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THE IMPACT OF MENTAL HEALTH FACTORS ON DISEASE ACTIVITY IN PRIMARY SJÖGREN'S SYNDROME

by: LÁSZLÓ MÓDIS, MD

SUPERVISOR: ANTAL BUGÁN, PHD

CO-SUPERVISOR: ANTÓNIA SZÁNTÓ, MD, PHD

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By László Módis, MD

Supervisor: Antal Bugán, PhD
Co-Supervisor: Antónia Szántó, MD, PhD

Doctoral School of Health Sciences, University of Debrecen

Head of the **Defense Committee**:	Mariann Harangi, DSc
Reviewers:	Szabolcs Kéri, DSc
	Szilvia Szamosi, PhD
Members of the Defense Committee:	Ferenc Túry, PhD
	Oguz Kelemen, PhD

The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen
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1. Introduction

1.1 Theoretical background

1.1.1 The bio-psycho-social and spiritual (BPSS) model of health and disease

1.1.1.1 The bio-psycho-social (BPS) model of health and disease

The biopsychosocial (BPS) model, proposed by Engel in 1977, was developed to overcome the reductionism of the biomedical paradigm. It interprets health and illness not solely as biological processes, but as the result of interactions between biological, psychological, and social factors. In contrast, the biomedical model is based on the body–mind dualism, defines disease primarily through laboratory findings, and neglects subjective experiences, psychosocial circumstances, and the role of the doctor–patient relationship.

The intellectual roots of the BPS approach can be traced back to Schrödinger's definition of life and von Bertalanffy's general systems theory. From these stems its core principles, such as hierarchical systems interactions, circular causality, nonsummativity, equifinality, and homeostasis. Based on this, the development of disease can be understood as the interplay of predisposing, precipitating, and maintaining factors—for example, genetic vulnerability, stress, and lifestyle effects.

Attempts to further develop the model, such as the “life-context” approach, emphasize the integration of personal life history and the meanings attributed to illness. Although the BPS model has often been criticized for its theoretical vagueness and methodological uncertainties, empirical findings in biology, psychology, and the social sciences over recent decades increasingly support its validity. This underlines its applicability in understanding and holistically treating chronic and complex illnesses, including autoimmune diseases.

1.1.1.2 Spirituality

1.1.1.2.1 Definition of spirituality

Spirituality is a complex concept without a universally accepted definition. Most descriptions, however, share common elements: it is a biologically grounded and universal phenomenon expressed through connectedness and transcendence. Spirituality motivates individuals to seek contact with the numinous and search for meaning in life, realized through self-transcendence and the experience of unity with all existence.

In the approaches of Cloninger and Piedmont, transcendence plays a central role. Cloninger defines spirituality as an inner longing for immortality, achieved through identification with the wholeness of nature. In this view, self-transcendence represents a unifying state of consciousness, often attained through prayer or meditation. Piedmont similarly describes self-transcendence as a broader perspective, in which one perceives unity and an unbreakable bond with others and the world. It functions as a fundamental intrinsic source of motivation that can be expressed beyond religious contexts and is considered a broader concept than spirituality itself.

1.1.1.2.2 Spirituality and religiosity

Spirituality and religiosity are closely related but distinct concepts. Religiosity is tied to tradition, community, and institutions, while spirituality is a personal search for connection with the sacred. Thus, religious practice does not necessarily entail spiritual experience, just as spirituality can exist outside religious frameworks. The two often overlap but emphasize different aspects.

In modern society, religion is often seen as rigid and outdated, while spirituality appears liberating and attractive, yet both have drawbacks. The absence of rituals may foster excessive individualism, depression, and narcissism, while the “market of spirituality” can involve manipulation and exploitation.

Fromm distinguished between biophilic religion (life-affirming, liberating) and necrophilic religion (dogmatic, authoritarian). Biophilic religion exerts its beneficial effects together with spirituality. Ultimately, the two should not be opposed, but examined in terms of whether they stem from intrinsic motivation and genuinely connect to transcendence. Pargament argued that religion is the framework for meaning-making, while spirituality is its heart and soul.

1.1.1.3 The relation between spirituality and health

Numerous studies confirm that spirituality and religiosity positively affect health: individuals tend to live healthier lives, avoid harmful behaviors, and enjoy greater longevity. These effects are partly mediated by lifestyle but also by direct mechanisms. Research shows that spiritual practices can reduce mortality risk even after normalizing the statistical models for lifestyle factors.

Several factors contribute to this relationship: social support from religious communities, the spiritual framing of life events, and the role of religious/spiritual coping. Positive coping provides meaning and comfort, while negative coping may lead to guilt, anxiety, and depression.

Among spiritual practices, meditation is the most studied, showing benefits such as lowering blood pressure, enhancing immune function, and improving psychological well-being. Spiritual guidance and religious rituals also support coping with suffering and foster the development of inner resources.

1.1.1.4 Spirituality and chronic diseases

In chronic illness, the BPS paradigm emphasizes not only biological, psychological, and social aspects but also the importance of spiritual questions. Diagnosis often raises existential and religious concerns, where meaning-making and spiritual coping play a central role. A holistic approach that integrates spirituality can aid rehabilitation and the discovery of new life goals.

Research shows that severe illness can be seen as a spiritual journey or teacher, fostering post-traumatic growth. Frank's theory identifies three narratives of coping: restorative, chaos, and quest stories, each reflecting different ways of engaging with suffering.

However, integrating spirituality into health models remains controversial. Critics argue that much research lacks scientific rigor, spirituality in medicine may pose ethical risks, and

religious elements can be misapplied in therapy. Furthermore, negative religious coping may lead to guilt, doubt, and psychological distress.

1.1.1.5 Biological background of the interplay between spirituality and health

Psychoneuroimmunology (PNI) research provides clear evidence of the link between spirituality and physical health. Religious-spiritual practices have been associated with increased immune cell counts and favorable cortisol regulation in HIV-positive men and cancer patients. Hungarian findings suggest that religious/spiritual struggles may independently lead to neurobiological changes rather than being secondary to depression.

Meta-analyses show that spiritual interventions (e.g., mindfulness) can improve mental health and stabilize neuroendocrine-immune processes, especially among cancer survivors. Although studies are still limited, current evidence supports the practical relevance of spirituality in physical health, not only its theoretical importance.

1.1.2 Psychoneuroimmunology

1.1.2.1 Introduction to psychoneuroimmunology

Psychoneuroimmunology (PNI) emerged in the 1960s and studies the interaction between the nervous and immune systems as mediated by psychological factors. Stress plays a central role: through the HPA axis it can shift cytokine balance, weakening immunity and contributing to allergic and autoimmune processes. Chronic stress and maladaptive coping reduce natural killer cell activity and increase vulnerability to cardiovascular, metabolic, and cancerous diseases.

The key terms in PNI are coping and control. Effective coping requires a sense of control, which can be strengthened by social support, favorable environments, and positive emotions such as love, hope, and humor, while weakened by loneliness, pessimism, and depression. Animal studies have also shown that social behavior modulates immune responses, underlining the social embeddedness of psychoimmunological competence.

1.1.2.2. Interactions between the neuroendocrine- and immune systems

The foundation of PNI lies in the interaction between the nervous and immune systems, both serving adaptation and homeostasis. These interactions occur at multiple levels: across the whole organism, between organs, and at the cellular level. Examples include the anti-inflammatory role of VIP and other neuropeptides, the complex interplay between the

sympathetic nervous system and immune cells, and the anti-inflammatory effects of cholinergic signaling.

A classical pathway is the HPA axis with glucocorticoid-mediated immunomodulation, whose dysfunction can contribute to autoimmune diseases and psychological symptoms. Sex steroids also play a key role, as illustrated by symptom changes during pregnancy. Additional processes include immune cell opioid production and the regulation of hormone and neurotransmitter receptors.

Overall, the neuroendocrine and immune systems form a complex network through shared mediators and receptors, the mapping of which will benefit from advanced omics approaches.

1.1.2.3. Analogies between mental and immune functions

One key analogy in PNI is the concept of the self, which holds central importance in neuroscience, psychology, and immunology alike. The idea of the immune self is crucial for understanding autoimmunity and tolerance, yet it remains uncertain and evolving. Beyond the classical self–non-self theory, newer approaches—such as Jerne's autoreactive network theory and Matzinger's danger theory—offer alternative explanations of immune function. Processes like thymic selection, peptide-HLA complexes, and heat shock proteins also play major roles in shaping immune identity.

From Tauber's philosophical perspective, the immune self is not a fixed entity but a dynamic process shaped by experiences. Identity emerges through the interaction of biological and psychological dimensions.

Another analogy is cognition: the immune system perceives signals from its environment as patterns, which it processes into representations. This view provides an alternative to clonal selection theory and emphasizes the immune system's capacity for learning, memory, and adaptation.

1.1.2.4 Psychoneuroimmunology of autoimmune diseases: rheumatoid arthritis

According to the PNI approach, neuroendocrine dysfunction, psychological stress, and certain personality traits influence the onset and progression of autoimmune diseases, including rheumatoid arthritis (RA). Dysregulation of the HPA axis and altered cortisol and prolactin responses contribute to inflammation. Personality traits such as perfectionism and stressful life events also increase risk.

Inflammatory cytokines affect not only disease activity but also mood and behavior. A positive outlook and internal control are linked to better outcomes, whereas depression and helplessness worsen prognosis.

Cognitive-behavioral therapy, psychoeducation, mindfulness, and hypnotherapy can reduce symptoms, improve quality of life, and complement pharmacological treatment. Thus, the psychoneuroimmunological perspective offers complex, holistic therapeutic options in RA.

1.2 Primary Sjögren's Syndrome

1.2.1 Brief description of the disease

Sjögren's syndrome (SS) is a chronic autoimmune disease that primarily affects the lacrimal and salivary glands, leading to dryness of the eyes and mouth, fatigue, joint pain, and various extraglandular manifestations (e.g., vasculitis, neuropathy, interstitial lung disease, lymphoma). It occurs predominantly in women (9:1 ratio) and can appear as a primary condition or as secondary to other autoimmune diseases. Common biomarkers include ANA, anti-Ro/SS-A, and anti-La/SS-B antibodies, while minor salivary gland biopsy is key for diagnosis.

1.2.2 Pathogenesis

Its pathogenesis centers on abnormal activation and apoptosis of epithelial cells, causing inflammation, autoantigen release, and T- and B-cell activation. Cytokines, interferons, and BAFF amplify these processes, leading to chronic immune response, autoantibody production, and an increased risk of lymphoma.

1.2.3 Diagnostics

Patients most often present with glandular symptoms, but the classification system also includes those with extraglandular manifestations to ensure proper care.

Lacrimal gland dysfunction is assessed with the Schirmer test and Ocular Staining Score, while salivary dysfunction is measured by sialometry. Minor salivary gland biopsy has both diagnostic and prognostic value, as ectopic germinal centers indicate a more severe course. Among serological tests, anti-Ro/SS-A positivity is the key marker. According to the ACR/EULAR criteria, at least four points are required for diagnosis, including either serological or histological positivity.

1.2.4 Disease activity

The ESSDAI (EULAR Sjögren's syndrome disease activity index) allows for the objective measurement of disease activity and the separation of homogeneous patient groups. Symptoms are classified according to 12 domains, and based on the score, disease activity is classified as low, moderate, or high. The ESSPRI (EULAR Sjögren's syndrome patient reported index) measures the severity of the three leading symptoms of the disease (pain, dryness, fatigue) as experienced by the patient on a 10-point scale and then asks about the feeling of dryness experienced in each part of the body.

1.2.5 Therapy

Although prognosis is generally good, quality of life is significantly impaired. No effective treatment exists for fatigue; glandular symptoms are managed with tear and saliva substitutes or pilocarpine. Systemic immunosuppressive therapy is used in cases with at least moderate activity. Among targeted therapies, rituximab is currently available in Hungary.

1.2.6 Epidemiology

The disease typically begins in middle age, with diagnosis often delayed by several years. Incidence and prevalence figures vary widely across countries, partly due to differing diagnostic criteria. Lowest icinódence was reported in France (0.7/100,000) and the highest in Canada (26.1/100,000). Prevalence is ranging from the lowest in France (22–32/100,000) to the highest in China (330–770/100,000).

1.3 Hypotheses

Temperament and character dimensions, together with other psychological factors, influence the onset, course, and activity of the disease.

Biological activity indicators, such as pSS-specific autoantibody levels, correlate more with biological parameters, while subjective complaints correlate more with psychological and spiritual elements.

Among personality traits, we expected harm avoidance to be the strongest predictor of subjective disease burden (ESSPRI), as it is associated with neuroticism and serotonergic functioning.

Anxiety, depression, low self-esteem, and poor social support were hypothesized to be associated with higher activity.

Spirituality was expected to be a protective factor, but its effect may vary: individual spiritual practices tend to be beneficial, while religiosity may have a negative effect.

Spirituality was expected to have a beneficial effect not only on subjective symptoms but also on immune parameters.

2. Literature review

2.1 Psychoneuroimmunology of the disease in focus: neuroimmunomodulation in Sjögren's syndrome

2.1.1 Effects of the nervous system on the immune functions

The interaction between the central nervous system (CNS) and the immune system is crucial in pSS, especially in mediating psychological influences on biological processes. The anti-inflammatory reflex has been proposed but not conclusively proven, with vagus stimulation and lymphocyte recruitment as possible mechanisms. Catecholamines play a regulatory role, as Th1 lymphocytes are activated via β2-adrenergic receptors, influencing disease progression. The most important neuroendocrine pathway is the HPA axis, whose dysfunction is associated with psychological changes and reduced elimination of Th1 precursors. Estrogen and the HPG axis also contribute, particularly in perimenopausal women. Finally, local neuroendocrine mechanisms affect salivary gland function, with VIP shown to reduce inflammation and improve secretory activity.

2.1.2 Effects os the immune functions ont he central nervous system

The interaction between the nervous and immune systems is reciprocal, as seen in fever and in immune effects on the HPA axis. Proinflammatory cytokines trigger sickness behavior, leading to fatigue and reduced social activity, involving the limbic system. Cytokines also regulate synaptic function: TNFα and others from microglia play key roles in synaptic plasticity. Overall, in pSS, immune mechanisms significantly affect the CNS, contributing to affective symptoms and maladaptive stress responses, though these phenomena cannot be explained solely by neural changes.

2.2 Overview of research outcomes concerning mental health in primary Sjögren's syndrome

In line with the BPS and BPSS models, a study applied the BETY-Biopsychosocial Questionnaire to 91 patients at hospitalization and after one week of treatment. Results significantly correlated with multiple quality of life, pain, and psychological measures, as well

as ESSPRI scores. This confirms that assessing biopsychosocial dimensions is relevant in pSS, and the questionnaire is a useful tool for comprehensive patient follow-up.

2.2.1 Depression and anxiety

In Sjögren's syndrome, the most frequent psychological disorders are depression and anxiety. Contributing factors include chronic illness, fatigue, sleep disturbances, and a typically high level of neuroticism. Patients with depression show higher disease activity, elevated ESR, stronger pain, more unemployment, and lower education. Depression also impairs cognition (working memory, executive and verbal memory) and is strongly linked to fatigue, considered its main independent predictor. ESSDAI and ESSPRI scores negatively correlate with depression, anxiety, and quality of life. Anxiety occurs at least as often as depression, associated with anti–α-melanocyte-stimulating hormone antibodies as well as oral and swallowing difficulties. It clearly reduces quality of life, though its origins and triggers remain poorly understood and warrant further research.

2.2.2 Personality

Several studies suggest characteristic personality traits in pSS. Early MMPI research showed elevated hypochondriasis, hysteria, and depression scales, forming a "V-type" conversion pattern linked to psychogenic pain. This was confirmed in a Finnish sample, with one study emphasizing hypochondria and hysteria, and another depression, but showing 77% agreement overall. Using the EPQ, psychoticism, neuroticism, and obsessiveness were identified as typical traits, reinforcing the role of hypochondria. A Serbian NEO PI-R study found high neuroticism with low extraversion and agreeableness, resembling rheumatoid arthritis profiles. Although evidence remains limited, findings indicate that certain premorbid personality traits may influence the onset and course of the disease.

2.2.3 Stress, coping strategies, resilience

A Swedish study found that in pSS, mental fatigue is the main stressor, often leading to low mood and isolation, though patients frequently showed a "fighting spirit." Social support proved crucial for adaptive coping. Alongside fatigue, dryness of eyes and mouth and sleep disturbances were the most burdensome symptoms, and patients reported higher stress levels than cancer patients. Key social stressors included unemployment and low education, with women's disadvantaged position further increasing vulnerability. pSS patients also reported

more negative life events overall, most often related to the loss of close relatives. Premorbid coping strategies often involved maladaptive patterns such as denial and emotional withdrawal. One of the few studies on resilience showed that higher resilience reduced depression, anxiety, and fatigue but was unrelated to disease activity, highlighting the need for further research in this area.

2.2.4 Cognitive functions

Among cognitive impairments in Sjögren's syndrome, the most common are deficits in executive functions and verbal memory, strongly linked to pain, depression, and mental fatigue. Cognitive symptoms may precede disease manifestation by up to two years, making them early predictors. Illness-related cognitions, especially pain catastrophizing and negative illness appraisal, significantly reduce quality of life, even more than in other autoimmune diseases, underscoring the importance of psychoeducation and cognitive-behavioral therapy.

2.2.4.1 Mental fatigue

Mental fatigue is the most disabling symptom, severely affecting daily functioning and quality of life; recommended management focuses on teaching exercises to reduce fatigue.

2.2.5 Other mental symptoms

2.2.5.1 Sexuality and body image

In pSS, many symptoms have both biological and psychological origins. One such symptom is sexual dysfunction, linked partly to vaginal dryness and partly to psychological factors. A 2017 study showed that women with pSS were significantly less satisfied with their sexual life compared to healthy controls, though the exact pathogenesis and psychosocial impact remain unclear. Body image disturbance is also important, influenced mainly by disease activity, oral health, and anxiety.

2.2.5.2 Quality of life

Quality of life is a key research focus, as most patients report significant impairment. In a Dutch cohort, 83% reported reduced quality of life, primarily due to mental fatigue, tendomyalgia, joint involvement, comorbidities, and limited mobility. Data from China highlighted the major role of pain and fatigue. Accurate assessment of quality of life is crucial for developing effective therapeutic strategies.

3. Study population and methods

3.1 Participants

The study population consisted of patients from the Autoimmune Sjögren Outpatient Clinic at the University of Debrecen. Inclusion criteria were confirmed primary Sjögren's syndrome and preserved cognitive function. Patients attend follow-up visits every 3–6 months. In the first phase, 127 patients were assessed, with 117 included in the final analysis (105 women, 12 men; mean age 59.6±13.2 years). In the second phase, focusing on the role of spirituality, 112 patients were included (101 women, 11 men; mean age 59.9±12.2 years). The study followed the Declaration of Helsinki and was approved by the Institutional Ethics Committee (approval no. 5614-2020). All participants provided written informed consent.

3.2 Study variables

3.2.1 Sociodemographic factors

At study entry, a questionnaire recorded sociodemographic data: gender, age, type of residence, education, smoking, chronic illnesses, marital status, and satisfaction with family relationships. In the second survey, we also assessed religiosity, spiritual commitment, denominational affiliation, and the regularity and weekly duration of individual spiritual practices (e.g., prayer, meditation). Practices performed at least once a week were considered regular.

3.2.2 Biological variables

Biological variables were defined as laboratory results from routine blood tests collected during follow-up visits, in parallel with questionnaire completion. These included cell counts (neutrophils, lymphocytes, platelets), hemoglobin, complement levels (C3, C4, CH50), as well as serum levels of immunoglobulin G, rheumatoid factor, and the autoantibodies anti-Ro/SSA and anti-La/SSB.

3.2.3 Psychological variables

3.2.3.1 The Temperament and Character Inventory (TCI)

After blood sampling and medical examination, patients completed the 240-item revised Temperament and Character Inventory (TCI-R) using a 5-point Likert scale. The questionnaire includes four temperament (novelty seeking, harm avoidance, reward dependence, persistence) and three character scales (self-directedness, cooperativeness, self-

transcendence). Temperament has a genetic basis and correlates with neurotransmitter levels, while character dimensions reflect personality maturity and subjective well-being.

3.2.3.1.1 Temperament traits

Temperament consists of innate traits observable from early childhood and partly predictive of later behavior. These traits are rooted in implicit, procedural, and presemantic memory and are closely linked to neurotransmitters: novelty seeking is associated with dopamine, harm avoidance with serotonin, and reward dependence with noradrenaline. Their emergence follows an evolutionary hierarchy: harm avoidance appears in all animals, novelty seeking in some species, and reward dependence only in reptiles and more advanced animals.

3.2.3.1.1.1 Novelty seeking

Novelty seeking is an inherited tendency to pursue new stimuli and rewards while avoiding punishment. High levels are linked to impulsivity, exploratory behavior, irritability, and distractibility, whereas low levels correspond to thoroughness, loyalty, and persistence. It is associated with the dopaminergic system, especially midbrain neurons that form the Behavioral Activation System (BAS), which drives reward-seeking and punishment avoidance. Persistently high dopaminergic activity is often seen in ADHD and substance use. Its subscales are:

- *Exploratory excitability (NS1)*
- *Impulsiveness (NS2)*
- *Extravagance (NS3)*
- *Disorderliness (NS4)*

3.2.3.1.1.2 Harm avoidance

Individuals with high harm avoidance tend to be cautious, anxious, and shy, whereas those with low levels are confident, calm, and energetic. Harm avoidance is linked to the Behavioral Inhibition System (BIS), involving the septohippocampal system, serotonergic pathways, and cholinergic projections. Its subscales are:

- *Anticipatory worry (HA1)*
- *Fear of uncertainty (HA2)*
- *Shyness with strangers (HA3)*
- *Fatigability and asthenia (weakness) (HA4)*

3.2.3.1.1.3 Reward dependence

Reward-dependent individuals are socially sensitive, empathetic, and persistent, placing high value on praise and social reinforcement. In contrast, those with low reward dependence are more emotionally detached, less responsive to social cues, and quickly lose interest in unrewarding activities or relationships. Reward dependence is associated with the noradrenergic system, which is crucial for learning and forming new associations. Anatomically, major noradrenergic pathways originate in the locus coeruleus and project broadly to limbic structures (hippocampus, amygdala, septum) and the neocortex. Its subscales are:

- *Sentimentality (RD1)*
- *Openness to warm communication or social sensitivity (RD2)*
- *Attachment (RD3)*
- *Dependence on approval by others (RD4)*

3.2.3.1.1.4 Persistence

Individuals with high persistence are determined, ambitious, and often perfectionistic, achieving outstanding performance. In contrast, those with low persistence tend to be indecisive and easily discouraged. Neurobiologically, persistence is associated with brain reward and motivation circuits, particularly the ventral striatum, anterior cingulate, and orbitofrontal cortex (Brodmann area 47). Its subscales are:

- *Eagerness of effort (PS1)*
- *Work hardened (PS2)*
- *Ambitious (PS3)*
- *Perfectionist (PS4)*

3.2.3.1.2. Character traits

Character refers to individual differences in responsiveness shaped by self-concepts. While temperament is genetically based and rooted in implicit memory, character builds on explicit, declarative memory with epigenetics as its biological background. Depending on the scope of self-concepts, three levels can be distinguished: autonomous individual, social, and universal. These correspond to the character subscales: self-directedness, cooperativeness, and self-transcendence.

3.2.3.1.2.1 Self directedness

Self-directedness is the most reliable indicator of the presence or absence of personality disorders. It reflects self-determination—the ability to control and adapt behavior in line with

chosen goals and values. It develops through stages of taking responsibility, identifying meaningful goals, building problem-solving skills, and achieving self-acceptance and inner harmony. Its subscales are:

- *Responsibility (SD1)*
- *Purposefulness (SD2)*
- *Resourcefulness (SD3)*
- *Self-Acceptance (SD4)*
- *Congruent Second Nature (SD5)*

3.2.3.1.2.2 Cooperativeness

Cooperativeness represents the next stage of character development, reflecting one's ability to identify with and accept others. The scale spans between willingness to cooperate and self-centered hostility. Low cooperativeness is a common feature across all personality disorders. Individuals with high cooperativeness are tolerant, empathic, and helpful, while those with low levels tend to be hostile and self-focused. Traits such as empathy, generosity, and respect for others' rights are considered signs of maturity in developmental psychology and are emphasized in various religious traditions as markers of advanced moral character. Its subscales are

- *Social acceptance (CO1)*
- *Empathy (CO2)*
- *Helpfulness (CO3)*
- *Compassion (CO4)*
- *Principles (CO5)*

3.2.3.1.2.3 Self-Transcendence

Self-transcendence refers to the ability to identify with what lies beyond the self, grounded in the recognition that everything in the world forms part of a greater whole. This manifests in the state of "unitive consciousness," where boundaries between self and others dissolve and the individual experiences themselves as an integral part of creation. According to Maslow, people with high self-transcendence often experience moments of absorption or self-forgetfulness, where deep concentration leads to transpersonal identification. Such experiences foster spiritual acceptance and insights that transcend analytical understanding. Like the other character dimensions, the subscales of self-transcendence can be viewed as steps of a developmental process:

- *Self-Forgetfulness (ST1)*
- *Transpersonal Identification (ST2)*

- *Spiritual Acceptance (ST3)*

3.2.3.2 Beck Depression Inventory (BDI)

To assess depressive symptoms, we used the short Hungarian version of the Beck Depression Inventory, consisting of 9 items. The questionnaire evaluates factors such as social withdrawal, sleep disturbance, fatigue, hypochondria, pessimism, and self-blame. Responses were given on a 0–3 Likert scale, with higher scores indicating greater symptom severity.

3.2.3.3 State-Trait Anxiety Inventory (STAI)

To measure anxiety, we used a 40-item questionnaire that separately assesses state and trait anxiety. State anxiety reflects momentary, situation-dependent distress, whereas trait anxiety indicates a stable predisposition to anxiety. Each subscale consists of 20 items, rated on a 4-point Likert scale, with higher scores reflecting higher anxiety levels.

3.2.3.4 Basic Self-Esteem (BSE) Scale

The essence of basic self-esteem is the acceptance of intrinsic needs—primarily the need for love and, in an analytical sense, sexual and aggressive instincts. Basic self-esteem is also trait-like, regardless of how the individual currently feels about themselves.

3.2.3.5 The Medical Outcomes Study Social Support Survey (MOS-SSS)

Social support is essential for mental and physical health, as it provides experiences of love, care, appreciation, and belonging. It can be measured with questionnaires that identify its different forms. In Hungarian studies, three main types were distinguished: emotional-informational support, support based on positive social interaction, and instrumental support.

3.2.3.6 Spiritual Trascendence Scale (STS)

Spiritual transcendence is regarded as an independent personality factor, assessed with the Spiritual Transcendence Scale. The scale consists of 24 items and a later study identifies five subscales in it: joy of prayer and meditation, universal connectedness, closeness to the deceased, unity of humanity, and the sense of a higher purpose.

3.2.4 Disease activity/disease burden

In assessing pSS disease activity, the main outcomes were disease activity and burden. Subjective activity was measured by the ESSPRI questionnaire, evaluating dryness, fatigue, and pain. Objective activity was determined by the ESSDAI index, covering twelve organ

domains. Additionally, SSA and SSB autoantibodies were considered as outcome variables, as they are present in most patients and indicate more severe disease progression.

3.2.5 Statistical analysis

Following data collection, statistical analyses were performed. In the first study, machine learning-based statistical methods were used, while in the second study, traditional statistical tests were applied.

3.2.5.1 Machine learning statistics

Data processing was performed in Python using scikit-learn. The dataset was split into training (80%) and test (20%) sets and standardized with Z-transformation. Feature selection was done with LASSO, and variable importance was assessed by permutation methods. Three algorithms were applied to predict ESSPRI, SSA, and SSB levels: LASSO regression, elastic net, and support vector regression. Model performance was evaluated using R^2 and MSE with 10-fold cross-validation, repeated 100 times. Analyses were run with four different input sets: biological, psychological, sociodemographic, and combined variables.

3.2.5.2 Traditional statistics

Four patients were excluded due to incomplete responses, and analyses were conducted with SPSS. Patients were grouped in two ways: spiritual vs. non-spiritual, and religious vs. non-religious. This resulted in 48 non-spiritual and 60 spiritual participants, while 55 were classified as non-religious and 53 as religious. Group comparisons were performed using t-tests or Mann-Whitney U tests depending on distribution, with transformations applied when necessary. The effects of spirituality, prayer/meditation, and its duration were assessed through linear regression. In addition, binary logistic regression was used based on the main markers of disease activity and burden (ESSDAI, ESSPRI, SSA, SSB). All regression analyses were adjusted for potential confounders such as gender, age, disease duration, residence, education, marital status, smoking, religiosity, spirituality, and prayer/meditation.

4. Results

4.1 Results of machine learning analysis

4.1.1 Descriptive statistics of the questionnaires

The seven trait-scale of the TCI proved to be reliable (α= 0.72-0.86), whereas the internal consistency of the subscales was lower (α= 0.48-0.77). The BSE aggression (α= 0.56) and

libido (α= 0.63) subscales were also less reliable, whereas the BDI, STAI, and MOS-SSS (α= 0.82-0.93) proved to be highly reliable instruments.

4.1.2 The selected variables

Among the biological variables, immunoglobulin G and rheumatoid factor were key predictors across all outcomes: they showed positive associations with SSA and SSB levels, and negative associations with ESSPRI scores. Platelet count was also an important predictor, with higher values linked to lower SSA and SSB levels, while hemoglobin concentration was negatively related to SSB. Among psychological variables, trait anxiety was a major negative predictor of both SSA and SSB, whereas state anxiety was positively associated with ESSPRI. The level of fatigue and asthenia was a strong positive predictor of ESSPRI, while conscientiousness was inversely related. Age, as a sociodemographic factor, was associated with lower SSA and higher ESSPRI scores. Additional relevant predictors for ESSPRI included libido, extravagance, hemoglobin, and depression severity.

4.1.3 Model performance

For ESSPRI, SVR showed the best performance with the full dataset, while ENR also performed well using psychological variables. SSA and SSB predictions were most accurate with biological data, where LASSO regression was the strongest. The overall best result came from the SSB LASSO model trained on biological data ($R^2 = 0.44$).

4.2 Results of traditional statistical analysis

4.2.1 Comparison of immune parameters and disease activity/burden markers between spiritual and non-spiritual groups

Spiritual patients showed significantly lower disease activity measured by ESSDAI (2.18 vs. 2.88; $p = 0.010$) and reported milder vaginal dryness (2.13 vs. 3.51; $p = 0.041$). No differences were observed in IgG, RF, SSA, SSB, ESSPRI scores and items, or hematological parameters (Neu, Ly, Hgb, Thr, complement activity). In the religious or highly religious group, lymphocyte counts were higher (1.69 vs. 1.39; $p = 0.019$), while perceived dryness was lower (4.81 vs. 5.89; $p = 0.035$) compared to the less religious group.

4.2.2 Linear relations between spirituality, engagement in regular prayer/meditation, duration of prayer/meditation and immune parameters, disease activity/burden markers

Based on linear regression analysis, higher spirituality was associated with lower SSB levels (B = -13.495; p = 0.016) and ESSDAI scores (B = -1.859; p = 0.012), but greater mental fatigue (B = 1.222; p = 0.020) and oral dryness (B = 1.293; p = 0.040). IgG showed a borderline negative correlation (B = -3.324; p = 0.067), while no significant associations were found with RF, SSA, or ESSPRI. Regular prayer/meditation predicted reduced SSA (B = -16.414; p = 0.009), skin dryness (B = -1.682; p = 0.005), and tracheal dryness (B = -1.852; p = 0.005). In contrast, religiosity was linked to higher IgG (B = 3.732; p = 0.045), SSA (B = 15.731; p = 0.027), and SSB (B = 14.744; p = 0.012). Duration of prayer/meditation showed similar associations and a positive link with C3 (B = 0.043; p = 0.038).

Among STS subscales, only few results emerged: joy of prayer/meditation correlated with reduced vaginal dryness (B = -0.118; p = 0.038), while universal connectedness and higher purpose predicted lower C3 levels (B = -0.020; p = 0.003; B = -0.026; p = 0.026). Closeness to the deceased was linked to greater fatigue (B = 0.276; p = 0.014).

4.2.3 Logistic relations of religiosity, spirituality, engagement in regular prayer/meditation, duration of prayer/meditation and ESSDAI, ESSPRI, SSA and SSB

Based on logistic regression analysis, religiosity predicted higher SSB levels (OR = 4.048; p = 0.021), while greater spirituality was linked to lower ESSDAI scores (OR = 0.184; p = 0.003). Individual participation in spiritual practices predicted significantly lower SSB (OR = 0.238; p = 0.025) and a trend toward lower SSA (OR = 0.342; p = 0.067). No significant associations were found for ESSPRI or SSA. Longer prayer/meditation duration was associated with more favorable outcomes: lower ESSDAI (OR = 0.680; p = 0.045), ESSPRI (OR = 0.714; p = 0.049), and SSB (OR = 0.547; p = 0.012). No significant effects emerged for STS subscales.

5. Discussion

5.1 Summary of the key findings

Machine learning analyses showed that biological variables were the strongest predictors of SSA and SSB antibodies, with immunoglobulin G (IgG), rheumatoid factor (RF), and platelet count playing the key roles. Among psychological variables, only trait anxiety emerged as a significant negative predictor. For ESSPRI scores, the best predictive performance came from

combining biological, psychological, and social factors, with fatigue/asthenia, state anxiety, and conscientiousness being the most relevant.

The second study revealed strong links between spirituality, spiritual practices, and disease activity. Spiritually engaged patients had lower SSA and SSB levels and reduced ESSDAI scores, while regular prayer/meditation further reinforced these beneficial effects. Logistic regression indicated that each one-point increase in spirituality reduced the likelihood of clinically detectable disease activity by 81.6%.

5.2 Interpretation of the results

The interpretation of the results is elaborated below, grouped according to output variables, followed by the discussion of some general considerations.

5.2.1 SSA and SSB

Depression and anxiety are well-known in pSS, but their relation to autoantibody production has been underexplored. Our findings suggest that higher trait anxiety was inversely associated with SSA/SSB levels, indicating that in seronegative cases symptoms may stem more from psychosomatic mechanisms (e.g., somatization, alexithymia) than immune activity. This aligns with evidence for distinct pSS disease clusters reflecting different biological and psychological pathways.

Spirituality, particularly prayer/meditation, was linked to lower SSA/SSB levels, reduced ESSDAI scores, and higher C3 complement, suggesting an immunomodulatory effect. Since spiritual practice duration is modifiable, it may carry therapeutic potential. In contrast, religiosity correlated positively with IgG, SSA, and SSB, likely reflecting negative religious coping and stress-induced immune dysfunction.

Overall, religiosity appeared tied to external social norms, while spirituality reflected an internal orientation. Spirituality tended to reduce, whereas religiosity increased perceived stress and maladaptive coping, underscoring the need to study their effects separately.

5.2.2 ESSPRI

In the first study, IgG and RF emerged as negative predictors of ESSPRI, highlighting the reciprocity between biological and psychological disease burden. ESSPRI was particularly sensitive to psychological factors: state anxiety showed a positive association, while the Harm

Avoidance–Fatigue (HA4) subscale pointed to shared biological mechanisms of fatigue and mood symptoms (e.g., serotonin metabolism). Conversely, the Cooperativeness–Conscientiousness (CO5) subscale was negatively linked to ESSPRI, suggesting that social and spiritual traits may buffer disease perception.

In the second study, ESSPRI was most strongly tied to perceived skin dryness, which negatively correlated with spiritual practice, possibly reflecting difficulties in boundary transcendence. Tracheal dryness also showed sensitivity to spirituality, consistent with the role of breathing in spiritual exercises. However, higher spirituality also correlated with increased mental fatigue and xerostomia, pointing to the potential role of religious/spiritual struggle.

5.2.3 Spirituality and immunity - possible links in the background

Findings indicate that spirituality—particularly prayer and meditation—interacts with immune function and overall health. Stress appears central in this psychoneuroimmunological chain: while stress exacerbates autoimmune hyperreactivity, prayer/meditation may reduce stress and enhance immune regulation. Spirituality also fosters positive emotions (hope, gratitude, compassion), which lower pro-inflammatory cytokines such as IL-6. Similar anti-inflammatory effects have been reported in both Buddhist meditation and Christian prayer. Conversely, pro-inflammatory cytokines promote fatigue and depression, potentially explaining the inverse association between ESSPRI fatigue scores and time spent in spiritual practice.

5.2.4 Possible neurobiological connections

Neuroinflammation, cytokine signaling, and blood–brain barrier disruption contribute to neuropsychiatric symptoms in pSS. Elevated pro-inflammatory cytokines (e.g., IL-6, TNFα) are linked to depression, fatigue, and cognitive decline, while antibody-mediated neural injury and small-vessel vasculitis may also play a role. Spiritual experiences activate the brain's reward system (nucleus accumbens, prefrontal regions), enhancing immune regulation and potentially reducing autoimmunity. Reduced activity in the left inferior parietal lobe, associated with self-boundary dissolution and immune modulation, may further explain the inverse correlation between spiritual practice duration and ESSDAI scores in pSS.

5.2.5 Methodological and other conclusions

Machine learning models performed differently across outcomes: for SSA and SSB, ENR and LASSO outperformed SVR due to largely linear associations with biological predictors. For ESSPRI, models were more similar, but SVR performed best when biological, psychological, and social factors were combined, suggesting complex nonlinear interactions. Social variables (sex, education, residence) showed little effect, except for age, which correlated negatively with SSA and positively with ESSPRI. This aligns with findings that older patients more often present seronegative forms, while symptoms like dryness and fatigue are common in aging itself. The limited social effects may reflect measurement constraints or small sample size.

5.3 Limitations

Our study has several limitations. Both investigations were based on small, geographically restricted samples, limiting generalizability; future research should include independent cohorts for external validation. The cross-sectional design precludes firm causal inferences, as relationships between disease activity and psychological/spiritual factors may be bidirectional. Proposed biological mechanisms (e.g., neurobiological, autonomic pathways) remain speculative since no direct measures were included. In the first study, unmeasured psychological factors (e.g., childhood trauma, coping, cognition), psychiatric comorbidities, medications, and substance use may have influenced results. Finally, some questionnaire subscales showed low internal consistency, a limitation also reported in other samples (Greek, Turkish, Croatian).

5.4 Possible future research and clinical directions

Our findings suggest that monitoring state and trait anxiety in pSS can inform personalized care, indicating distinct biological versus psychological vulnerabilities. Incorporating tools such as the STAI into routine rheumatology may reduce reliance on purely biological therapies, while brief interventions (CBT, psychoeducation, digital modules) can support holistic management.

Psychological factors, including anxiety, likely play a central role in pSS pathophysiology, warranting further studies on unmeasured variables, the mental effects of immunotherapies, and neurobiological mechanisms of psychoneuroimmunology.

The second study highlighted the beneficial role of spirituality—especially personal prayer and meditation—which correlated with immunological markers and disease activity.

Encouraging spiritual practices and assessing spiritual attitudes may have therapeutic potential, though it is important to differentiate spirituality from religiosity: negative religious coping can be harmful, while inner spirituality appears protective.

Overall, integrating psychological and spiritual dimensions into care may enable a bio-psycho-socio-spiritual (BPSS) health model for managing chronic autoimmune diseases such as pSS.

5.5 Conclusions

These findings provide novel insights into the multidimensional nature of primary Sjögren's syndrome (pSS). Using machine learning, we showed that biological disease activity is primarily driven by immunological parameters, whereas patient-reported outcomes are strongly shaped by psychological factors, particularly state and trait anxiety. Importantly, spirituality—especially individual practices such as prayer and meditation—emerged as a protective factor, associated with reduced disease activity and symptom severity, while religiosity may, in some contexts, exert adverse effects.

Taken together, these results suggest that pSS cannot be fully understood through a purely biomedical lens. Instead, its course is influenced by dynamic interactions between biological, psychological, and spiritual domains. Future research should employ longitudinal and mechanistic approaches to clarify causal pathways and integrate psychoneuroimmunological markers. Clinically, our findings highlight the need for holistic, patient-centered care models that incorporate psychological screening and spiritual resources alongside conventional immunological assessment. Such integrative approaches may ultimately reduce disease burden, improve quality of life, and open novel therapeutic avenues in the management of pSS.

6. Summary

Primary Sjögren's syndrome (pSS) is a complex autoimmune disease influenced not only by biological, but also by psychological and spiritual factors. In this dissertation, the results of two empirical studies are summarized aiming to understand disease activity in pSS through a holistic lens, based on the bio-psycho-social-spiritual (BPSS) model of health and disease.

In the first study, data from 117 pSS patients were analyzed using machine learning algorithms to identify the most important biological (e.g., IgG, RF, SSA, SSB, blood cell

counts), psychological (personality traits, self-esteem, anxiety, depression), and social factors (social support, sociodemographic status) contributing to disease burden. The outcome variables were SSA/SSB autoantibodies (biological activity) and the ESSPRI index (subjective symptom burden). The results showed that biological markers were the strongest predictors of autoantibody levels, while psychological factors played a major role in subjective disease burden. Surprisingly, lower trait anxiety was associated with higher biological activity, whereas current anxiety and the temperament trait "Fatigability" were linked to greater symptom burden.

The second study examined the spiritual attitudes and practices of 108 patients, and their relationship with immunological parameters and disease activity markers. The findings indicated that individuals engaged in personal spiritual practices (e.g., prayer, meditation) had significantly lower SSA/SSB autoantibody levels and lower ESSDAI/ESSPRI scores. Notably, spiritual engagement was strongly associated with decreased perceptions of skin and tracheal dryness. These effects are likely mediated by psychoneuroimmunological mechanisms, such as stress reduction, increased positive emotions (e.g., gratitude, hope), and autonomic nervous system regulation. It is important to note that spirituality and religiosity had different impacts: religious struggle was associated with worse psychological and immunological outcomes, emphasizing the need to distinguish between external religiosity and inner spiritual attitude.

These findings confirm that disease activity in pSS is shaped not only by biological but also by psychological and spiritual dimensions. Integrating a holistic approach into clinical practice—based on the regular assessment of mental state and spiritual activity—may contribute to more personalized and effective disease management. This approach may also open new avenues for therapeutic strategies and research in autoimmune diseases.

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8. List of publications

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List of publications related to the dissertation

1. **Módis, L.**, Matuz, A., Aradi, Z., Horváth, I. F., Szántó, A., Bugán, A.: Unveiling psychobiological correlates in primary Sjögren's syndrome: a machine learning approach to determinants of disease burden.
Front. Psychiatry. 16, 1-11, 2025.
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Sci. Rep. 14 (1), 1-9, 2024.
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List of other publications

3. **Módis, L.**, Aradi, Z., Horváth, I. F., Bencze, J., Papp, T., Emri, M., Berényi, E., Bugán, A., Szántó, A.: Central Nervous System Involvement in Primary Sjögren's Syndrome: Narrative Review of MRI Findings.
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