive repercussions with the illness itself; or, on the contrary, it can activate resources, often unexpected, that can circulate positively. The family is a fundamental resource and an ally in the care of illness; illness and its course can influence relationships within the family unit (Moi, 2013)."

To initiate interaction with the group, T asks questions such as: *"How do you see changes in your family's dynamics since you developed the illness? What resources have helped your family cope with illness-related issues?"*

2. Family Relationships

T distributes a worksheet with Intervention 1A (*Family relationships*) and Intervention 1B (*Family functioning*) and says: *"Now let's analyze the dynamics in your families more deeply. Here is an assignment with two parts. In the first part, you will write your family members' names in the circles and draw the relationships with each of them. There are instructions for the different types of lines and the distance from your own circle. Then, the second part concerns family functioning - beliefs, organization, and communication."*

T should first use the diagram portion as a family map for each participant; then, the second part opens the topics for discussion. T asks for examples in order to explore participants' family dynamics. **Then it focuses on how these family aspects have changed since the chronic illness began and how the illness affects relationships.** This is the central point. T asks questions such as: ***"When you feel unwell, who offers you useful help (practical, emotional, informational)? Who do you perceive as support? When you experience illness-related fatigue, do you seek support within the family? Fatigue is often invisible - what happens when others do not understand?"***

T concludes this part: *"Since relationships are dynamic and do not remain the same over time, you need to reflect on changes, especially after significant events."*

PART 2 - Relationships beyond the family

T says: *"After analyzing family relationships, we will now focus on all social relationships - people such as extended family members, friends, coworkers, neighbors, physicians, and others who may provide important support. I am giving you another task, where you will create a diagram including all people who are important in your life. There are instructions on how to complete the diagram."* T distributes Intervention 2 (*Building a relationship map*).

T opens a new discussion with questions similar to those asked in the family section but now concerning the entire social support network. **If none of the participants mention physicians, T asks some physician-related questions, exploring whether participants view them as a source of support.**

At the end, T asks how social functioning can be improved and what changes participants can make to enhance it. T may write suggestions on the board.

PART 3 - Communication

1. Psychoeducation: Communication skills

T says: *"After discussing your relationships and their connection to illness outcomes such as fatigue, communication emerged as an important area to examine in detail."*

T explains the purpose of assertive communication, the difference between passive, aggressive, and assertive communication, and why expressing expectations helps in obtaining practical help and preserving relationships:
Purpose of assertive communication
Assertive communication serves to express needs, emotions, and opinions in a clear and respectful manner. The goal is to protect oneself without undermining the other person, fostering more authentic and cooperative relationships. When one is assertive, misunderstandings are reduced, tension decreases, and shared solutions become easier to find. This style allows one to be honest and direct without being passive or aggressive, creating a climate of trust and collaboration.

Passive communication
Passive communication is characterized by avoiding conflict and not expressing what one truly thinks. Those who communicate passively tend to say "yes" out of fear of disappointing others or creating tension, even when they would prefer to say "no." This often leads to feeling

overlooked or misunderstood, building frustration, and experiencing unbalanced relationships because others do not know the person's true needs.

Aggressive communication
Aggressive communication is a style in which one imposes their point of view, often through a harsh tone, criticism, or pressure. This approach may yield immediate results but generates distance, withdrawal, and resentment. Others may comply out of fear or to avoid conflict, but they do not feel respected. Over time, relationships weaken and cooperation becomes more difficult.

Assertive communication
Assertive communication is a balance between passivity and aggression. It consists of directly expressing one's feelings and needs while maintaining respect and listening to the other person. Being assertive means recognizing the value of both oneself and the other. This style facilitates cooperation, clarifies expectations, and helps address difficulties and limitations without unnecessary conflict.

Why expressed expectations help to obtain practical help
Clearly expressing expectations helps others understand what we truly need, avoiding the need for them to "guess." People are more willing to provide concrete help when the request is specific and honest. Without clear communication, we risk feeling disappointed and attributing shortcomings to others that actually arise from our failure to express our needs.

Why expressed expectations preserve relationships
Sharing expectations assertively reduces misunderstandings and prevents resentment. When we are transparent, we give the other person the opportunity to respond honestly and realistically, promoting balanced and reciprocal relationships. Stated expectations create space for dialogue, negotiation, and shared agreements. This strengthens the bond and makes the relationship healthier and more stable over time.

T writes on the board a structure for assertive communication:
Describe (fact) → Feeling (what you feel) → Need/Specific requested behavior
[e.g., "When you enter without asking if I need help with the groceries and I have to stand up quickly (situation), I feel overwhelmed and fatigued (feeling). Could you please ask me first whether I have enough energy today, or postpone it? (request)"].

2. Practical component
T invites participants to provide examples of effective and ineffective communication related to managing illness. T then presents an example of assertive communication with a family member and a non-assertive example (in therapist/client role), explaining them through the model.
If the group is not very interactive, T may propose scenarios and ask how participants would behave. For example: asking the physician to dedicate five additional minutes to discuss fatigue and treatment expectations.

Example of assertive communication:
"Doctor, in recent weeks I have experienced severe fatigue (situation). This makes me feel frustrated and helpless (feeling). I would like you to dedicate five minutes to discuss how the therapy affects my fatigue and which practical strategies we can consider (specific request)."

If the group remains inactive, T may directly describe examples to analyze together, such as:
(a) If the physician minimizes: "I understand that we are focusing on inflammation. However, fatigue limits my daily activities. May I leave you a diary of the past two weeks so you can review it later?" - How would you respond?
(b) If a family member reacts: "I didn't mean to offend you. I hadn't realized. How can I help you next time?" - This can be an excellent starting point for defining a concrete behavior together.

After listening to comments, T provides suggestions such as the importance of using first-person statements, making specific requests, and maintaining a calm tone. Finally, T asks: *"Which statements seemed most effective? Which were assertive and which were not? What obstacles emerged during the examples?"*

3. Obstacles to communication and boundary management

T says: *"Obstacles to communication represent all the barriers that prevent people from clearly expressing their needs and emotions."*

T invites participants to reflect on these barriers and lists them on the board to make them visible and easily identifiable. *"Among the most frequent obstacles are the fear of being perceived as weak, which leads to avoiding statements like 'I am tired' or 'I need help'; shame, which can block sharing of symptoms, fears, or personal difficulties; anger, which may transform into withdrawal, irritability, or impulsive responses; rigid family habits, such as environments where 'problems are not discussed'; and lack of time during medical visits or professional meetings, which may leave the person feeling rushed and unable to communicate everything they consider important."*
To improve communication, T proposes some practical strategies that can be integrated into daily life and within the context of illness. *"One strategy is using a shared signal within the family - a gesture or keyword that enables quick, non-confrontational communication of an immediate need, such as needing a pause or rest. Another strategy concerns the ability to set respectful boundaries, learning to say 'no' or 'let's talk about it later' without guilt and without aggression, thus protecting one's energy while maintaining cooperation."*

"Another useful tool is preparing brief scripts before medical appointments, allowing the person to arrive with clear ideas about what to say, which symptoms to report, and which questions to ask, reducing the risk of forgetting important information due to anxiety or time pressure. Finally, a fundamental step for more effective communication is learning to express emotions assertively, using first-person statements and describing what one feels without accusing the other. This approach, together with scheduling dedicated moments for discussion with family members, contributes to a more open, respectful, and collaborative relational climate."

4. Conclusion

T concludes this part by emphasizing that participants also play an active role as communicators: *"Attentive communication means being fully present in the moment, paying attention both to our own thoughts and emotions and to those of the person we are speaking with. By practicing this type of communication, we can deepen our connections with others, build stronger relationships, and foster a sense of empathy and understanding.*

Active listening goes hand in hand with mindful communication. It requires being fully engaged and attentive to what the other person is saying, without judging or interrupting. This type of *listening allows us to truly hear and understand the speaker's message, promoting more meaningful and productive conversations and, ultimately, improving our relationships."*

Homework

Assignment 1: Guided questions

T says: "*Write clear responses (maximum 200 words per question) to the questions in the worksheet* (T distributes Assignment 1) *regarding social support. Bring the completed worksheet to the next session for discussion."*

Assignment 2: How to better reward your friends and ask for their help

T says: *"To satisfy your emotional needs, it is important that relationships be mutually rewarding. Think about how you can reward your friends, help them understand you, strengthen your bond with them, and expand your social network. (*T distributes Assignment 2*). In the left column are eleven strategies useful for this purpose; in the right column, give examples of how you might integrate them into your daily life."*

Assignment 3: Plan and practice a conversation

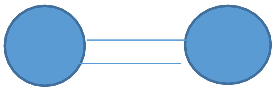
T says: *"Choose one of the following people: a family member, a close friend, or a healthcare professional. Plan a short conversation (max 10 minutes) to talk about your fatigue and your expectations (use the Describe → Feeling → Need/Specific requested behavior scheme). Before speaking, write the script in a few lines. After the conversation, complete the brief form* (T distributes Assignment 3). *Bring the completed form to the next session for discussion."*

Intervention 1A: Family relationships

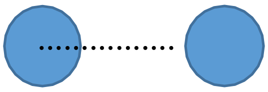
The purpose of this intervention is to deepen the understanding of one's family dynamics. This tool is used to represent an individual's relationships at a personal and social level; it helps to understand the family system involved in a person's life.

At the center you are placed with "Me," inside a large circle at the center of the diagram. Smaller circles around the central one represent the different relationships.

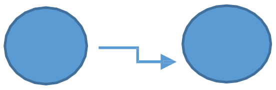
Lines connect the smaller circles to the central circle. The type of line provides information on the nature of the connection. For example, a double line indicates a strong and positive connection between the two elements.



A **solid line** indicates a **strong connection**.



A **dotted line** shows that the connection is **distant**.

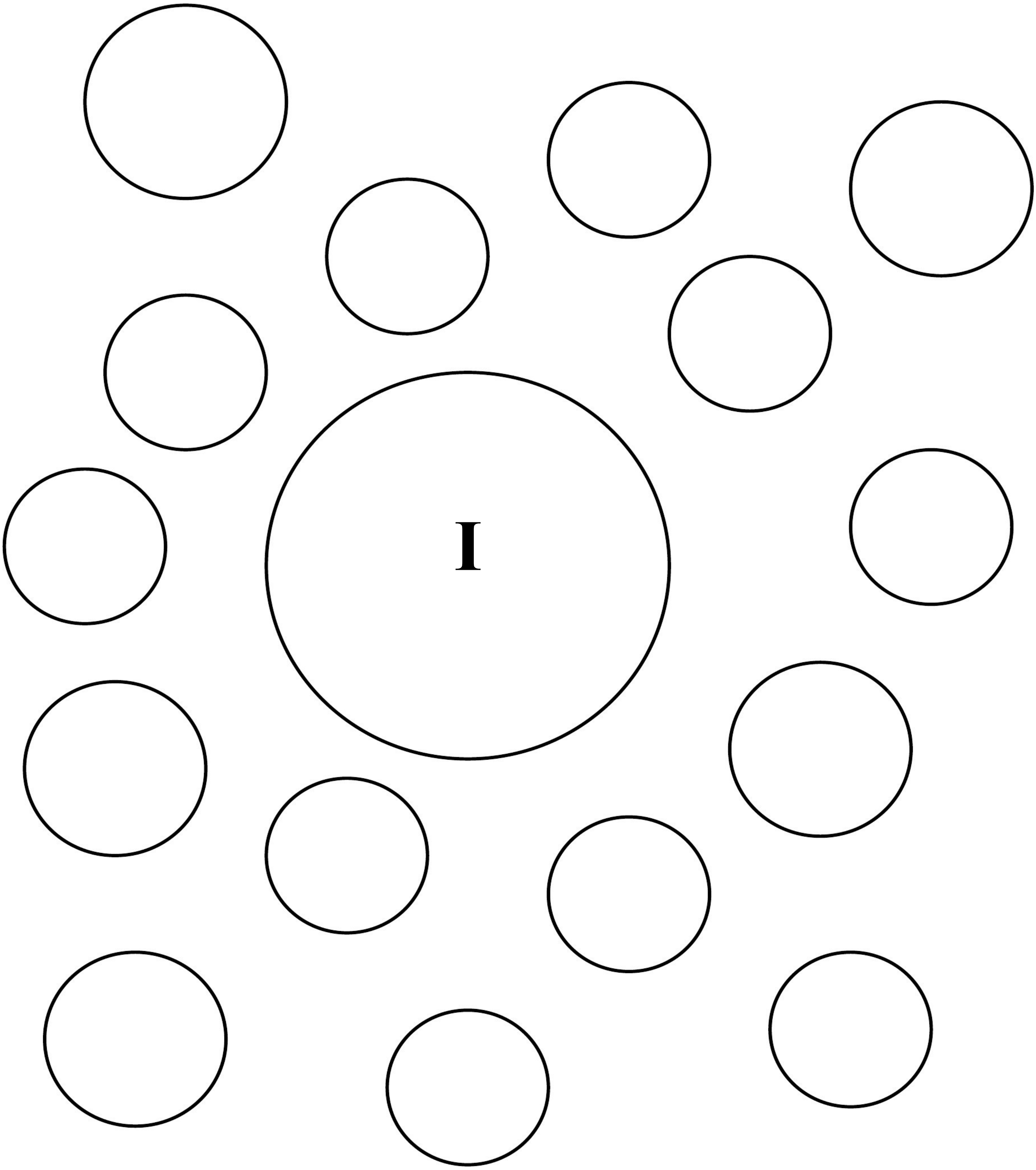


A **zigzag line** may indicate a **stressful connection**.

The **thickness of the line** can be used to show the intensity of the relationship.
The **arrows** at the ends of the line indicate **the direction of influence**.
If a relationship is **mutually positive and strong**, the line will have **an arrow on both sides**.
If the influence flows in **only one direction**, the arrow will be placed only at one end.

For example, if a person receives a service such as healthcare or social assistance, the arrow will point only toward the person at the center, because it is not a reciprocal relationship.

Your diagram



Intervention 1B: Family functioning

The following tables concern beliefs, organization, communication, power, and recursive dynamics in the family. In each part of each table, choose one of the descriptions that best describes you and your family (options indicated with a, b, c…).

1. BELIEFS (rules, relationships)

Beliefs are shared constructs that guide action and keep the family system in balance.

1.1 Beliefs about the family	
a. family as a secure base	b. family as a source of pressure
a. unity	b. individualism
a. harmony and peace	b. expressible conflict
1.2 Beliefs about rules and norms	
a. rigid rules	b. flexible rules
a. implicit rules	b. explicit rules
1.3 Beliefs about the person (self and others – family members)	
a. effective self	b. powerless self
a. reliable other	b. threatening other
a. flexible identity	b. rigid identity
1.4 Beliefs about the relationship	
a. reciprocal relationship (“I influence you, you influence me”)	
b. hierarchical relationship (“One leads, the other follows”)	
c. symmetrical relationship (equality, comparison)	
d. complementary relationship (differentiated functions)	
1.5 Beliefs about emotions	
a. expressed emotions	b. repressed emotions
a. vulnerability accepted	b. vulnerability forbidden
a. conflict as growth	b. conflict as threat

2. ORGANIZATION (Structure, roles, boundaries)

It concerns how the system is configured and distributes tasks, powers, obligations.

2.1 System structure	
a. hierarchical structure	
b. egalitarian / horizontal structure	
c. chaotic structure (absence of stable roles)	
d. structure with strong subsystems (coalitions, alliances)	
2.2 Roles	
a. defined roles	b. confused roles
a. stable roles	b. unstable roles
a. roles assigned by others	b. self-assumed roles
2.3 Boundaries	
a. rigid boundaries (low permeability)	
b. diffuse boundaries (too much permeability)	
c. clear boundaries (good balance)	
2.4 System life cycle	
a. stable system	
b. system in transition (e.g., birth, separations, job changes)	
c. system in acute crisis	

3. COMMUNICATION

3.1 Communication patterns		
a. circular (“I influence you and vice versa”)		
b. linear-causal (“you started it”)		
c. paradoxical (double, contradictory messages)		
d. avoidant (conflict avoidance)		
e. over-explanation / over-analysis		
3.2 Modes of expression		
a. direct	b. indirect	
a. explicit	b. implicit	
a. assertive	b. aggressive	c. passive
3.3 System communication rules		
a. “We do not talk about problems”		
b. “Anger is not allowed”		
c. “Harmony must always be maintained”		
d. “Everything must be shared”		
e. “The leader decides”		
f. (your example)		

4. POWER (distribution of influence)

4.1 Types of power
a. authoritarian
b. collaborative
c. delegated
d. oscillating
4.2 Control strategies
a. reward
b. punishment
c. emotional blackmail
d. silence / withdrawal
e. overperformance

5. FEEDBACK LOOPS (recursive dynamics)

a. **Functional cycles**	b. **Dysfunctional cycles**
• Support–gratitude • Request–adequate response • Boundary–respect	• Pursuit–withdrawal • Accusation–defense • Symmetrical escalation • Shame cycle • “Scapegoat” cycle

Intervention 2: Building a relationship map

Analyze the map of your relationships and identify which people can provide you with support.
You may classify people according to how close you perceive them to be:

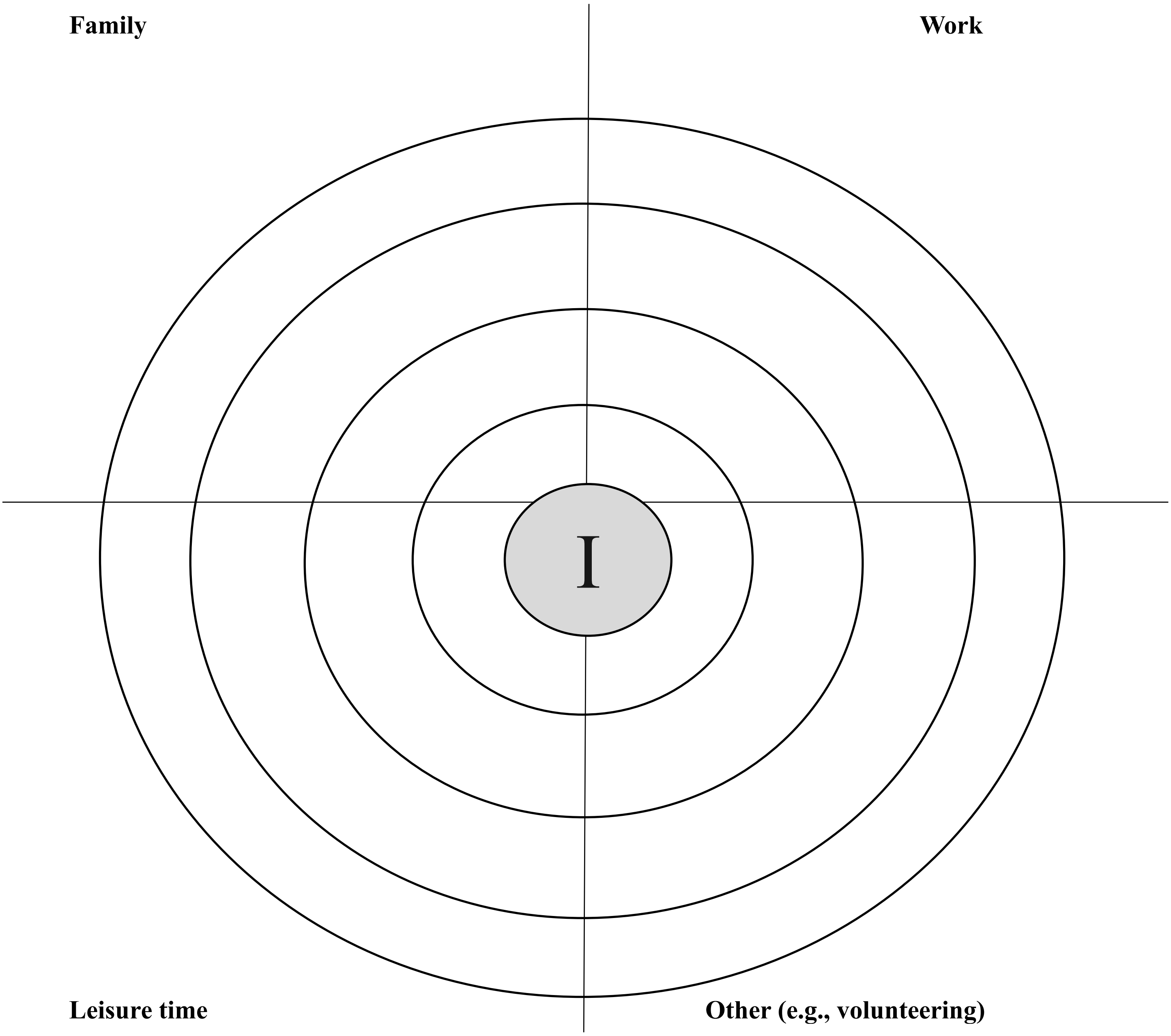
1. **People you consider a primary source of support:**
   These may be people you could not do without and to whom you are particularly close and attached, e.g., partner, sister, parents, friends.
2. **People to whom you are fairly close:**
   These may be colleagues, classmates.
3. **People you know you can turn to for solving specific problems:**
   These may be the doctor, the lawyer, the shopkeeper on the corner, the bank branch manager. They may represent sources of information or support.

These people may be:

- members of your family;
- childhood friends or neighbors;
- people you meet through work or professionals you encounter in life because they provide a service or are paid for the corresponding service;
- people you meet during your leisure time or during social activities (e.g., volunteering…).

PLACE THE PEOPLE…

First look at the circles on the next page and then try to place as many people as possible. The closer the circles are to the center, the more the people you indicate constitute a source of support for you.
It is important that you define where people are on the map. A colleague may actually be a good friend, someone close to you.
You may have a psychologically and emotionally distant relationship with your parents and may not consider them a primary source of support.



Type of support	Name (optional)	Role	Where to find them?
Someone I can trust and rely on			
Someone I can talk to freely			
Someone I can have fun with			
Someone who makes me feel good			
Someone who is a good source of information			
Someone who is a good source of useful and sincere advice			
Someone I can turn to when I have difficulties and problems			
Someone to share good news with			
Someone who helps me analyze myself			
Someone I feel close to			
Someone who encourages me and stimulates me toward new ideas, interests, and people			

Now that you have defined the map of your support network and where your main sources of support are located, you are able to think about how to extend it.

Assignment 1: Guided questions

Write clear responses (maximum 200 words per question) to the questions in the form concerning social support.

1. **How satisfied are you with your relationships/the current level of social support?** Do you have all the help you need? Are you satisfied with the quality and quantity?

2. **If you were to describe ideal relationships**, what would be different (concrete examples: more contacts, more practical help, emotional listening, less judgment)?

3. **If you decided to work toward achieving relationships closer to the ideal**, what concrete actions would you need to take (at least 3 measurable and achievable actions in the next 2 months)?

4. **What should you believe about yourself or others in order to be motivated to act?** (e.g., “I believe that asking for help does not make me a burden” or “I believe that small changes can bring benefits”).

Assignment 2: How to better reward your friends and ask for their help

Instructions: To satisfy your emotional needs, it is important that your relationships with others be mutually rewarding. Think about how you can reward your friends, help them understand you, strengthen your bond with them, and expand your social network. In the left column are eleven strategies useful for this purpose; in the right column provide examples of how you might integrate them into your daily life.

How to better reward my friends and obtain more support from them	**Examples**
1. Are you a “depressing” conversation partner? 2. “Do my friends need to understand that I am in the ‘validation trap’ and that I need to be validated?” 3. Learn to ask for help. 4. When you seek validation, also keep your interlocutor in mind. 5. Validate the validator. 6. Also talk about positive aspects: things you are doing that may be helpful to you. 7. If you talk about a problem, also propose a solution. 8. Do not appear to be your own worst enemy. 9. Initiate a positive relationship with positive activities. 10. Respect the advice offered to you. 11. Try to become part of a broader community.	

Assignment 3: Plan and practice a conversation

Instructions: Choose **one** of the following people: a family member, a close friend, or a healthcare professional. Plan a brief conversation (max 10 minutes) to talk about your fatigue and your expectations (use the Describe (fact) → Feeling (you feel) → Need/Specific requested behavior scheme). Before discussing it, write the script on paper in a maximum of 6 lines. After the conversation, complete this short form:

1. With whom did you speak (role)?

   ____

2. Date/time: ________________
3. Duration of the conversation (min): _______
4. What you said (1–2 sentences):_____________________________________

   ____

   ____

5. How the other person responded (1–2 sentences): ________________________

   ____

   ____

6. What concrete result was agreed upon (if present): _______________________

   ____

   ____

7. How you felt afterward: ____

   ____

   ____

8. What would you change next time?

   ____

   ____

   ____

SESSION 9: Stress management; Pain and fatigue in arthritis

Session goals:
The primary objective is to explore how stress affects fatigue in rheumatic diseases, to recognize one's personal stressors, and to learn concrete stress-management techniques, including simple relaxation strategies applicable in daily life.
The secondary objective of this session is to understand the relationship between pain, fatigue, and negative emotions, learning to identify the factors that intensify discomfort and to explore practical and psychological strategies to address them.

Pre-introduction

T opens the session with some open questions: *"How are you today? How have the past two weeks been?"*
Then invites participants to share the homework: *"How did you find the tasks? Were you able to explore the aspect of social support - was it useful? Did you find ways to improve communication?"*

PART 1 - STRESS

1. Introduction and psychoeducation

T introduces the topic of the day: *"What is stress for you? How would you describe it?"*
T writes the participants' terms and brief descriptions on the board around the word *'STRESS'*.

Then T summarizes: *"Stress is a natural physiological mechanism that is activated when a person perceives being unable to manage demands, events, or thoughts that generate emotional or mental tension. When faced with a threat or challenge, the body releases adrenaline and cortisol, activating the fight-or-flight response. Under normal conditions, balance is restored, but prolonged stress can have negative effects on physical and mental health. The response to stress varies according to experience, personal abilities, emotional state, and personality traits."*

T asks: *"According to you, what types of stress exist?"*

Then T summarizes:

"Acute stress
It is an immediate response to new or demanding situations, such as avoiding an accident; it may also derive from intense but pleasant experiences. Brief episodes are not harmful and help adaptation. Acute stress may, however, become severe in life-threatening situations, fostering disorders such as PTSD, or become episodic when it recurs frequently due to ongoing worries or work pressures, with possible negative effects on mind and body.

Chronic stress

It appears when a stressful condition lasts weeks or months, such as financial, family, or work problems. It can become so habitual that it is not recognized, even though it affects well-being. If unmanaged, it increases the risk of physical and psychological disorders: cardiovascular disease, hypertension, weakened immune system, gastrointestinal issues, anxiety, depression, irritability, and insomnia.
Understanding the link between stress and health is fundamental, especially during phases of life with many responsibilities, in order to adopt preventive strategies and protect quality of life. Uncontrolled chronic stress profoundly compromises psychophysical functioning; therefore, awareness of its effects is essential to develop effective management methods."

2. Stress and illness
T asks: *"A stressful situation you experienced in recent weeks? Was it connected in some way with the illness?"*

Then T asks: *"How does stress impact fatigue?"*
T explains: *"In rheumatologic diseases, stress can intensify fatigue. When the body perceives being unable to manage demands or difficulties, it releases hormones such as adrenaline and cortisol. If this state persists, stress becomes chronic and can increase inflammation, worsen pain, and make it more difficult to recover energy.*
People with rheumatologic diseases are particularly sensitive to the effects of stress, as the illness itself represents a constant source of tension and concern. External situations (such as family, work, or financial issues) may also contribute to maintaining a continuous state of stress, amplifying tiredness and reducing quality of life."

T asks/offers concrete examples:
"• An uncertain medical visit → increased tension → worsening of fatigue the following day.
• Overload of family responsibilities → hyperactivation → difficulty recovering physically."

3. Personal stressors
T explains the task and hands out a sheet (*Intervention 1: Personal stressors*): *"Write the main sources of stress present in your life. Rank them according to perceived intensity, from the most intense to the least intense. Indicate the level of stress they provoke on a scale from 1 (minimal stress) to 100 (maximum stress). Finally, explain how and to what extent the specific stressor influences or contributes to your level of fatigue."*

T explains that the hierarchy helps identify where to intervene first and asks participants to present their lists of stressors, discussing the major stressors (stressful situations). A crucial point is discussing how stress is connected to illness and, in particular, to fatigue. If participants are not very interactive, T proposes some stressors to start the discussion: work or bureaucratic deadlines; unpredictable illness symptoms; family conflicts; financial worries; the sense of losing control over one's routine.

Ultimately, T guides the discussion among participants to explore strategies already used to reduce stress: *"How do you deal with stress related to arthritis?"* Examples that may emerge include managing unpredictable symptoms, continually justifying oneself to colleagues or relatives, and a fear of worsening.

T concludes that recognizing stress is the first step in reducing its impact on fatigue.

4. Stress and fatigue: explicit connection

The therapist introduces the "stress–fatigue cascade," illustrating it also on the board: *"Stress → tension → worsening of sleep → increase in pain → increase in fatigue → reduction of activity → further stress."*
T then explains: *"It is a 'vicious cycle': when stress increases, the body becomes more tense, sleep worsens, and this intensifies pain and tiredness, reducing the ability to carry out daily activities. This reduction leads to feeling even more overwhelmed, further feeding stress."*

The therapist emphasizes that even small reductions in stress can generate a significant increase in energy, especially in people with arthritis, where stress and inflammation tend to reinforce each other. *"One of the most effective ways to reduce stress is to organize the day better, distributing energy more evenly."*

T introduces the task on priorities (*Intervention 2: Priority list*): *"Try to compile a weekly list of activities by distinguishing what is essential, useful, or optional, assigning each a high, medium, or low priority."*

Opening the discussion on the task, T guides the group to recognize that clearly defining priorities helps avoid overload, reduces daily pressure, and creates space for recovery. Finally, T highlights how good priority management supports better control of stress, one of the most relevant factors in reducing long-term fatigue in people with arthritis.

5. Relaxation techniques

T explains: *"The way we breathe directly influences how we feel. When anxious, we tend to breathe too quickly or too deeply, entering hyperventilation, which in turn increases anxiety symptoms. To relax, however, it is important to slow the breath: inhale normally and exhale slowly.*
With practice, it is possible to learn to recognize and correct dysfunctional breathing, beginning to train in moments of calm, then using the technique in stressful situations.

Diaphragmatic breathing, also called abdominal breathing, is typical of the relaxation state. When we are stressed, we tend to breathe rapidly with our chest; in such cases, shifting to diaphragmatic breathing can help us feel more relaxed. Diaphragmatic breathing is a skill that requires training; therefore, we recommend practicing daily when relatively calm, so that this type of breathing becomes easier when under stress."

T explains to participants how to practice breathing exercises:
"It is easier to practice when lying down or sitting. To ensure you are breathing correctly, you can place one hand on the chest and the other on the abdomen.
To begin, inhale normally through the nose, imagining directing the air toward the belly or diaphragm, 'bypassing' the chest. Feel the abdomen expand.
Exhale through the mouth, making a sound like 'shhh.' When exhaling, feel the abdomen flatten. Before inhaling again, expel all the air.
This rhythm should be fine; it is not necessary to pause between inhaling and exhaling. Continue breathing this way for a few minutes."

T invites participants to try the exercise and then asks whether they noticed differences in calmness, muscle tension, or other bodily sensations.

T concludes by explaining that stress management is one of the most influential factors in long-term fatigue and that slow, deep breathing reduces activation of the sympathetic nervous system, helping to decrease tension, pain, and fatigue.

PART 2 - Pain and fatigue

1. Psychoeducation: the link between pain and fatigue

T introduces the topic by explaining that pain in arthritis is not only a physical experience but involves biological, cognitive, and emotional systems.

T asks participants how often they feel pain during the day, what type of pain it is, and what their first associations with pain are. On the board, in the center, T writes *'pain'* and around it all associations, what it is connected to, what influences pain, or what pain influences (using arrows to mark direction).

T describes how the continuous presence of pain can increase fatigue through various mechanisms: muscle tension, reduced sleep, constant worry, and reduction of pleasurable activities. Pain can be amplified by stress, anxiety, and anger, but fatigue also reduces the cognitive resources needed to manage pain.

2. Strategies for pain

The therapist introduces the topic by stating: *"Now let's focus on psychological strategies useful for managing pain. In previous sessions we explored thoughts and emotions associated with fatigue; today we will try instead to identify those related to pain."*

The therapist then presents the task (*Intervention 3: Automatic thought record*) saying: *"Try to identify the pain, the situation, the thoughts and emotions associated with it, and attempt to reframe the thought in a more realistic way."*
To facilitate comprehension, the therapist may provide an example:

> *Automatic thought: "I will never be able to get better."*
> *Emotions: "I feel frustration and sadness because the pain limits me."*
> *Alternative thought: "There are harder days and better days; I can still work on what is under my control."*

Once the task is completed, T begins a discussion asking how participants found the exercise and invites them to share their examples. T proposes further questions, such as: *"At what times of the day do you feel more pain? Is there an activity or situation that increases it? Are there thoughts or emotions that accompany it? Which emotions do you tend to feel when the pain increases? Is there a strategy that you think might be useful?"*

T then draws attention to the ABC model, emphasizing the importance of using it as a daily self-management tool, not only for fatigue but also for pain. T takes examples from participants and writes on the board how the ABC model can be applied. T helps the group notice recurring patterns, and may also provide examples: worsening with stress or overload; intensification with lack of sleep; increase after conflicts or strong emotions.

3. Dealing with pain

T opens the discussion: *"What do you actually do when pain appears? Which strategies work better and which less? When pain surprises you, how do you react emotionally?"*

T then recalls that it is possible to integrate strategies addressed in previous sessions to correct dysfunctional behaviors. For example:

- *"We discussed the importance of pacing and the boom-and-bust cycle: setting limits and regulating the intensity of activities can reduce the perception of effort and pain."*
- *"In another session we talked about self-compassion. Reducing self-criticism ('I should be able to manage') helps decrease tension and fatigue; a kinder attitude toward oneself may also influence the subjective perception of pain."*

Finally, T asks participants whether any of these approaches, or others encountered previously, might be useful in their daily experience and invites them to provide concrete examples.

Homework

Assignment 1

T says: *"The task concerns strategies for managing pain. In the table, write the situations in which pain appears, how strong it is, which thoughts and emotions arise, which strategies you use, and whether they are effective."*

Assignment 2

T explains: *"Practice a relaxation technique every day (breathing) and note:*
- *level of stress before and after*
- *level of fatigue during the day*
- *any benefits or difficulties"*

T invites participants to share in the next session what they observed.

Intervention 1: Creating a hierarchical list of personal stressors

Instruction: Write down the main sources of stress present in your life. Arrange them according to perceived intensity, from the most intense to the least intense. Indicate the level of stress they cause on a scale from 1 (minimal stress) to 100 (maximum stress). Finally, explain how and to what extent each specific stressor influences or contributes to your level of fatigue.

Order by intensity	**Stressor**	**Stress level (1-100)**	**Influence on fatigue**
1.			
2.			
3.			
4.			
5.			
6.			
7.			
8.			
9.			
10.			

Intervention 2: List of priorities

It is essential to know what is important and what is not. If you are like most people, you probably spend a great deal of time on activities that have rather low priority (such as browsing the internet, ruminating, watching television) or that may be irrelevant to achieving your most important goals. Using the table below, list the activities that have high, medium, and low priority.

High priority	Medium priority	Low priority

Intervention 3: Record of automatic thoughts

Try to identify the pain, the situation, the associated thoughts and emotions, and attempt to reframe the thought in a more realistic way.

Type of pain	Situation	Automatic thought	Emotions	Alternative thought

Assignment 1: Strategies for managing pain

Write down the situations in which pain occurs, how strong it is, which thoughts and emotions emerge, and which strategies you use and whether they are effective.

Situations	**Pain level** (1-100)	**Thoughts**	**Emotions**	**Strategies used**	**Effectiveness of strategies**

SESSION 10: HEALTHY HABITS AND SLEEP HYGIENE

Session goal

To enhance participants' understanding of how sleep and fatigue interact, and to develop practical, personalized strategies, through psychoeducation and behavioural planning, to improve healthy habits, sleep hygiene, manage fatigue, and cope more effectively with negative emotions.

Pre-introduction

T begins the session with general, spontaneous questions such as: *"How are you today? How have the past two weeks been? Have there been any changes in fatigue?"*
Then T asks about the homework, inviting spontaneous sharing: *"How did the homework on stress and pain go? Did you find it difficult or was it useful?"*
T waits for spontaneous discussion. If participants struggle to start, T facilitates with: *"Would anyone like to share an example?"*

T summarizes by highlighting the importance of being aware of situations that trigger stress or pain and of strategies to overcome those situations.

Part 1 - Healthy habits and behaviours

Introduction

T says: *"Many people with arthritis report that fatigue limits their activities more than joint pain itself. Today we will work together on how daily habits and behaviours can influence our energy and well-being."*

1. Psychoeducation on fatigue and healthy habits

T illustrates the biopsychosocial model, which helps explain how thoughts, emotions, and daily behaviours can amplify or reduce the sensation of fatigue: *"The biopsychosocial model is essential for understanding how to support healthy habits and behaviours, because it considers the person as a whole: body, mind, and life context. According to this approach, fatigue, pain, and well-being do not depend solely on biological processes but are also influenced by emotions, thoughts, social relationships, lifestyle, and the quality of daily routines.*

Recognizing this interaction allows you to understand that, although you cannot control the illness, you can influence many factors that affect symptoms and energy. Small changes in habits, such as pacing, moderate physical activity, improved sleep, stress management, fatigue self-monitoring, and balanced nutrition, thus become powerful tools for reducing fatigue, increasing the sense of control, and improving quality of life. In other words, the biopsychosocial model helps you see how every daily choice can contribute, even gradually, to your overall well-being."

T encourages discussion on healthy habits and behaviours. T may write on the board, in the center, "healthy habits" and around it the healthy habits that participants already practice or wish to practice. T must distinguish these two categories (habits already performed and not yet performed) in order to focus on habits and behaviours not yet implemented, discussing with participants the reasons they do not perform them and how they could start. Then T also discusses healthy habits with the group, emphasising their importance. T concludes that a healthy lifestyle requires effort and active engagement.

2. Intervention 1 - "My day - energy"

Each participant receives a sheet on which to represent, through a timeline, the progress of their energy throughout the day. They are asked to note moments of decline and the activities or situations that precede them, to increase awareness of their personal patterns. The goal is to identify at least one moment in the day in which to insert a healthy habit.

T invites participants to share what they discovered, while T guides the group reflection on recurring elements and possible opportunities for change. T asks facilitative questions: *"What surprised you? Where do you see the possibility of inserting a small change?"*

3. Strategies for change

T asks questions such as: *"Which habits already help you manage fatigue? Which behaviours worsen it? What are the main obstacles you encounter when trying to change habits? What would help you overcome at least one of them?"*

The guided discussion explores strategies, difficulties, and facilitators related to changing habits. The group reflects on what already helps in fatigue management, which behaviours worsen it, and which obstacles arise when attempting change. The conversation strengthens personal motivation and self-efficacy, valuing participants' experiences and solutions. T concludes by naming all the strategies identified with the group, emphasising that strategies must be realistic and practiced frequently in order to be effective.

PART 2 - Sleep Hygiene

Introduction

T says: *"Now we will focus on sleep. Sleep is a crucial factor in fatigue: we know that many people with rheumatic diseases report disturbed sleep, interrupted nights, or non-restorative sleep. Today, we will try to understand why this happens and what we can do in daily life."*

1. Psychoeducation - the importance of sleep

T explains: *"Quality sleep plays a fundamental role in maintaining a healthy life. During the night our body goes through different stages, including deep sleep and REM (rapid eye movement) sleep, both essential for cognitive functions, memory consolidation, and emotional well-being.*

Lack of adequate rest can cause numerous health problems, such as increased stress, weakened immune functioning, and decreased cognitive abilities. Conversely, prioritizing sleep improves overall health and daily well-being.

Sleeping sufficiently and with good quality supports cognitive functioning, emotional resilience, and physical vitality. It is a key factor in maintaining optimal attention, *reducing stress, and promoting healthy ageing. Placing sleep at the center of our habits means taking a proactive step toward a balanced and more mindful life."*

T opens the topic of sleep problems: "The most common sleep problems are difficulty falling asleep and waking frequently during the night. These issues may be linked to anxiety, which can originate from negative thoughts and disrupt the ability to fall asleep. Another common problem is waking too early in the morning and being unable to fall back asleep, or simply not feeling rested upon waking. These problems may be related to depression. Another issue concerns sleeping too much, which can result from feelings of sadness and depression and/or an attempt to avoid thinking about the illness."

T assesses whether it is time to begin general discussion about sleep (*"How would you describe the quality of your sleep?").* If not, T concludes this part saying: *"Sleep hygiene refers to a set of habits and behaviours that promote more regular and restful sleep. Today we will discuss how to work on this."*

2. What is sleep hygiene?

T introduces the definition: *"Sleep hygiene refers to a set of habits and behaviours that promote more regular and restful sleep."*

T presents the main principles:

1. Regular and predictable routine
   - Going to bed and waking up at the same time every day
   - Avoiding long naps during the day
   - Creating a bedtime ritual that signals the body that it is time to slow down

2. Favourable environment
   - Quiet, dark bedroom at a cool temperature
   - Mattress and pillow suitable for joint pain
   - Removing electronic devices and blue light

3. Behaviours before bedtime
   - Avoiding caffeine and nicotine after the afternoon
   - Avoiding heavy evening meals
   - Avoiding activating activities (discussions, work, intense cognitive tasks)

4. Associating the bed ONLY with sleep
   - No TV, smartphones, tablets
   - If unable to sleep after 20–30 minutes, get up and return to bed only when sleepy

T opens discussion: *"Which of these rules do you already use? Which seem difficult? Why?"*

3. Link between sleep and other factors

T introduces: *"Sleep and fatigue have a circular relationship: poor sleep increases fatigue, and fatigue worsens sleep. Even when sleeping a 'sufficient' number of hours,* *many people with arthritis report waking 'more tired than before.' Other factors such as pain, inflammation, stress levels, and medications can also influence sleep quality. Let us try to recognize these patterns and the link between sleep and other factors."*

T writes a large word 'SLEEP' on the board and, around it, notes: pain, morning stiffness, nighttime awakenings, stress, anxiety, intrusive thoughts, morning fatigue, daytime sleepiness, irritability, and difficulty concentrating.

T asks: *"Which of these elements affect you the most? Which do you notice most often?"* After discussion, T concludes: *"As you have seen, sleep is not an isolated phenomenon: it is connected to the body, mind, and emotions."*

4. Intervention 2 - Building a sleep routine

T hands out the sheet *"Intervention 2: Sleep routine,"* saying: *"Write an evening and morning routine to maintain for two weeks. Indicate the required elements."* T then asks: *"Which changes do you think might be most realistic for you? Which seem difficult?"*

5. Strategies to improve sleep

T facilitates: *"Which strategies have you already tried to improve sleep? Which ones have worked and which have not?"*

T proposes some solutions: *"You can do stretching, relaxation techniques (long and deep breathing), listen to calm music, read something light, avoid screens, and write recurring thoughts in a journal."*

T connects with previous sessions: *"You can use the strategies learned in previous sessions to improve sleep as well:*

- *stress management → reduced physiological arousal*
- *pacing → less evening activity = less nighttime pain*
- *thought management → less rumination in bed."*

Conclusion

T summarizes the key concepts and the importance of healthy habits and behaviours. T also emphasises that sleep is a complex biological process influenced not only by the body but also by emotions and thoughts. T reminds participants that sleep hygiene consists of a set of habits that can significantly improve sleep quality and that routine is the most important element for long-term results. T also highlights that even small daily changes, if maintained consistently, can help reduce fatigue.

Finally, T invites participants to reflect and asks: *"What is the main point you are taking away from this session?"*

Homework

Assignment 1 - Sleep diary (symptom monitoring)
T says: “In the first homework task you must indicate each morning how you feel upon waking, the level of pain and stiffness, morning emotions and thoughts, as well as possible factors that influenced your sleep.”

Assignment 2 - Acquiring a habit
T says: “Choose one habit (other than improving sleep) to practice daily, noting each time it is performed and observing whether any changes, even small ones, are noticeable in your fatigue level. This homework helps maintain continuity between the session and daily life, supporting gradual but concrete change.”

Assignment 3 - A sleep routine
T says: “This homework was completed during the session, in which you built a sleep routine for the next two weeks. At home, check if you want to make any modifications and then try to follow it.”

Intervention 1: “My day - energy”

The horizontal line represents your day, with times and the main activities throughout the day (you may choose between a workday and the weekend). Mark with a curve (above the line) the trend of your energy (high, medium, low).

Note next to the low-energy points which activities or habits precede them (for example: “I was sitting for too long,” “I skipped my break,” “Stressful discussion,” “I did not sleep well”). Try to highlight at least one moment of the day in which a healthy habit could be inserted.

wake-up time bedtime

Intervention 2: Sleep routine

Planning for 14 days

Bedtime: ________
Wake-up time: ________

Evening ritual (choose 2–4):

1. ____
2. ____
3. ____
4. ____

Things to avoid in the evening:

☐ electronic devices after ___
☐ caffeine after ___
☐ stressful discussions
☐ stimulating activities
Other: ___________________________________

Environmental modifications:

☐ reduce light
☐ lower temperature
☐ eliminate noise
☐ change pillow/mattress position
Other: ___________________________________

Personal goal for 14 days:

Assignment 1: Sleep diary (symptoms and sensations)

To be completed every morning

Every morning fill in the *Diary* indicating how you feel upon waking, the level of pain and stiffness, morning emotions and thoughts, as well as possible factors that may have influenced your sleep.

Date: _______________

1. How did I feel upon waking?
☐ Rested
☐ Quite rested
☐ Tired
☐ Very tired

2. Pain upon waking (0–10): ______

3. Morning stiffness (minutes): ______

4. Predominant emotions in the morning:
☐ Calm
☐ Irritability
☐ Sadness
☐ Anxiety
☐ Other: ___________

5. Recurrent morning thoughts:

6. Factors that may have influenced sleep:
☐ Stress
☐ Pain
☐ Temperature
☐ Temperature
☐ Persistent thoughts
☐ Sleep during the day
Other: ___________________________________

Session 11: Summary of skills and integration

Session goal

Consolidate the skills acquired throughout the entire intervention, integrate self-management tools, and develop a personalized fatigue-management plan that can support participants in the long term.

Pre-introduction

T greets the participants and asks how they are and how the past two weeks have been. Then T asks how the homework related to healthy habits went. T encourages participants to share their experiences regarding the tasks.

Introduction

T asks questions about the entire intervention, such as: *"What was the easiest and most natural part of this intervention? What was the most difficult? Have you noticed changes in fatigue management compared to the beginning of the program?"*

T must emphasize the importance of viewing the program as a continuous process rather than something that ends with the final session.

Part 1 - Review of the main contents of the program

T says: *"Today we will review all the work carried out during all the sessions and develop a plan to manage potential critical situations that may occur in the future. In addition, we will touch on other strategies that may be helpful now that our work is coming to an end."*

T begins with a brief recall of the fundamental principles of the program, asking participants to name them while T writes them on the board. The list should include: *energy management and pacing, recognition and regulation of emotions, cognitive monitoring and restructuring, behavioral activation, assertive communication and social support, stress management, sleep, self-care and healthy habits, and sleep hygiene.*

T asks the questions: *"Which concepts or skills have helped you the most and why? To what extent have you been able to integrate that skill into your life? Did you encounter obstacles, and which ones?"*

In the end, T tries to understand whether some fundamental principles are still unclear or need to be repeated, and then summarizes the required principles together with the participants.

Part 2 - Recognizing possible obstacles and preventing relapses

T reminds participants that relapses or fluctuations in fatigue are normal, but that they can be managed as much as possible. T recalls the strategies for managing the boom and bust cycle.

T introduces the topic by saying that it is possible to think ahead about how to handle difficult moments or periods of worsening fatigue and asks: “What obstacles could hinder the maintenance of the new habits?”
T distributes the task (*Intervention 1: Early Warning Signs*) saying: *“Create a personal list of early signs indicating a possible relapse (physical, emotional, behavioral). As strategies for the early signs, use the techniques from the program (for example: cognitive restructuring, pacing, relaxation techniques).”*
T discusses with the participants the early warning signs and the ways and strategies to manage those situations.

Part 3 - Development of the individual fatigue-management plan

T says: *“Are there situations, thoughts, or emotions that still make you feel in difficulty (or that you believe could do so in the future)? Develop a plan in advance to manage them and thus also manage fatigue.”*
T distributes the task (*Intervention 2: The Fatigue-Management Plan*) saying: *“Write a concise version of the fatigue-management plan, as a reminder so that you can recall it. If in the future you find yourself in a difficult situation, it is likely that it will resemble another one you have faced in the past. Refer to previous cognitive restructurings that will help you face similar situations.”*

Participants may use their past cognitive restructurings as a form of continuous refreshment, if needed.

T asks participants to briefly present their own plan, and the group provides constructive feedback.

Part 4 - Strategies for maintaining skills after the group

T initiates discussion with the following questions: *“How can the tools be integrated into daily routines? What should be done when motivation decreases? Which practices become ‘non-negotiable’?”*
T emphasizes the importance of continuity, where small daily actions, routines, and micro-habits help sustain autonomy and encourage ongoing personal growth.

Homework

Assignment 1
Write a concluding reflection on:
– The skills acquired.
– The changes observed in your way of dealing with fatigue.
– How you imagine maintaining the improvements over time.
– Which aspects remain difficult and how to address them.

Assignment 2
Finalize and apply the fatigue-management plan.
Observe how it works in daily life and note any necessary adjustments.

Intervention 1: Early warning signs of relapse (physical, emotional, behavioral)

Draft a personal list of early warning signs that may indicate a potential relapse (divided into physical, emotional, and behavioral signs) and include for each the strategies you can adopt to address them.

	Early warning signs	**Strategies**
Physical		
Emotional		
Behavioral		

Intervention 2: The Fatigue-Management Plan

This plan consists of identifying and recording the specific situations that tend to trigger your fatigue. For each of them, you must record the automatic thoughts and related emotions that arise. Subsequently, you must formulate and write an alternative thought that is more balanced and constructive in order to carry out an immediate cognitive restructuring. Finally, in the designated section, you must indicate the additional practical strategies (e.g., pacing, relaxation techniques, sleep routine, social support) that you can activate to effectively manage the situation and mitigate its impact.

Situation	**Automatic thought**	**Emotion**	**Alternative thought**	**Strategy**

Assignment 1: Concluding reflection

Write a concluding reflection on:

A. The skills acquired.

B. The changes noticed in your way of dealing with fatigue.

C. How do you imagine maintaining improvements over time?

D. Which aspects remain difficult and how to address them.

Session 12: Closing session and follow-up planning

Session goal

Conclude the program, acknowledge the progress made, strengthen continuity of the skills acquired, and define a personal follow-up plan. The session also aims to celebrate the work accomplished, enhance motivation, and reinforce the sense of belonging and mutual support.

Pre-introduction

T greets the participants, asking how they are and how the last two weeks have been. T then asks participants to share their experience in applying the fatigue-management plan and the final reflections written during the week.

Introduction

T says: *"We have spent the past months working together to help you understand and recognize fatigue and other factors related to rheumatologic diseases. Now we have reached the final session of our work together."*

T focuses on whether participants feel ready to end the intervention. T should briefly speak with participants about the emotions they feel regarding the end of the intervention. If some participants feel anxious at the thought of the intervention ending and wonder whether they will be able to cope on their own, T pauses and discusses these fears with the group and the support strategies for moving forward independently.

Part 1 - Final review of the program

T begins the discussion: *"Looking back over the 24 weeks, what differences do you notice in yourselves? Is there something you now know how to do better?"* Each participant presents a turning point, small or large, and then the group provides comments in rotation (*"what I have seen change in you"*). T strengthens self-esteem and internal motivation.

T asks participants how they feel subjectively after these twelve sessions regarding the illness. If there has been improvement or worsening, T initiates a discussion in that direction. T may ask questions such as: *"Let's talk about what has improved and also about the areas you would like to improve in the future."*

T then asks participants about their preferred strategies (*pacing, meaningful activities, emotion regulation, cognitive restructuring, relaxation techniques, assertive communication, self-monitoring*) and reinforces continuity.

Part 2 - Follow-up

T explains that follow-up increases the likelihood of maintaining results and emphasizes the importance of micro-habits and light self-monitoring.
T hands out the assignment (*Intervention 1: Follow-up plan*), asking participants to write a plan for the next three months, including goals, habits, strategies, and support.

T opens a discussion on the completed task, focusing on the plans created by the participants. T asks: *"How can you recognize that you are moving forward or falling back? What will I do concretely to get back on track?"*

Part 3: Completing the questionnaires

T hands out all questionnaires administered at the end of the intervention and again explains how to complete them, stating that they are the same questionnaires completed at the beginning.
After completing the questionnaires, T asks participants to express their level of satisfaction with the intervention and provide suggestions on how it could be improved, in order to modify the intervention for future groups.

Conclusion

T summarizes the main themes: change, competence, resilience, continuity.

T encourages participants to remain as active as they were during the intervention, adhering to the strategies learned: *"I believe you have done tremendous work learning the various techniques taught during the intervention. However, as with any other skill, whether training, practicing a sport, or driving, you will improve, and the techniques will become more natural only with repeated practice. Improvement continues even after the intervention ends. For this reason, it is important that you keep practicing the techniques learned during treatment so that they become more natural and automatic."*

T thanks the participants and informs them that in the coming months, they will have two booster sessions to consolidate what they have learned.

At this point, if T believes that some participants need more intensive therapy, after the session T suggests additional targeted treatment.

Intervention 1: Follow-up plan

For the next three months and the skills learned during the sessions, answer the following questions.

1. **Goals for the next 3 months**

2. **Daily, weekly, and monthly habits**

3. **Strategies for addressing relapses and periods of high fatigue**

4. **People/resources to involve for support**

5. **Reminders or rituals to help you remember to use the skills**

Booster 1: Consolidation of the strategies learned and relapse prevention

Session goal

Strengthen the skills acquired during the program and encourage reflection on how they have been applied in daily life after the end of the intervention.

T opens the session with a sharing moment in which participants are invited to describe the progress achieved, the difficulties encountered in implementing the strategies, and what has been most helpful in managing fatigue.

This is followed by a brief psychoeducational review of the program's core concepts: fluctuations in fatigue, the role of emotions and thoughts, the importance of activity planning, and coping strategies. T explores with participants how these tools have been maintained over time and which obstacles have hindered their use.

The central part of the session is dedicated to relapse prevention: early warning signs and personalized strategies to address them promptly are discussed. Through concrete examples and group discussion, T reinforces self-efficacy and the ability to intervene before fatigue or stress increases.

T concludes the session with a summary of the most effective strategies and with the assignment to monitor one's energy levels and note which tools were applied.

Booster 2: Long-term maintenance and future planning

Session goal

Focus on long-term maintenance and on developing a sustainable fatigue-management plan.

T begins with a discussion of the assigned tasks, examining how participants managed the most challenging situations and which strategies proved most helpful in preventing relapses.

This is followed by an in-depth review of the self-regulation skills developed: managing difficult thoughts, recognizing emotions, using relaxation techniques, and maintaining healthy routines such as sleep, physical activity, and activity organization. T discusses with participants how to integrate these skills stably into everyday life, even in the presence of changes, stress, or new challenges.

The central part of the session is dedicated to creating a personal long-term wellness plan, which includes realistic goals, strategies for maintaining them over time, and resources to activate in difficult moments (family, healthcare, and social). The group, together with T, works to identify concrete ways to maintain motivation, develop rewarding habits, and continue the personal-growth process initiated during the intervention. T writes the proposals on the board.

T concludes the session with a collective reflection on the importance of mutual support, on the personal progress achieved over time, and on how each participant can continue to cultivate a satisfying and meaningful life despite the presence of arthritis and fatigue.