# THE ROLE OF CLINICAL, BIOLOGICAL, AND SOCIOECONOMIC FACTORS ON THE DEVELOPMENT OF RESILIENCE IN WOMEN WITH AUTORIMMUNE RHEUMATIC DISEASES: A CROSS-SECTIONAL STUDY

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**Master Degree in Epidemiology**

**Bogota, 2019**

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**Bogota, 2019**

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**Master in Epidemiology**
**Universidad del Rosario – Universidad CES**

**Bogota, 2019**

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## ACKNOWLEDGMENTS

I want to thank my family, who are my stimulus and constant inspiration. I thank my mentor and professor, Dr. Juan Manuel Anaya for his trust, support and guidance, for giving me the opportunity to think about the right way of doing science and to see beyond those things that other people do not perceive. I thank my tutor, Dr. Yeny Acosta, for her significant contributions to improve each aspect of this work. I thank all associates of CREA for fruitful and constructive commentaries. I thank my professors who provided me the necessary to accomplish this work. And last but not less, a special acknowledge to all patients who accept to contribute to this research.


*"Medicine is a science of uncertainty and an art of probability"*

Sir. William Osler

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## ABSTRACT

### BACKGROUND

Resilience is considered the capability to positively respond to adverse events. Since this capacity in considered a “continuum” process, long-term stressors and psychosocial factors are thought to be crucial for resilience development, especially in those patients with chronic inflammatory systemic diseases. However, the role of clinical, biological and socioeconomic characteristics in autoimmune rheumatic diseases (ARDs) is still unknown.

### OBJECTIVE

To evaluate the association between resilience and socioeconomic, biological and clinical factors in four autoimmune rheumatic diseases (ARDs) namely: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren’s syndrome (SS) and systemic sclerosis (SSc).

### METHODS

A cross-sectional study in 188 women with SLE (n= 70), RA (n= 51), SS (n= 32), and SSc (n= 35) was done. Resilience was evaluated by the “Brief Resilience Scale”, whereas independent factors including age, age at onset, duration of disease, socioeconomic status, excersice, severity of symptoms and polyautoimmunity (PolyA) were evaluated by surveys and chart reviews. A panel of 15 serum cytokines and 14 autoantibodies were evaluated simultaneously. Bivariate, classification and regression trees (CART), and multiple linear regressions were used to analyze data.

### RESULTS

CART analysis showed that patients younger than 48 years with SLE, RA, and SSc who had low socioeconomic status showed the lowest resilience scores, whereas those

patients between 48 and 66 years exhibited the highest resilience levels despite socioeconomic status. Interestingly, regular physical activity was associated with highest resilience in SSc. In addition, Interleukin-6 (IL-6) was associated low resilience scores (β= -0.581120, *p*=0.02) and with severity of symptoms (β=1.8395, *p*=0.04) in SSc. Neither PolyA nor severity of symptoms influenced resilience in the four ARDs studied. Cytokine levels did not significantly differ between groups based on regular physical activity.

**CONCLUSIONS**

Resilience is a continuum trait associated to socioeconomic status and age. In addition, IL-6 and exercise are key factors for resilience in SSc. These results highlight the relevance of biological and socioeconomic factors in the development of resilience in autoimmunity.

**KEY WORDS**

Resilience, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, Sjögren's syndrome.

# 1. PROBLEM FORMULATION

## 1.1 PROBLEM STATEMENT

It has been calculated that 40,1% of people worldwide suffers any kind of mental illness during their lifetime (1). Several factors such as violence, income, insurance and socioeconomic status (SES), have been associated with their development (2). According to the national survey of mental health, Colombia has a high prevalence of psychiatric illnesses (i.e., 40%) when compared with other countries, especially in those patients with chronic conditions, and the problem is growing in comparison with the previous mental surveys (1), becoming a serious and critical problem in the field of public health.

The autoimmune rheumatic diseases (ARDs) are a chronic group of diseases affecting 5% people worldwide (3), and recent studies have shown an increase in their incidence (4). It has been found that mental illnesses are common in these patients. For example it has been calculated that up to 65% of patients with ARDs suffers major depressive disorder (MDD) (5–9), and in Colombia, for systemic lupus erythematosus (SLE), it reaches the edge of 36% (10). This suggest that psychiatric domains in this group of patients deserves attention, and the conduction of studies in the field of psychology is mandatory.

Resilience, define as the ability to bounce back after a stressful event (11), has been closely related with psychiatric illnesses (12). Some studies have shown that nearly 8.9% of patients with ARDs exhibit low resilience (i.e., SLE) (13), and factors such as activity of disease and low SES have been previously associated with its development (14). However, data of this field in patients with ARDs in Colombia are scarce, and the role of clinical and biological factors associated with resilience in this group of patients are still to be clarified.

## 1.2 JUSTIFICATION

Resilience is a concept that ascended in the field of psychology in the second half of the twentieth century. This is considered one of the core sources for investigation in positive psychology (15). Shortly, it is defined as *"the ability of human beings to positively respond to adverse events"* (15–17). Since individuals with chronic diseases are repetitively exposed to negative experiences, resilience emerged as the foremost trait in patients suffering of these illnesses, including ARDs. Activity of disease, severity of symptoms, and decline of functional capacity, set a high charge of stress to the individual (18). Therefore, resilience in these groups of patients may play a crucial role in outcomes, since the greater the patient's resilience, the lower vulnerability and deleterious effects of the condition (17,19).

Resilience relies on several features that can promote it such as active coping, optimism, social support, perseverance, happiness, and existential aloneness (11). In adulthood, the ability to coping is influenced by tense events that increase allostatic load (i.e., the physiological consequences accumulated through aging, as a result of repeated or chronic exposure to stress) and theoretically result in physiological and psychological damage (20). In fact, resilience is a crucial factor in coping with illness, and in the case of ARDs, it has been found that behavioral training programs in resilience improves quality of life and increase the odds of better outcomes (21,22). Thus, scrutinizing the factors associated with resilience is crucial in the multidisciplinary management of ARDs.

On the other hand, the role of biological factors in resilience is unknown (12). Cytokines levels and autoantibodies production have been associated with development of psychiatric manifestations (23), and it has been hypothesized that impairment of limbic system (e.g., olfactory tract, amygdala and hippocampus) by cytokines and autoantibodies, are the main mechanisms associated with mental illnesses (24). However,

a study of these factors in the development of resilience in ARDs has not been conducted so far. Thus, the study of biological, sociodemographic and clinical factors associated with resilience for future implementation of clinical management in ARDs is mandatory.

## 1.3 RESEARCH QUESTION

What are the clinical, biological and sociodemographic factors associated with resilience in patients with ARDs?

# 2. THEORICAL FRAMEWORK

## 2.1 AUTOIMMUNE RHEUMATIC DISEASES

The ARDs are chronic diseases that affect nearly the 5% of population, especially women (80%) (25). These diseases are typically observed in patients with genetically susceptibilities that can be modify by either risk or protection factors (26). The ARDs are considered polygenic diseases due to the interaction between *HLA* and *Non-HLA* genes, which are crucial in their pathophysiology (26). However, the etiology and clear pathophysiological mechanisms remain elusive. In fact, the interaction between genetic, and environmental factors has been proposed as the main triggering influence for autoimmunity (27). The latter, known as autoimmune ecology, is define as the interactions between individuals and their environment that lead to a breakdown in immune tolerance that allow the development of ARDs (28). It has been stated that these interactions shape immunological system (29).

In recent years, the understanding of ARDs is based on the mosaic of autoimmunity, which describes their multifactorial origin, as well as the diversity in the expression of these diseases (30). This suggests that different factors involved in autoimmunity could influence the emergence of different illnesses. However, it is common that ARDs share signs and symptoms (subphenotypes), pathophysiological mechanisms and outcomes, a phenomenon known as *"autoimmune tautology"* (31).

These commonalities across ARDs are evident in biological and sociodemographic factors. For example, several ARDs exhibit antibodies profiles that are similar to those found in other illnesses (32). Furthermore, cytokines are crucial in the development of ARDs (33). Some of them have been associated with the development of subphenotypes. In SLE, the role of IL-1β, IL-6 and IL-8 in lupus nephritis has been reported (34–39), and

some patients showed high levels of IL-23 and IL-12, which were associated with anti-double-stranded DNA (dsDNA) positivity (40). In the case of SSc, IL-5, IL-6, IL-13 and IL-17 were linked to skin fibrosis (41,42), and interstitial lung disease (43,44). Whereas a reduction in immunomodulatory cytokines, IL-10, is distinctive in patients with SSc (45).

In RA, high IL-6 levels were associated with bone erosions at onset, and anti-third generation cyclic citrullinated peptide antibodies (anti-CCP3) positivity, whereas in patients with SS, the IL-17 was associated with severity of disease (46). Nevertheless, the physiological functions in the human body arise from the interactions between tissues and cells (i.e., systems medicine) (47), and neither positive antibodies not levels of cytokines by their self, fully explain the pathophysiological mechanisms underlying ARDs. Thus, other environmental and socioeconomic factors are thought to influence the appearance of these conditions.

In this sense, sociodemographic factors have also been associated with the development of ARDs. The SES is considered a hierarchical social classification connected with several consequences in health and disease. Ancestry, income, occupational class, educational level, and social class are considered the main factors associated with SES stratification (48). In ARDs, low SES has shown to be associated with worse outcomes. For example, patients with low SES and RA may present high levels of activity of disease, worse physical, and mental health, and reduced quality of life (QOL) (49–51). In this line, higher levels of poverty in subjects with SLE has been associated with elevated rates of mortality (52), and poor access to health care influence the incidence of end-stage renal disease in poverty-stricken areas (53). These data suggest the interaction between internal and external factors in the development of autoimmunity, advocating for the simultaneously study of biological and socioeconomic factors, and their role in outcomes and quality of life.

### 2.1.1. RHEUMATOID ARTHRITIS

Epidemiologically, RA is one of the most prevalent ARD. It is a common disease that affects all population groups with an important frequency of presentation that varies between 0.5 and 1% (54). It mainly affects the joints, but it may produce extra-articular manifestations, such as pulmonary fibrosis, rheumatoid nodules, vasculitis, and several subphenotypes (54). It has a harmful impact on the ability to perform daily activities, including domestic tasks and work, considerably affecting the QOL (55).

The predisposition for the development of RA seems to be multifactorial, given the low relative concordance between identical twins (i.e., 15%). The alleles of the *HLA-DRB* region with the known shared epitope have a great influence on the development of the disease, but there are controversies about its effect in different populations, and the genetic polymorphisms associated with RA are not enough to explain the development of the illness. It is considered that a mixture of genetic susceptibility and exposure to certain endogenous (i.e., hormonal) and exogenous factors (i.e., smoking or infections) explains the mechanism by which RA is produced (56).

Two antibodies have been linked to the pathogenesis and diagnosis of RA. The anti-CCP3 is an antibody with a high specificity for RA but with moderate sensitivity. On the other hand, the rheumatoid factor (RF) show high sensitivity but low specificity (57), thus, both autoantibodies are frequently used simultaneously. Classification of RA is typically made by the fulfilling of the 1987 American College of Rheumatology (ACR) classification criteria (58), and the main tool to assess activity of disease the is the Disease Activity Score 28 (DAS 28) (59). However, a clinometric approach through the routine assessment of patient index data 3 (RAPID3), has proven to be a reliable tool to measure severity of symptoms (60).

The most common cause of death in patients with RA is cardiovascular disease, given the high incidence of coronary heart disease and the formation of atheromatous plaques in the majority of people (61). Furthermore, an increased incidence and prevalence of bipolar disorder, anxiety and depression in RA has been described (62), thus suggesting the high burden of psychiatric disorders in this illness, and evidencing the high impact of RA on outcomes, costs, and QOL.

### 2.1.2. SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is a multifactorial disease characterized by a loss of tolerance in the innate and adaptive immune system, with a large component of genetic and environmental susceptibility (63). Its prevalence reaches up to 178 per 100.000 inhabitants and it is higher in non-Caucasian population (64). The survival of SLE patients has increased radically over the years, from less than 50% in 1950 to 95% at the beginning of this century. However, the mortality rate compared with healthy individuals is four times higher (65). A worse prognosis in most series of cases is associated with high levels of creatinine, hypertension, nephrotic syndrome, anemia, hypoalbuminemia, hypocomplementemia, presence of antiphospholipid antibodies, male sex, ethnicity and low SES at the time of diagnosis (66).

Genetic, environmental and immunological factors have been associated with the development of SLE. Regarding genetic factors, a coaggregation of 50% to 59% of SLE between monozygotic twins has been found (67). In addition, more than 20% of patients with SLE have first-degree relatives with autoantibodies, and 5% to 12% of them develop SLE, confirming the genetic burden in the disease (68). The most frequent *HLA* alleles associated with this disease are *DR-2*, *DR-3*, *B8*, and *DQW1*. Among the non-genetic factors, exposure to drugs (i.e., hydralazine, procainamide, D-Penicillamine, thiazides,

anticalcics, ACE inhibitors, sulfonamides), ultraviolet radiation, Epstein-Barr virus and exposition to hormonal compounds (estrogen and pregnancy) have also been associated with the development of SLE (29). In the immunological level, four basic processes have been identified: failure in apoptosis, defective passive cell death, faulty anergy/ignorance and loss of immunoregulation (67).

Regarding antibodies, almost all patients with SLE present a positive test for antinuclear antibodies (ANAs), and most have one or more of the specific antibodies for SLE (i.e., anti-dsDNA and anti-Sm antibodies) (69). Although the 2012 classification criteria for SLE have shown a good performance, the 1997 ACR criteria for SLE are still the most used in the clinical setting (70), and most of studies apply them. In addition, regarding activity of disease, the SLE Disease Activity Measure (SLEDAI) is considered the gold standard. However, similar to the case of RA, clinimetric approaches have shown that the Systemic Lupus Activity Questionnaire (SLAQ) has a good reliability to measure severity of symptoms (71).

At the clinical level, patients with lupus may present with malar erythema, discoid lesions, photosensitivity and oral ulcers. At joint level they may present non-erosive arthritis of more than two joints. Other patients exhibit serositis (i.e., pleuritis, pericarditis), kidney disease also known as “lupus nephritis”, and hematological compromise (i.e., leukopenia, lymphopenia, thrombocytopenia or hemolytic anemia) (72).

Disability in patients with SLE is common mainly due to chronic fatigue, arthritis, and kidney disease. The main cause of death in the first decade of the disease is the high activity of the disease, renal failure, and infections (66). Additionally, patients usually show depressive symptoms, anxiety, fatigue and a marked commitment in daily activities that affect the QOL (73,74), that makes the SLE one of the ARDs with the greatest impact in terms of public health.

### 2.1.3. SYSTEMIC SCLEROSIS

SSc is an ARD that is characterized by dysregulation of innate and adaptive immunity associated to fibrosis of the skin, internal organs and vasculopathy (75). Although skin fibrosis is the most common clinical feature, compromise in the lungs, kidneys, gut, and heart are crucial for clinical outcomes (76). This disease is more common in women (77), and northern Europe and Japan have shown the lowest incidence of the disease (77).

This illness is produced by the interaction of environmental and genetic factors that initiate a systemic and chronic process characterized by vascular obliteration, inflammation, and fibrosis (78). Damage of endothelial cells, secondary to continuous inflammation driven by immune cells, is considered the main mechanism implicated in the pathogenesis of SSc. Prominent mediators of cell activation and damage include the IL-6 and IL-13, which are considered the main players in fibrosis development (79). The initial approach to optimal management of SSc is to determine the disease phenotype and disease stage (80). Actually the most used classification criteria for SSc are the 2013 ACR/European League Against Rheumatism classification criteria (81), and severity of symptoms in this disease have been recently approach by the scleroderma skin patient-reported outcome (SSPRO) (82,83).

Autoantibodies in this subset of patients is characterized by positivity for ANAs than include anti-centromere antibodies subunit B (anti-ACApB), anti-topoisomerase I antibodies (ATAs) (84) and anti-RNA polymerase III (85). These autoantibodies have been associated to CREST (i.e., calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia) syndrome and different subphenotypes including systemic compromise (i.e., lungs and kidneys) or limited presentation (84,85).

These patients typically show burdensome symptoms of psychological distress determined by disfiguration, pain, fatigue, and marked impairment for daily life occupations (86,87), thus showing the high burden of disease on QOL (88,89). It has been described that symptoms of depression in SSc are common (90–92), and nearly 65% of SSc patients develop MDD (7,8). Pain and the physical domains have a critical role in QOL and depression in these patients (93,94), thus suggesting the pivotal role of psychiatric manifestations in this disease

### 2.1.4. SJÖGREN'S SYNDROME

SS is a systemic disease characterized by lymphocytic infiltration of the exocrine glands, with the consequent dryness of the mucous membranes, mainly oral (xerostomia) and ocular (xerophthalmia). This syndrome, previously considered an autoimmune exocrinopathy, is currently classified as an autoimmune epithelitis since the target of the inflammatory response is the glandular epithelium. The SS has a high prevalence especially in the elderly, and given its systemic commitment significantly compromises the QOL (95). Although it can start at any age, including in childhood, women between the fourth and fifth decade of life are the most affected. The prevalence of SS is close to 1%, and is present in up to 30% of patients with another ARD (i.e., polyautoimmunity [PolyA]) (96).

Its etiology seems to be mediated by genetic, environmental and hormonal factors. It is believed that the mechanism of disease production occurs in three phases: a first one mediated by environmental factors, cytomegalovirus infections or Epstein Barr virus, with the subsequent chronic activation of the immune response that causes damage to the glandular tissue and the appearance of the characteristic symptoms (97). Extraglandular manifestations occur in one-third of patients with SS. Patients with SS have more fatigability, low-grade fever, Raynaud's phenomenon, myalgia and arthralgia. Renal

involvement includes interstitial nephritis and renal tubular dysfunction with or without acidosis. It can occur with small and medium vessel vasculitis being the most common manifestations: purpura, urticaria, skin ulcerations, glomerulonephritis and mononeuritis multiple (96).

Anti-Ro and anti-La antibodies occur in approximately 60% of patients with this disease and are associated with early onset, longer duration of the disease, extraglandular manifestations, enlarged parotid gland, and lymphocytic infiltration (98). The revised American-European Consensus Group for SS (99), are the most used criteria for classification of SS, and severity of symptoms could be measured by the EULAR SS patient reported index (ESSPRI) (83,100).

The main complications of the disease are derived from the insufficient symptomatic treatment. Tooth loss, oral candidiasis, periodontal disease, and corneal ulcers are preventable with appropriate management. Hematological neoplasia is one of the complications with greater impact in SS, patients have up to 50 times more risk of developing non-Hodgkin's lymphoma or lymphoma associated with mucosal tissue (MALT) compared to healthy individuals (101).

In addition, sicca symptoms are associated with depression, symptoms of fatigue and anxiety, and low-perceived QOL (102), and up to 38% of patients with SS showed overt depression. This data support the high burden of psychiatric manifestations in patients with SS and advocate for the study of the associated factors of these conditions, to develop of new strategies of prevention and treatment in this group of patients that aim to improve QOL and reduce health-related costs associated to adverse outcomes.

## 2.2 RESILIENCE

Resilience is define at the ability to bounce back or recovery to the previous levels of functioning following a stressful event (11). However, several definitions have been previously attributed to this ability: adaptation to stress, resistance to illness, and functioning above the norm in spite of stress (11,103). Thus, the comparison of results about this ability across the studies is difficult. In this sense, the concept that refers to the individual's ability to recover after acute or chronic stress exposure could be considered as the most accurate definition (15–17). From the conceptual point of view, we could consider resilience as a homeostatic state in which the individual is capable to maintain the balance between internal and external stressors, and it is influenced by either successful or unsuccessful adaptations to previous adversities in the course of life (104).

In the early studies on resilience, they were focused in the resistance to adverse events in children with difficult breeding (105). However, with the come of years, resilience turns in a different direction pointing out to psychosocial determinants that improve or jeopardize resilience development (106). In recent years it has been identified that resilience is directly related to the presence of MDD, anxiety and stress-associated negative emotions (107,108), thus suggesting that this ability is a key factor for mental illness as well as other traits in behavior including QOL. Currently, depending on a specific stressful event, resilience could be classify in two types: 1) passive resilience, and 2) active resilience. The former is characterized by ability maintain natural functions to evade adversity, whereas the latter is considered to deal with stress in a positively manner, getting some benefit of this “training” (109).

Resilience depends on different characteristics or factors that can promote it, such as optimism, active coping, social support, happiness, perseverance, meaningfulness and existential aloneness (11,103,110). However, it is well known that the development of

resilience is influenced by life-long experiences that determine the ability with coping with the illness. Some life events, including the intrauterine stressors (i.e., corticoids administration or food deprivation), postpartum (i.e., maternal separation and maternal care behavior), stressful situations in infancy and adolescence have been related to resilience development (12,23,103). Thus, it is frequently considered that it is a trait embracing a group of features that allow subjects to adapt to the circumstances they encounter (104), suggesting that adaptability of this trait is a continuum process influenced by multiple factors through life, that may affect outcomes in children and adults (105,106).

In adulthood, the active coping is affected by life-stressful events, such as diagnosis of either a chronic or acute disease, which increase allostatic load, potentially resulting in physiological and psychological changes that may lead to the development of disorders like depression and anxiety (12,111–113). Since resilience refers to the ability of an individual to response to adverse factors, it becomes difficult to define it. For example, adversity can include social rejection, early life stress, depression and chronic enduring stressful experiences that can include diagnosis of an illness or living with chronic disability conditions (109). As shown above, ARDs are characterized by a high burden of disease (i.e., allostatic load) that ultimately lead to biological and psychological dysfunction, supporting the notion that these diseases are more prone to have a failure in response to face adversity.

The neurological basis for resilience has made enormous advances in recent years. It has been recognized that changes in the medial prefrontal cortex may have deleterious effects in depressive and negative-like behaviors in humans and mice (109), which are ultimately connected with resilient behavior. In addition, hippocampal, ventral tegmental area and nucleus accumbens pathways have shown to be associated with changes in response to stress secondary to organic changes. In this sense, the cytokine hypothesis of depression states that psychiatric manifestations are influenced by an increase in peripheral

inflammatory cytokines which lead to an enhanced activity in the hypothalamo-pituitary-adrenal (HPA) axis, decreased neurogenesis, neurodegeneration, oxidative stress and serotonergic dysfunction (12,23). These molecules communicate with central nervous system (CNS) through neural pathways (vagus nerve activates microglia to produce proinflammatory cytokines IFN-γ, IL-1β, and IL-6), vascular mechanisms (cytokines activate receptors in endothelial cells which increase production of prostaglandins and nitric oxide promoting inflammation) or infiltration across circumventricular organs (112,114,115) which finally lead to changes in glutamate and serotonin concentrations, developing behaviour changes in humans and fluctuating capacity to adequate response to adversity (12). In fact, resilience, and a constellation of multiple psychiatric disorders, are established by influence of multiple systems including hypothalamic-Pituitary-Adrenal (HPA) axis, autonomic system, immune system and the brain (12,116,117). Thus, the study of either cytokines or inflammatory mediators in chronic conditions is essential to understand the role on these molecules in the ability to positively response to stress.

Management of resilience has focused on psychological and behavioral therapy, which have been effective for improving response to adversity (109). Other strategies such as stress inoculation training, the life skills education-based program, intensive mindfulness meditation training and the child caregiver advocacy resilience programs have proven to improve resilient traits (109). However, other approaches such as regular physical activity have shown some benefits in psychiatric conditions. Exercise increase the sympathetic nervous system and the HPA axis. Although it is considered an stressing phenomenon (118,119), intermittent regular, and repeated exposure to exercise, with enough time to recover in between, can lead to physiological ‘stress training’ which finally benefit patients to respond psychological and physical stress. This is driven by the secretion of inflammatory cytokines that continuously stimulate the CNS leading to the adaptability of the brain to stressful events (118). In depressed patients physical activity may be beneficial to face major stressors (120). Thus, the association between resilience and

exercise supposed a new field of study and may help to introduce new strategies in “resilience training” especially in chronic conditions including the ARDs, improving outcomes and QOL.

Measuring resilience is complex due to several factors associated with coping with stress, cultural basis and the use of different questionnaires to assess this trait (109). Initially, Bartone *et al*.(121) studied the impact of a military air disaster on the health of assistance workers. In this study, authors focused on the ability of patients to resist the adversity using a resilience-like scale. However, this approach did not provided information about personal competence and acceptance of self and life which are crucial for facing adversity, thus Wagnild and Young developed a new scale aiming to include these aspects of resilience (122). Nevertheless, these measures have not been widely used or applied in different populations, hindering the generalizability of these scales. Thus, in 2003, a new scale was developed. The connor davidson resilience scale (CDRS) was able to detected changes in resilience secondary to therapy, and it was in line with the theory of thriving despite of stress (104). However, the number of items included in the CDRS may hinder the applicability and reproducibility across studies. The brief resilience scale (BRS) was developed to perform an easiest evaluation of resilience with a high reproducibility. This questionnaire is composed with 6 items, each item ranges from 1 (strongly disagree) to 5 (strongly agree), with higher scores indicative of greater psychological resilience. It showed a high reliability with other scales including the CDRS (123). This instrument has been recently validated in Spanish (124), and it has been previously used in the study of resilience in rheumatoid conditions (125).

### 2.2.1. RESILIENCE AND AUTOIMMUNE RHEUMATIC DISEASES

Data about the role of resilience in patients with ARDs is scarce and only few approaches in this topic have been conducted. Since resilience is considered a “continuum”, the role

of age and duration of disease have been the center for the study of this trait. In this sense, older patients and with longer duration of disease exhibit low resilience when compare to younger subjects in chronic diseases (16,126). Some studies have shown that patients with SLE showed high resilience levels and it was negatively associated with duration of disease (13,19,126). Other factors such as years of education, occupation, gender, and SES have been associated with resilience in chronic conditions (16). Few years of formal education and low SES is frequently associated to psychiatric illnesses, especially after stressful life events in women (17). However, previous reports showed that individuals with RA and SLE did not exhibit difference in resilience according to occupation, years of education nor SES (13,126).

Resilience is currently considered major factor in the development of psychological features in individuals with ARDs. Tan-Kristanto *et al.*(127) found that Anxiety and depressive symptoms were associated with low resilience in patients with MS. This was in line with the evidence in patients with SLE in which those individuals with low resilience exhibit highest levels of depression (13), and it was influenced by low SES (128). In patients with RA, resilience predicted changes in positive interactions, and it negatively correlated with vulnerability which include anxiety, depression, pessimism emotionality and interpersonal sensitivity (19). Thus, these diseases exhibit a high burden in psychological domains which ultimately correlate with the appearance of psychiatric manifestations, and resilience play a major role in this process.

Allostatic load of disease, has been recognized as a factor for psychiatric and psychological manifestations (129). Some diseases seem to have a greater impact than others in QOL, especially those patients with deprived social support networks (16). Social dysfunction and physical disability are associated with maladaptation to diseases (130). This processes could be influenced by activity of disease, clinical features and comorbidities (103). Although in patients with RA resilience was not correlated with activity

of disease, it seemed to mediate the association between activity of disease and mental QOL (14). This is similar to those patients with multiple sclerosis (MS) in which resilience was associated with QOL, thus suggesting this trait has a unique role in nonphysical functional outcomes (131), and in some patients with MS, resilience may help to reduce depression/anxiety symptoms and improve QOL irrespective of the physical disability level (132). In fact, resilience was crucial in the relationships between mental health outcomes and social support in individuals with MS (133).

Although some studies have suggested that resilience do not influence physical outcomes, it is clear that coping with the illness in some patients may have a considerable influence in physical domains in subjects with MS, such as chronic pain (133). In a qualitative approach for resilience in MS, it was found that physical fatigue was considered a key mediator to improve response to stress, together with negative thoughts, feelings, and social stigma (133). On the other hand, patients with RA, in which arthritis and arthralgia are tightly associated with QOL, resilience mediated the interaction between pain and negative effects (134). Thus, data suggest that physical and mental outcomes are directly associated to resilience. In this sense, it is tempting to speculate that severity of symptoms, activity of disease and PolyA, may influence the resilience in patients with ARDs, which could be suitable of intervention in a health promotion and prevention approaches in this subset of patients.

Cytokines have been proven to play a key role in development of psychiatric illness (12). Misbalance among Th-1 and Th-2 profiles, produce a dysregulation of serotonin and glutamine seesaw, which lead to changes in behavior and stress response (12,114,135). Patients with ARDs are under continuous production of cytokines, which are thought to promote psychiatric symptoms and syndromes, including depression, sickness behavior and lack of good response to physical and psychological stress (103). Although the role

of cytokines in resilience has been studied in chronic diseases, no studies have been conducted in ARDs.

The public health impact of resilience has not been evaluated yet in ARDs. However, some studies have shown that interventions in this trait may promote better outcomes in autoimmune diseases such as MS. Everyday Matters program showed to improve resilience which was associated with gratification with social roles, better positive affect, well-being and low depressive symptoms severity (136). Although interventions for resilience in ARDs are not common, some authors have suggested that Interventions aimed at improving modifiable reserve capacity variables including resilience, may decreases depressive/anxious symptoms in patients with SLE (128). Other programs conducted in patients with RA (i.e., “Programa Fortaleza”), focusing on self-esteem, self-efficacy and emotional self-control showed improvements in resilience, self-transcendence, mood states, QOL, illness perception, and social support (137). Thus, the study of the multiple factors influencing resilience in ARDs may help to the formulation programs that may help to improve outcomes in this subset of patients, reducing the burden of disease and the global cost of these diseases in the health system.

## 3. HYPOTHESIS

Ho: Clinical, biological and socioeconomic factors are not associated with resilience in patients with ARDs.

Ha: Clinical, biological and socioeconomic factors are associated with resilience in patients with ARDs.

# 4. OBJECTIVES

## 4.1 GENERAL OBJECTIVE

**4.1.1** To evaluate the association of socioeconomic, clinical and biological factors with resilience in patients with RA, SLE, SSc and SS.

## 4.2 SPECIFIC OBJECTIVES

**4.2.1** To describe the socioeconomic, clinical and biological characteristics of patients in the four ARDs.

**4.2.2** To asses resilience in the four ARDs by the BRS.

**4.2.3** To measure severity of symptoms with either RAPID3 for RA, SLAQ for SLE, SSPRO for SSc, or ESSPRI for SS.

**4.2.4** To quantify the levels of autoantibodies and cytokines in the four ARDs.

**4.2.5** To analyze the associations of resilience with socioeconomic, clinical and biological factors through bivariate and multivariate analysis.

**4.2.6** To build a predictive model for resilience in ARDs through classification and regression trees (CART).

# 5. METHODS

## 5.1 METHODOLOGICAL APPROACH

Quantitative research.

## 5.2 TYPE OF STUDY

Cross-sectional study.

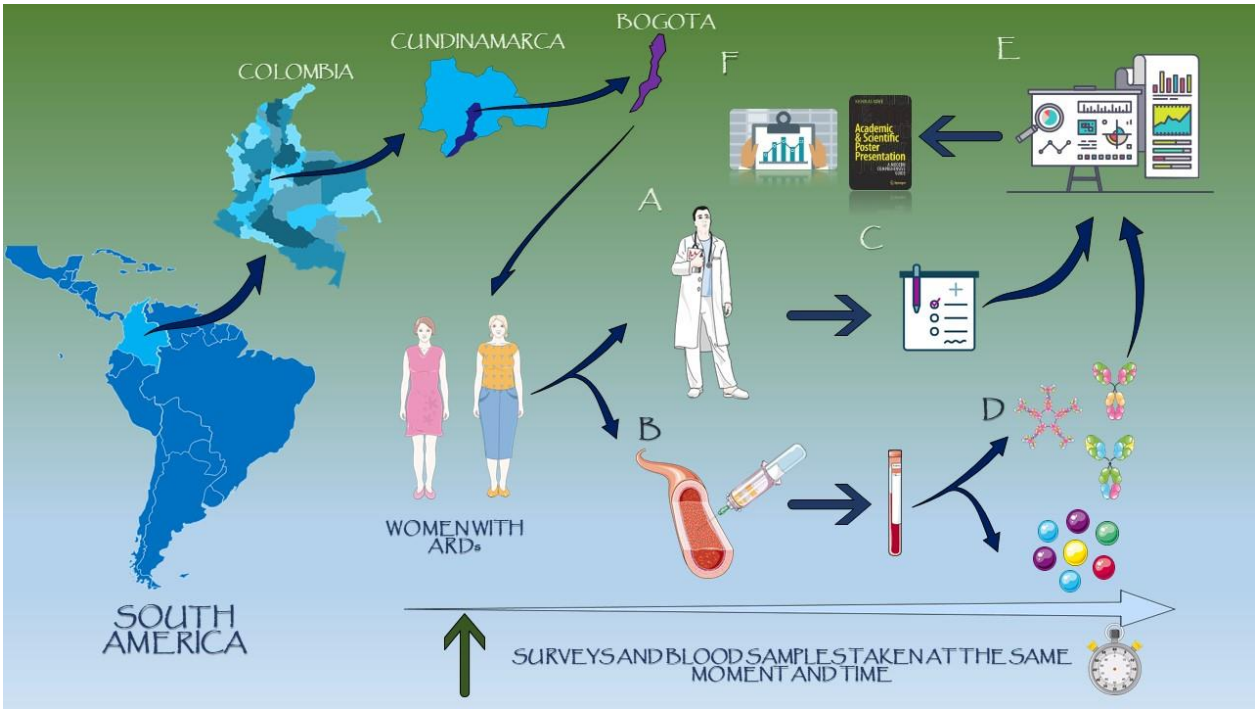


**Figure 1.** Cross-Sectional study design. **A.** Clinical records and survey fulfillment were conducted by expert physicians. **B.** Blood samples were obtained from patients by previously trained technicians and nurses. **C.** After fulfillment of formats and charts review, data were included in the data base. **D.** Blood samples were used to analyze the levels of cytokines and antibodies. **E.** Bivariate and multivariate analysis were done by R. **F.** Results were shown in congress presentations and in two academic papers.

## 5.3 POPULATION

The study was performed on 188 Colombian patients with SLE (n= 70), RA (n= 51), SS (n= 32), and SSc (n= 35). The subjects have been followed in a cohort at the Center for Autoimmune Diseases Research (CREA) in Bogota, Colombia. Subjects included in this study were all updated to get information about resilience, citokines and socioeconomic factors, which were not studied in previous works.

## 5.4 SAMPLE DESIGN

**5.4.1** Sample size: the hypothesis of this work is to find associations between clinical, sociodemographic and biological factors and resilience, however, information in this field in ARDs is lacking. Thus, we dicided to calculate the sample size for this study using the expected difference in the mean scores of resilience among the ARDs. In this case, a significant level of 5% and a power of 80% were selected. Some authors report resilience levels close to 3 in chronic conditions (123). A difference in resilience of 1.1 with a standard deviation of 1.5 was set for the study. The following formula was used to calculate the sample size:

$$n = 2\left[\frac{(Z_\alpha - Z_\beta)\ DE}{\mu_1 - \mu_2}\right]^2$$

**Zα** = 1.96, **Zβ** = –0.84, **DE**= 1.5, **μ1 - μ2** = 1.1

**n:** 2 [ (1.96 – (- 0.842)) * (1.5) / (1) ]$^2$

**n:** 2 [ 3.82]$^2$

**n:** 2 * 14.6

**n:** 29

The results indicated that a sample size of 29 patients in each disease (i.e., RA, SLE, SSc and SS) was necessary to show true statistical difference between groups.

In this study, a final sample size of 188 was obtained, with more than 29 patients in each group. This was secondary to the consecutive inclusion of patients to the protocol.

Since the hypothesis of this study is to find associations between factors and resilience in patients with rheumatological conditions, we aimed to construct multivariate models to explain resilience in ARDs. In this sense, we based on the formulas proposed by Green *et al.* (138) to calculate the sample size required to conduct reliable regression models.

A. For multiple regression models with focus on $R^2$: In this case, Green propose the formula $N > 50 + 8(k)$ (138), where $k$ is the number of factors that will be included in the regression analysis. In our case, we built models with resilience as dependent variable and maximum 4 factors in each regression. Thus, the minimum sample size require in this case would be:

$$=50 + 8(4)$$
$$=50 + 32$$
**=82 subjects**

B. For multiple regression models with focus on $\beta$ weights: In this case, it would be necessary to use the formula: $N > 104 + k$ (138), where k would be the number of factors to be included in the multivariate model. In this case, we built models with resilience as dependent variable and maximum 4 factors in each regression. Thus, the minimum sample size require in this case would be:

$$=104 + 4$$
**=108 subjects**

**5.4.2** Patient's selection: One hundred and Eighty-eight patients with SLE, RA, SSc and SS were selected by a non-probabilistic sampling (i.e., convenience sampling).

**5.4.3** Inclusion criteria: All patients included in the study were older than 18 years old and fulfilled either the 1987 ACR classification criteria for RA (58), the 1997 ACR criteria for SLE (70), the 2013 ACR/European League Against Rheumatism classification criteria for SSc, (81), or the revised American-European Consensus Group for SS (99).

**5.4.4** Exclusion criteria: Patients with infections prior a week of assessment, malignancy, and pregnancy, incapable to response the survey by themselves, younger than 18 years old or unfulfilling classification criteria were excluded of the study.

## 5.5 VARIABLES DESCRIPTION

### 5.5.1 Variables diagram

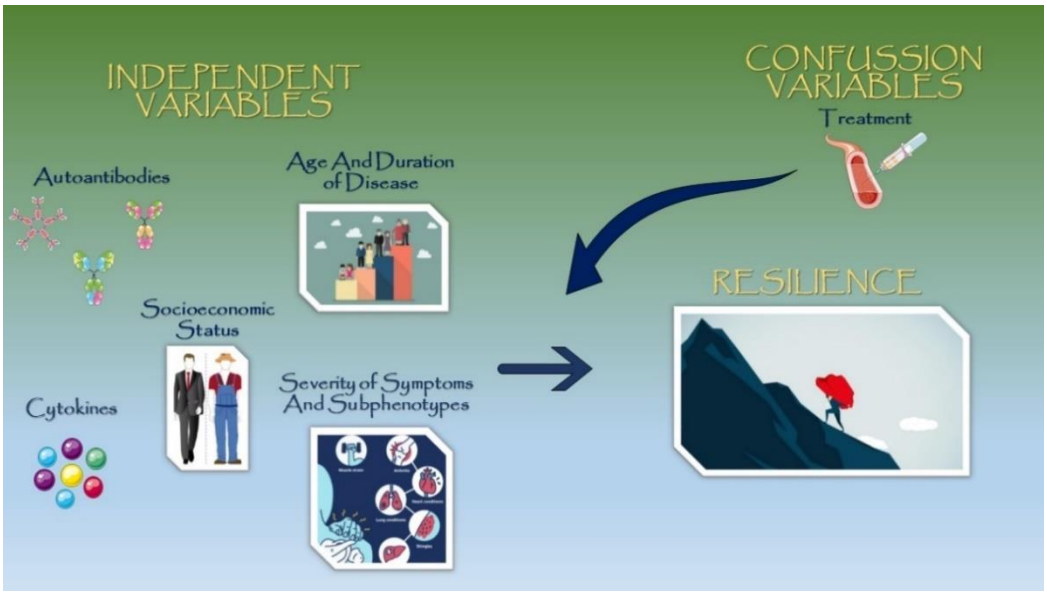


**Figure 2.** Variables diagram. Pictures taken and adapted from: 1, 2, 3, 4.

### 5.5.2 Variables table

The variables that were included in the study are shown in Appendix 1.

## 5.6 DATA COLLECTION

### 5.6.1 Sources of information

In this study, all data was obtained from primary sources of information.

### 5.6.2 Instruments for data collection

- A previously used format at CREA for inclusion of patients was applied (Appendix 2).

- Classification criteria for ARDs were assed with questionnaires previously validated and used at CREA (Appendix 3).

- Resilience was measured by the BRS questionnaire (Appendix 4).

- Severity of symptoms was assessed by the RAPID3, SLAQ, SSPRO and ESSPRI questionnaires (Appendix 5).

### 5.6.3 Data collection strategy

Patients were gathered one day in the same place at the CREA in previously scheduled meetings in March of 2017. Prior informed consent, patients were asked to complete the inclusion format (Supplementary 1) and a sample of blood was obtained to measure cytokines and autoantibodies, simultaneusly. Following, patients were asked to answer the BRS (Supplementary 3) and severity of symptoms

questionnaires (Supplementary 4). An expert physician confirmed the fulfillment of classification criteria by chart review and analysis of clinical history (Supplementary 2). Finally, at the end of the survey, all questionnaires were audited to confirm the fulfillment. All collected data were saved in a secure electronic database as previously established in the protocols of the CREA.

#### **5.6.4** Laboratory protocols

Serum samples were obtained in a state of fasting. A total of 14 autoantibodies were evaluated. Detection of IgG thyroperoxidase (TPO) and thyroglobulin (Tg) antibodies, IgG anti-CCP3, RF, IgM and IgG anti-cardiolipin antibodies (ACA), IgM and IgG anti-β2glycoprotein-1 (β2GP1) antibodies, IgG dsDNA antibodies, anti-SSB/La, anti-SSA/Ro, anti-ribonucleoprotein antibody (RNP), and anti-Smith (Sm) antibodies was done by Enzyme-Linked-Immunosorbent Assay (ELISA) (139). Antinuclear antibodies (ANAs) were evaluated by indirect immunofluorescence assay. Serum reactivity at a dilution of at least 1/80 was considered a positive result for ANA.

Concentration of 15 cytokines (IL-2, IL-10, IL-6, IL-8, IL-9, IL-13, IL-12/23p40, G-CSF, IFNγ, IFNα, IL-4, IL-1β, TNFα, IL-5, and IL-17A) in serum samples from patients was assessed by Cytometric Bead Array (CBA, Becton Dickinson Biosciences, San Diego, CA, USA). The test was done according to the manufacturer's protocols. Concentration of the cytokines was calculated using the FCAP Array™ Software (BD Bioscience) as reported elsewhere (32). Sample to test cytokines was available in 47 patients with RA, 67 patients with SLE, and 31 subjects with SS. All patients with SSc had enough serum to test cytokines.

## 5.7 ERROR AND BIAS CONTROL

### 5.7.1 ERROR CONTROL

#### 5.7.1.1. Sampling error

- All patients fulfilled classification criteria, and patients that cannot complete the instruments for data collection were excluded.
- Autoantibodies and cytokines were measured in all included patients except for some patients with RA (n= 4), SLE (n= 3), SS (n= 1), whose serum sample was insufficient to test these biomarkers. However, the number of subjects lacking of this test did not significantly differ with those with complete measurement.

#### 5.7.1.2. Measurement Errors

- Measurement of cytokines and antibodies by trained personnel.
- Standardized technique for measurement of autoantibodies (ELISA).
- Quality control by the manufacturer (INOVA Diagnostics).
- Expert physicians verified the fulfillment of all data collection templates.

### 5.7.2 Bias control

- Memory bias: Questioning of patients was guided by expert physicians.
- Confusion Bias: the results of resilience could be biased by age, duration of disease, occupation, SES, educational levels and treatment. However, a multivariate analysis model adjusted for these variables was conducted.

## 5.8 DATA ANALYSIS

**Table 1.** Analysis plan of data.

| Specific objective | Variables | Presentation | Measurements |
|---|---|---|---|

| | | | |
|---|---|---|---|
| To describe the socioeconomic, clinical and biological characteristics of patients in the four ARDs. | Quantitative continuous:<br>1) Age<br>2) Educational level<br>3) Duration of disease | Tables. | According to normality test, these variables were presented as median and interquartile range. |
| | Qualitative:<br>4) Socioeconomic status:<br>o Low<br>o Medium<br>o High<br>5) Occupation:<br>o Yes<br>o No<br>6) Polyautoimmunity:<br>o Yes<br>o No<br>7) Treatment:<br>o Yes<br>o No | Tables. | These variables were presented as relative frequencies according to each category within the variable. |
| To asses resilience in the four ARDs by the BRS. | Quantitative continuous:<br>1) Resilience:<br>A mean of total sum by the total number of questions answers in the BRS: 1 (lowest levels of resilience) y 6 (highest level of resilience). | Tables. | According to normality test, these variables were presented as median and interquartile range. |
| | Qualitative:<br>2) Resilience:<br>o Low resilience<br>o Normal resilience<br>o High resilience | Tables. | These variables were presented as relative frequencies according to each category within the variable. |
| To measure severity of symptoms with either RAPID3 for RA, SLAQ for SLE, SSPRO for SSc, or ESSPRI for SS. | Quantitative continuous:<br>3) RAPID 3: 0 to 30<br>4) SLAQ: 0 to 61<br>5) SSPRO: 1 to 105<br>6) ESSPRI: 5 to 30 | Description in text. | These variables were presented as relative frequencies according to each category within the variable. |
| To quantify the levels of antibodies and cytokines in the four ARDs. | Quantitative continuous:<br>IL-2, IL-10, IL-6, IL-8, IL-9, IL-13, IL-12/23p40, G-CSF, | Tables. | Since these variables did not accomplished normality, we decided to present them as |

| | | | |
|---|---|---|---|
| | IFNγ, IFNα, IL-4, IL-1β, TNFα, IL-5, and IL-17A en pg/ml | | being in the mean with standard deviation. |
| | Qualitative:<br>IgM RF, IgG CCP3, IgM and IgG ACA, IgM and IgG β2GP1, IgG dsDNA, IgG Tg and TPO, ANAs, anti-SSB/La, anti-SSA/Ro, anti-RNP, and Sm antibodies. | Tables. | These variables were presented as relative frequencies according to each category within the variable. |
| To analyze the associations of resilience with socioeconomic, clinical and biological factors through bivariate and multivariate analysis. | Quantitative continuous:<br>1) Age<br>2) Educational level<br>3) Duration of disease<br>4) Resilience<br>5) Cytokines<br>6) RAPID 3<br>7) SLAQ<br>8) SSPRO<br>9) ESSPRI | Tables.<br>Box plots. | Analysis between continuous variables was made by spearman correlation test. The association measure wes the $r^2$ coefficient. |
| | | | In the bivariate level, resilience was tested by Kruskal-Wallis and Mann-Whitney-U. These two tests evaluate the difference in ranks of a dependent variable according to factor levels. This was the association measure. |
| | | | In the multivariate analysis, a linear regression model was built. This model had the resilience as dependent variable. The association measurement was the β weights obtained. |
| | Qualitative:<br>1) Socioeconomic status<br>2) Occupation<br>3) Polyautoimmunity<br>4) Treatment<br>5) Resilience<br>6) Antibodies | Tables. | Analysis between qualitative variables was made by either Fisher or Chi-square tests accordingly. Independecy was considereded as the association measure. |
| To build a predictive model for resilience in ARDs through classification and regression trees (CART). | Dependent variables:<br>1) Quantitative resilience<br>Covariates:<br>2) Age | Classification tree | Multiple linear regressions and classification and regression trees (CART) analysis were used to |

| | | | |
|---|---|---|---|
| | 3) Duration of disease<br>4) Socioeconomic status | | evaluate the relationship between resilience and covariates. |

ARDs: Autoimmune rheumatic diseases; BRS: Brief Resilience Scale; RAPID: Routine Assessment of Patient Index Data 3; SLAQ: Systemic Lupus Activity Questionnaire; SSPRO: Skin Patient-Reported Outcome; ESSPRI: EULAR SS patient reported index; RF: Rheumatoid factor; CCP3: cyclic citrullinated peptide third-generation antibodies; ACA: Anticardiolipin antibodies; β2GP1: β2glycoprotein antibodies; dsDNA: Double-strand DNA antibodies; Tg: Thyroglobulin antibodies; TPO: Thyroid peroxidase antibodies; ANAs: Antinuclear antibodies; IFN: Interferon; TNF: Tumor necrosis factor; IL: Interleukin.

Briefly, a series of recursive subdivisions separated the data by dichotomization is done with CART analysis. The aim of this analysis is to identify, at each partition step, the best predictive variable and its best corresponding splitting value while optimizing a statistical criterion. A value of 0.05 was set as significant. R software version 3.3.2 was used to analyze data as previously described (83).

## 5.9 DISCLOSURE OF RESULTS

The main results of the study were published in two articles. The first, included information about socioeconomic and clinical data associated with resilience (83) (Appendix 6), whereas the second one comprised the results about cytokines and their possible role on resilience in SSc (140) (Appendix 7). In addition, these results were presented in national and international meetings with focus in autoimmunity (i.e., 5$^{th}$ Latin American Congress of Autoimmunity-LACA and 1$^{er}$ Congreso Colombiano de Autoinmunidad).

## 5.10 ROLE OF THE FUNDING SOURCE

This work was supported by Universidad del Rosario (ABN011) and Colciencias (Grant No 122254531722/Grant No0425-2013), Bogota, Colombia.

## 6. ETHICAL CONSIDERATIONS

As previously described in the protocol presented by Yhojan *et al.* (141). Ethical considerations were followed as formerly stablished at the CREA with approval by the institutional review board of the Universidad del Rosario**.**

### 6.1. POPULATION

Patients were contacted by the CREA staff of the Universidad del Rosario between January and February of 2017. The process was done according to the 1581statutory law of 2012 and the script to contact the patients is shown below:

> Buenos días señor / señora (**nombrar el paciente),** un gusto saludarlo/a
> Me llamo ***(su nombre)*** soy médico/enfermera del ***Centro De Estudio De Enfermedades Autoinmunes*** (CREA), de la Universidad del Rosario.
>
> En años anteriores usted quedó incluido con nosotros, dentro del grupo de pacientes con……. Hoy queremos saludarlo/a y saber cómo ha estado estos últimos meses.
>
> Antes que nada, para nosotros es un placer saber de usted nuevamente. Cuénteme cómo se encuentra……Gracias señor / señora (**nombrar el paciente).** Actualmente estamos llevando jornadas de seguimiento más personalizadas de nuestros pacientes con el fin de actualizar las historias clínicas, reunirnos y conocer otros pacientes que tienen la misma enfermedad y además aprender sobre qué es el Síndrome de Sjögren. ¿Le gustaría venir el día__ a las ___ a esta jornada?

Si responde SI, dar todas las indicaciones. Si responde NO, decir muchas gracias señor / señora (**nombrar el paciente**). Hasta una próxima oportunidad.

## 6.2. PATIENT VULNERABILITY

Patients in this study were at risk of subordination since all of them have been followed by in the CREA and most of the time they have been contacted by doctors. However, in this time, patients were contacted by CREA staff, which does not possess medical degree to avoid influencing their decision to attend. Further, if patient rejects the invitation, no retaliation was done, since they will be followed in the cohort despite their decision.

## 6.3. INFORMED CONSENT

Prior written consent was asked to begin the surveys and the blood sample acquisition. The informed consent format is shown in the Appendix 8.

## 6.4. DATA

All collected data was collected in a secure electronic database and all information obtained from their analysis was managed according to the1581 statutory law of 2012. The identity of the patients was codified and was not shown in any of the sections of this work. The use and storage of information was handled according to the resolution 839 of 2017, which states the management of clinical records in Colombia.

## 6.5. RISK

This study was carried out in compliance with the Act 008430/1993 of the Ministry of Health of the Republic of Colombia, which classifies it as minimal-risk research. The institutional review board of the Universidad del Rosario approved the study design.

# 7. RESULTS

## 7.1. General characteristics

The general characteristics of patients are shown in Table 2. Patients with SLE exhibited the lower age and age at onset, whereas patients with RA showed the longer duration of disease. Majority of patients with SLE were on middle SES and showed the highest rates of employment. Exercise, PolyA and BRS scores were not different among the four diseases studied (Table 2). The severity of symptoms in RA measured by RAPID3 showed a median value of 14 (5.75-22), the SLAQ for SLE was 16 (IQR 8.25–26), ESSPRI in SS was 6 (IQR 4.7–6.75), and the median for SSPRO in SSc was 52 (IQR 30.5–64).

A summary of therapy at the moment of the study is shown in Table 3. DMARDs were the most common therapy in RA and SSc, whereas immunosuppressors were the most common treatment in subjects with SLE. Predominantly, patients with SS showed the lower rates of treatment (Table 3).

The results of autoantibodies are shown in Table 4. As expected, specific autoantibodies of each disease were higher when comparing with other ARDs. RF and CCP3 in RA, ANAs and dsDNA in SLE, SSA/Ro and SSB/La in SS. Other autoantibodies such as ACA-IgG, ACA-IgM, β2GP1-IgG, β2GP1-IgM, Sm, TPO, and Tg were not different among diseases (Table 4). These results helped to confirm classification and diagnosis of patients included in the study.

**Table 2.** Overall characteristics of women with ARDs.

| Variable | RA (n: 51) | SLE (n: 70) | SSc (n: 35) | SS (n: 32) | *P*-value |
|---|---|---|---|---|---|
| | | SOCIODEMOGRAPHIC DATA | | | |
| Age (IQR) | 58 (48.5-63) | 50.5 (37.5-57) | 58 (51.5-62.5) | 64.5 (55.7-68.7) | <0.001 |
| Age at onset disease (IQR) | 36 (26-49) | 29 (22-40) | 48 (37-53.5) | 50.5 (40-58.25) | <0.001 |
| Disease duration (IQR) | 17 (10.5-26) | 13 (9-21.75) | 7 (4-13) | 12 (9-17) | <0.01 |
| Educational years (IQR) | 14 (8-17) | 14(11-16) | 11(9-16) | 13.5 (11-16) | 0.78 |
| Socioeconomic status (%) | | | | | |
| Low | 18 (35.3) | 19 (27.1) | 8 (22.9) | 3 (9.4) | <0.01 |
| Middle | 14 (27.5) | 39 (55.7) | 17 (48.6) | 15 (46.9) | |
| High | 18 (35.3) | 12 (17.14) | 10 (28.5) | 14 (43.7) | |
| ND | 1 (1.9) | | | | |
| Occupation (%) | | | | | |
| Employed | 30 (58.8) | 44 (63) | 20 (57) | 11 (34) | <0.01 |
| Unemployed | 20 (39.2) | 26 (37) | 15 (43) | 20 (63) | |
| ND | 1 (1.9) | | | 1 (3) | |
| Exercise (%) [a] | 22 (43.1) | 28 (40) | 23 (65.7) | 17 (53.1) | 0.071 |
| Polyautoimmunity | 14 (27.5) | 17 (24.3) | 14 (40) | 8 (25.8) | 0.408 |
| | | RESILIENCE ASSESSMENT | | | |
| Total BRS (IQR) [b] | 3.33 (3.1- 4.1) | 3.42 (3- 3.83) | 3.33 (2.8- 3.7) | 3.25 (2.95- 4) | 0.5 |

[a] At least 30 minutes three times per week; [b] multiple linear regression analysis, classification and regression trees (CART) were performed to evaluate the relations between BRS and disease, adjusting by duration of disease, age and socioeconomic status (Figure 2); [c] Low BRS: 1-2.99; [d] Normal BRS: 3-4.3; [e] High BRS: 4.31-6. RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis; SS: Sjögren's syndrome; IQR: Interquartile range; ND: No data; BRS: Brief Resilience Scale Total Score (i.e., total sum by the total number of questions answers)

**Table 3.** Treatment in patients with ARDs

| Treatment [a] | RA (n: 36) | SLE (n: 70) [b] | SSc (n: 30) | SS (n:18) |
|---|---|---|---|---|
| Immunosuppressors | 1 (2.8) | 45 (64.3) | 4 (13.3) | 2 (11.1) |
| DMARDs | 28 (77.8) | 14 (20) | 10 (33.3) | 1 (5.6) |
| Corticoids | 10 (27.8) | 39 (55.7) | 7 (23.3) | 2 (11.1) |
| Antimalarials | 7 (19.4) | 41 (58.6) | 5 (16.7) | 3 (16.7) |
| Biologics | 17 (47.2) | 9 (12.9) | 1 (3.3) | 0 (0) |

[a] Data corresponds to the number of patients under treatment (%). [b] Complete data about treatment was only available in SLE. RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis; SS: Sjögren's syndrome; DMARDs: Disease Modifying Antirheumatic Drugs.

**Table 4.** Autoantibodies in women with ARDs

| Autoantibody (%) [a] | RA (n: 51) | SLE (n: 70) | SSc (n: 35) | SS (n: 31)[b] | *P-value* |
|---|---|---|---|---|---|
| ANAs | 4 (7.8) | 59 (84.3) | 12 (34.3) | 16 (51.6) | <0.0001 |
| SSA/Ro | 11 (21.6) | 28 (40) | 12 (34.3) | 23 (74.2) | <0.0001 |
| SSB/La | 3 (5.9) | 5 (7.1) | 6 (17.1) | 15 (48.4) | <0.0001 |
| Sm | 0 (0) | 13 (18.6) | 2 (5.7) | 0 (0) | 0.0004 |
| RNP | 2 (3.9) | 27 (38.6) | 6 (17.1) | 5 (16.1) | <0.0001 |
| ACA IgG | 2 (3.9) | 13 (18.6) | 2 (5.7) | 1 (3.2) | 0.0153 |
| ACA IgM | 7 (13.7) | 11 (15.7) | 8 (22.9) | 2 (6.5) | 0.3119 |
| β2GP1 IgG | 0 (0) | 6 (8.6) | 1 (2.9) | 1 (3.2) | 0.1279 |
| β2GP1 IgM | 2 (3.9) | 7 (10) | 8 (22.9) | 3 (9.7) | 0.0473 |
| RF | 43 (84.3) | 24 (34.3) | 23 (65.7) | 20 (64.5) | <0.0001 |
| CCP3 | 39 (76.5) | 1 (1.4) | 2 (5.7) | 1 (3.2) | <0.0001 |
| dsDNA | 4 (7.8) | 33 (47.1) | 3 (8.6) | 6 (19.4) | <0.0001 |
| TPO | 14 (27.5) | 8 (11.4) | 6 (17.1) | 7 (22.6) | 0.1471 |
| Tg | 6 (11.8) | 5 (7.1) | 4 (11.4) | 6 (19.4) | 0.3558 |

[a] Data correspond to number of patients (%); [b] There was not enough sample to complete the measurement of autoantibodies in one patient; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis; SS: Sjögren's syndrome; ANAs: Antinuclear antibodies; Sm: Anti-Smith antibodies; RNP: Anti-ribonucleoprotein antibodies; ACA: Anti-cardiolipin antibodies; β2GP1: Anti-β2glycoprotein-1 antibodies; dsDNA: Anti-double-strand DNA antibodies; RF: Rheumatoid factor; CCP3: Third generation anti-citrullinated peptide antibodies; TPO: Anti-thyroperoxidase antibodies; Tg: Anti-thyroglobulin antibodies.

The summary of results of cytokines are shown in table 5. Almost every cytokine showed different concentrations across the four ARDs studied. Patients with RA showed the higher levels of IL-1β, IL-6, IL-13, and TNF-α among the ARDs, whereas those patients SS exhibited the highest levels of IL-4, IL-12/23p40, IL-17A and IFN-α. In SSc, the IL-8, G-CSF, and IFN-γ were the most predominant cytokines in comparison with other diseases. Any especial pattern of cytokines was not observed in patients with SLE (Table 5).

**Table 5.** Cytokine concentrations in women with ARDs.

| Cytokine[a] | RA[b] (n: 47) | SLE[c] (n: 67) | SSc (n: 35) | SS (n: 31) | *P-value* |
|---|---|---|---|---|---|
| IL-1β | 6.43 (16.30) | 0.97 (4.66) | 5.80 (11.90) | 5.80 (13.56) | 0.0002 |
| IL-2 | 5.50 (21.43) | 0.39 (2.23) | 1.18 (3.57) | 1.40 (5.80) | 0.06 |
| IL-4 | 2.30 (8.03) | 0.39 (2.01) | 2.50 (5.20) | 4.60 (9.00) | 0.0012 |
| IL-5 | 1.00 (2.70) | 0.17 (0.77) | 1.00 (2.22) | 0.45 (1.10) | 0.0026 |
| IL-6 | 6.20 (8.95) | 5.00 (28.1) | 4.84 (7.10) | 0.90 (3.40) | 0.0001 |
| IL-8 | 10.80 (8.40) | 12.67 (25.13) | 13.22 (7.60) | 9.50 (12.50) | 0.0041 |
| IL-9 | 0 (0) | 0.13 (0.75) | 1.02 (3.12) | 0.09 (0.50) | 0.0027 |
| IL-10 | 2.20 (5.61) | 0.60 (1.79) | 2.40 (4.60) | 0.98 (1.98) | 0.12 |
| IL-12/23p40 | 37.40 (76.40) | 27.10 (48.90) | 46.00 (76.50) | 52.50 (78.32) | 0.24 |
| IL-13 | 1.80 (5.20) | 0.02 (0.20) | 0.84 (3.0) | 0.36 (0.94) | 0.0019 |
| IL-17A | 31.30 (71.10) | 7.40 (33.90) | 34.70 (72.30) | 36.90 (69.80) | 0.0006 |
| G-CSF | 3.37 (7.90) | 2.20 (6.20) | 6.72 (12.30) | 3.80 (8.10) | 0.32 |
| TNF-α | 10.39 (21.71) | 2.11 (9.34) | 10.05 (20.60) | 7.92 (18.73) | 0.0005 |
| IFN-α | 13.20 (26.90) | 3.72 (12.20) | 14.80 (26.50) | 17.40 (28.10) | 0.0026 |
| IFN-γ | 0.20 (1.38) | 0.39 (2.10) | 0.66 (1.40) | 0.17 (0.95) | <0.0001 |

[a] Mean (standard deviation) in pg/mL; [b] results are based on 47 patients due to insufficient serum to test cytokines; [c] results are based on 67 patients due to insufficient serum to test cytokines; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; SSc: systemic sclerosis; SS: Sjögren's syndrome; IL: Interleukin; G-CSF: Granulocyte colony-stimulating factor; IFN: Interferon; TNF: Tumor necrosis factor.

## 7.2. CLINICAL STATUS, DEMOGRAPHIC FACTORS AND RESILIENCE

In the bivariate analysis, SES and exercise were associated with resilience in patients with SSc. Those patients with high SES and with regular physical activity (i.e., more than 30 minutes 3 times per week) showed the highest resilience scores in SSc (Figure 3). Duration of disease, age, age at onset, occupation, years of formal education, and PolyA were not associated with the BRS in any of the ARDs studied (Table 6).

**Table 6.** Correlations and associations of resilience with sociodemographic and clinical factors

| Disease | Age* | Age at Onset* | Duration of Disease* | Education Years* | Severity of symptoms* | SES** | Occupation*** | Exercise*** | PolyA*** |
|---|---|---|---|---|---|---|---|---|---|
| RA | 0.3 (0.07) | 0.2 (0.2) | 0.14 (0.32) | -0.28 (0.05) | 0.02 (0.87) | 0.7 | 0.31 | 0.12 | 0.28 |
| SLE | 0.12 (0.32) | 0.2 (0.2) | -0.04 (0.74) | 0.11 (0.4) | -0.08 (0.49) | 0.62 | 0.07 | 0.17 | 0.62 |
| SSc | 0.21 (0.22) | 0.24 (0.2) | 0.08 (0.64) | 0.3 (0.2) | 0.10 (0.58) | 0.012 | 0.7 | 0.008 | 0.59 |
| SS | 0.09 (0.02) | -0.05 (0.02) | 0.1 (0.99) | -0.05 (0.8) | -0.08 (0.67) | 0.58 | 0.9 | 0.64 | 0.85 |

* Correlation analysis of resilience and variables of interest by spearman coefficient test $r_s$ (*p-value*); ** *p-value* of Kruskal-Wallis test for resilience in SES; *** *p-value* of Mann-Whitney test for resilience in occupation, exercise and PolyA. RA: Rheumatoid Arthritis, SLE: Systemic Lupus Erythematosus, SSc: Systemic Sclerosis, SS: Sjögren´s Syndrome, SES: Socioeconomic status, PolyA: Polyautoimmunity.

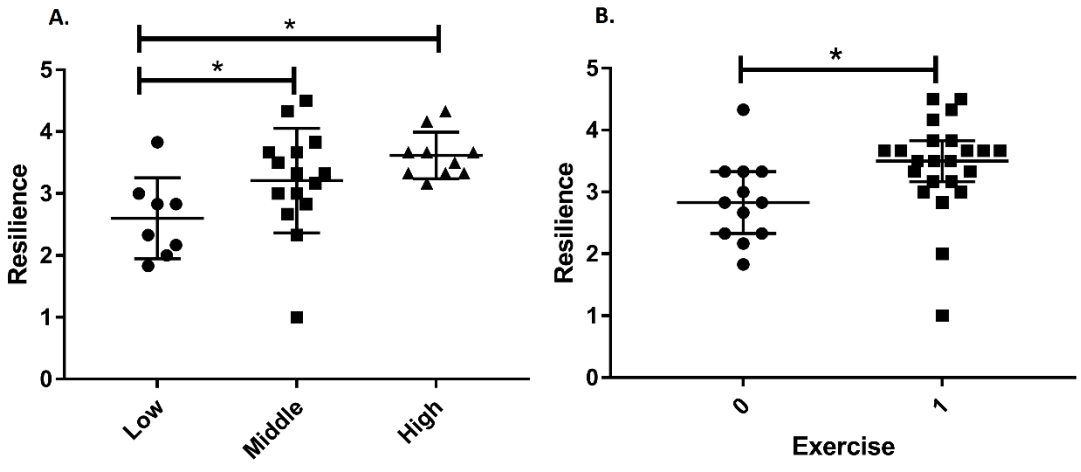


**Figure 3.** Resilience in patients with systemic sclerosis. A. socioeconomic status and B. exercise. *P < 0.05 for Mann-Whitney test. Taken and adapted from (83)

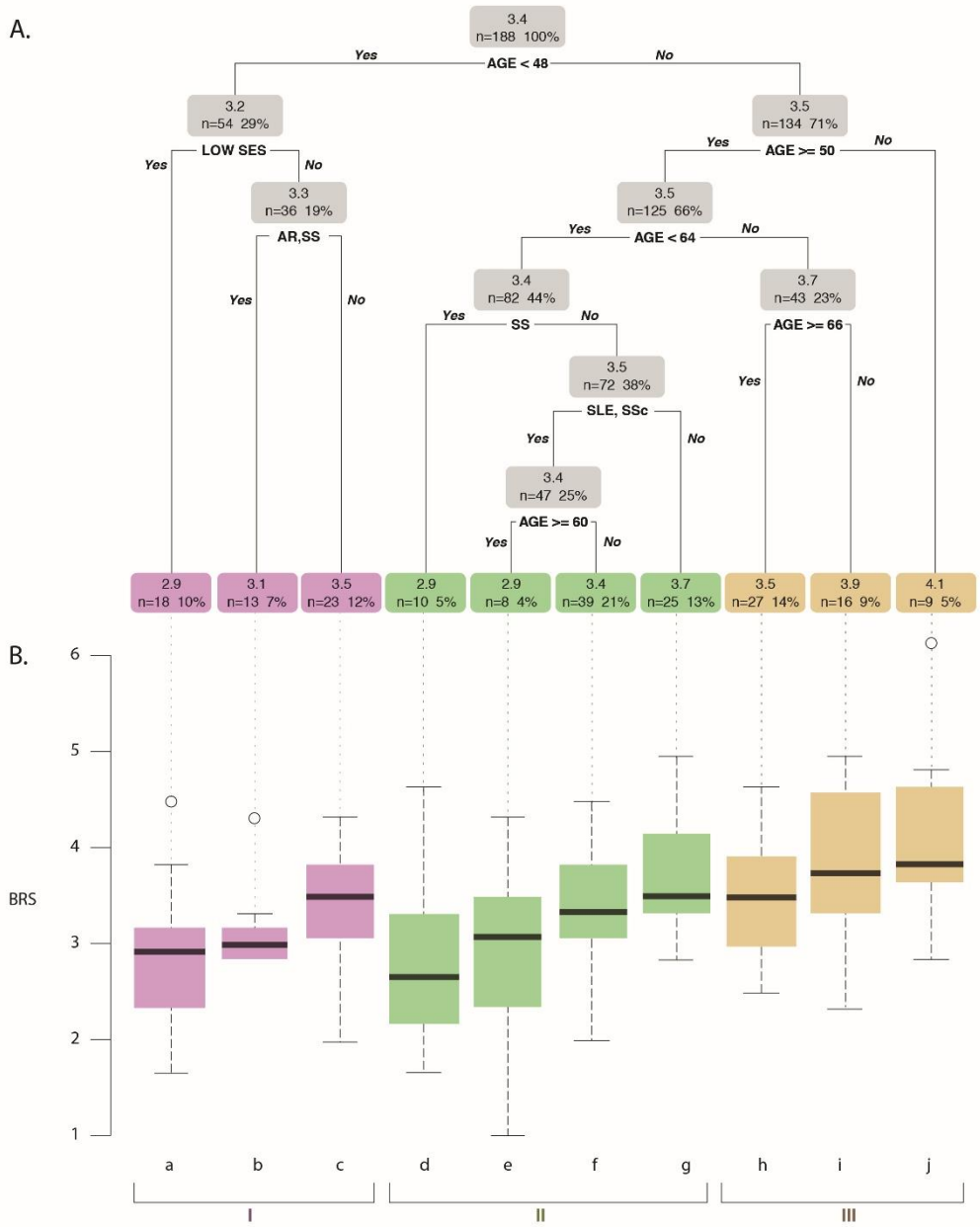


**Figure 4.** Classification and decision tree for resilience in autoimmune rheumatic diseases. A. decision rules for classification of patients concerning age, duration of disease, socioeconomic status, disease and brief resilience score (BRS) B. Distribution of BRS scores in the final decision tree. Three major groups were obtained from this analysis: purple box-plots represent the resilience levels in patients younger than 48 years old. Green box-plots include the resilience levels of those patients between 48 and 64 years old and yellow box-plots show the resilience in subjects with 48 to 66 years old. Inside every box-plot, there are patients of each disease. The following are the distributions of patients according to the box-plot name: a. SLE (50%), RA (28%), SSc (22%); b. RA (62%), SS (38%); c. SLE (91%), SSc (9%); d. SS (100% ); e. SSc (75%), SLE (25%); f. SLE (64%), SSc (36%); g. RA (100%); h. SS (45%), RA (22%), SLE (22%), SSc (11% ); i. SLE (37%), SS (31%), SSc (19%), SLE (13% ); j. SLE (56%), SSc (33%), RA (11%). RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis; SS: Sjögren's syndrome; SES: Socioeconomic status. Taken and adapted from (83).

Since a significant difference was observed for age, SES, and duration of disease among groups (Table 2), a multiple linear regression analysis was done. Results showed that resilience was higher in patients with RA in comparison with SSc (β= -0.432981, *p*= 0.01). Further, decision tree analyses revealed three patient groups (Figure 4). RA, SLE and SSc patients under 48 years old with low SES had low resilience scores (Figure 4-BI), whereas those between 48 and 64 years old with RA and SSc had highest BRS scores regardless of SES (Figure 4-BII). Patients between 48 and 66 years old with SLE and SS exhibited the highest resilience scores (Figure 1-BIII) and BRS was significantly higher in this group compared to patients under 48 years old with the same disease (Figure 4/BI-III). In addition, severity of symptoms was not associated with resilience scores in the four ARDs studied (Figure 5 and 6).

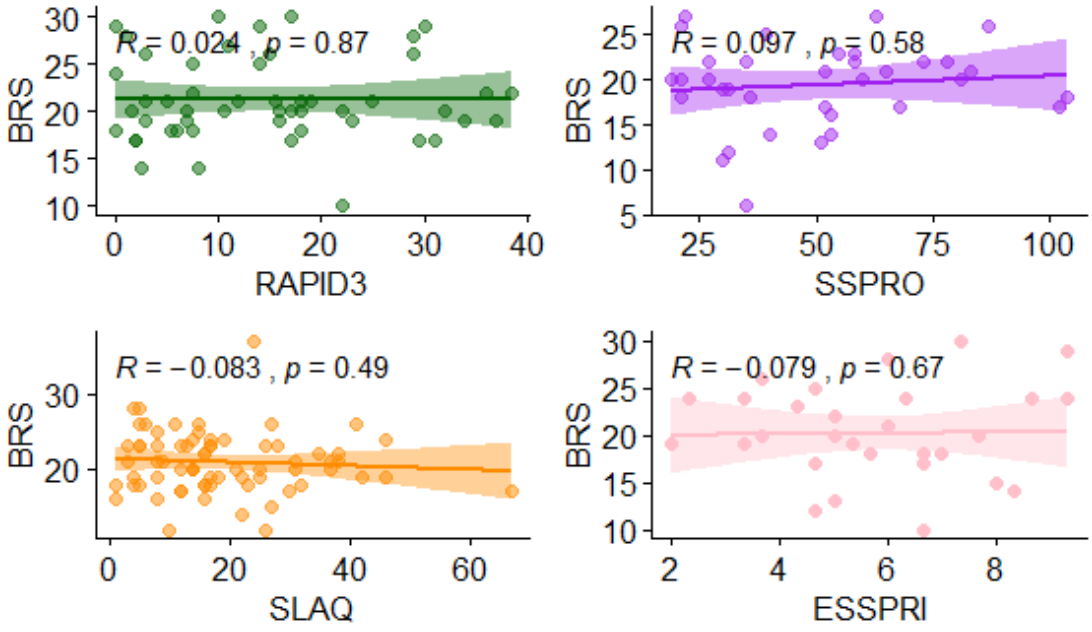


**Figure 5.** Spearman correlation analysis for resilience and severity of symptoms. The BRS scores were not correlated with RAPID3 in RA, SLAQ in SLE, SSPRO in SSc, nor ESSPRI in SS. RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis; SS: Sjögren's syndrome; BRS: Brief resilience scale; RAPID: Routine Assessment of Patient Index Data 3; SLAQ: Systemic Lupus Activity Questionnaire; SSPRO: Skin Patient-Reported Outcome; ESSPRI: EULAR SS patient reported index.

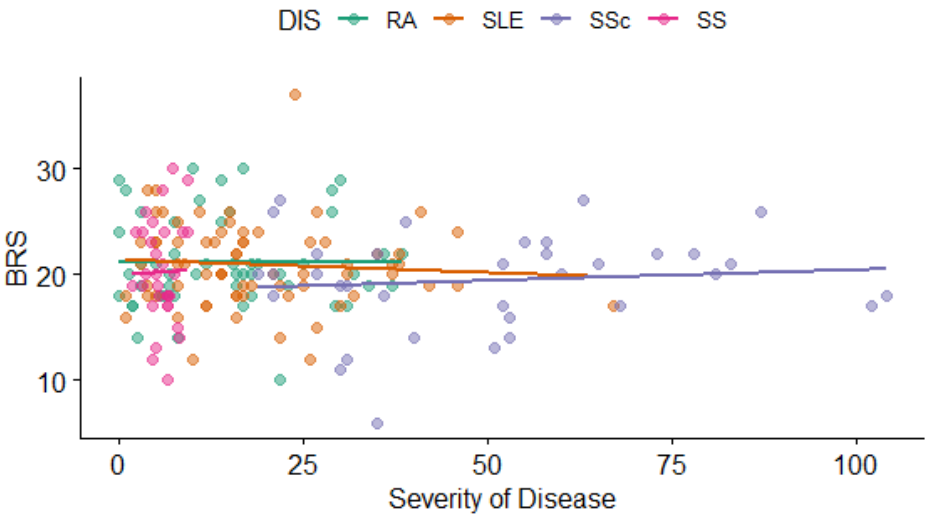


**Figure 6.** Scatter plot for resilience and severity of disease. Herein, an integrative picture of relationships between severity of disease and resilience across the four ARDs is presented. BRS: Brief resilience scale; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis; SS: Sjögren's syndrome.

## 7.1. CYTOKINES AND AUTOANTIBODIES IN RESILIENCE

Regarding autoantibodies, patients did not show differences in resilience according to autoantibodies positivity (Data not shown). The analysis for cytokines concerning resilience levels showed that IL-5, IL-8, IL-10 and IL-13, were negatively correlated with BRS scores in patients with SSc (Table 7). Interestingly, other cytokines were not correlated with resilience scores in the remaining ARDs.

Since cytokines were only associated with resilience in SSc, a multiple linear regression analysis was done in this subset of patients. Initially we tested for changes in cytokines according to treatment status in SSc. We realized that cytokines levels change across therapies (Table 8), thus we decided to conduct a multivariate analysis for BRS and cytokines with therapy as interaction term. IL-6 was associated with severity of symptoms measured by SSPRO ($\beta$ = 1.8395, $p$ = 0.0435) regardless of treatment (Fig. 7A), and with

low BRS scores (β = -0.581120, *p* = 0.0291) in those patients under therapy and regardless of severity of symptoms (Fig. 7B). These associations were found predominantly in individuals with limited subphenotype. Associations with other cytokines in SSc were not found with this approach, thus suggesting that therapy influenced the associations between some cytokines and resilience in the bivariate analysis (Table 7).

**Table 7.** Correlations between cytokines and resilience scores**.**

| **Interleukin [a]** | **RA** | **SLE** | **SSc** | **SS** |
|---|---|---|---|---|
| IL-1β | -0.15 (0.33) | -0.16 (0.19) | -0.18 (0.29) | -0.14 (0.44) |
| IL-2 | 0.29 (0.47) | 0.19 (0.13) | 0.15 (0.40) | -0.26 (0.15) |
| IL-4 | -0.20 (0.24) | -0.14 (0.24) | -0.22 (0.20) | 0.01 (0.94) |
| IL-5 | -0.13 (0.40) | 0.20 (0.10) | -0.45 (0.007) | -0.14 (0.46) |
| IL-6 | 0.04 (0.81) | 0.002 (0.99) | -0.30 (0.08) | -0.19 (0.30) |
| IL-8 | 0.21 (0.16) | -0.23 (0.06) | -0.38 (0.025) | -0.12 (0.54) |
| IL-9 | - | -0.53 (0.67) | -0.02 (0.93) | 0.29 (0.12) |
| IL-10 | -0.02 (0.89) | 0.07 (0.56) | -0.41 (0.015) | -0.24 (0.20) |
| IL-12/23p40 | -0.10 (0.53) | -0.07 (0.59) | -0.15 (0.38) | -0.11 (0.58) |
| IL-13 | 0.15 (0.33) | 0.04 (0.74) | -0.50 (0.002) | -0.05 (0.78) |
| IL-17A | -0.09 (0.55) | 0.05 (0.72) | -0.06 (0.73) | -0.11 (0.55) |
| G-CSF | -0.09 (0.57) | -0.04 (0.77) | -0.25 (0.15) | -0.14 (0.46) |
| TNF-α | -0.09 (0.53) | -0.009 (0.94) | -0.08 (0.65) | -0.06 (0.75) |
| IFN-α | -0.10 (0.51) | -0.00 (0.10) | -0.11 (0.54) | -0.07 (0.72) |
| IFN-γ | -0.02 (0.91) | 0.11 (0.37) | -0.07 (0.67) | -0.25 (0.18) |

**[a]** Spearman correlation analysis between cytokines and resilience $r_s$ *(p-value).* RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; SSc: Systemic sclerosis; SS: Sjögren's syndrome; IL: Interleukin; G-CSF: Granulocyte colony-stimulating factor; IFN: Interferon; TNF: Tumor necrosis factor.

**Table 8.** Associations of cytokines and treatment in systemic sclerosis.

| Variable | Immunosupressors | DMARDs | Corticoids | Antimalarials | All[a] |
|---|---|---|---|---|---|
| IL-1β | 0.4373 | 0.0109* | 0.3606 | 0.0765 | 0.0560 |
| IL-2 | 0.5702 | 0.4566 | 0.2454 | 0.3464 | 0.5911 |
| IL-4 | 1.0000 | 0.0016* | 0.1326 | 0.0765 | 0.0500 |
| IL-5 | 0.5001 | 0.1733 | 0.2665 | 0.1664 | 0.3033 |
| IL-6 | 0.2266 | 0.6796 | 0.9388 | 0.3683 | 0.8946 |
| IL-8 | 0.0240* | 0.2020 | 0.0329* | 0.4867 | 0.4212 |
| IL-9 | 0.1102 | 0.0903 | 0.7340 | 0.2840 | 0.2406 |
| IL-10 | 0.0505 | 0.2634 | 0.7656 | 0.1664 | 0.0921 |
| IL-12/IL-23p40 | 0.3930 | 0.5823 | 0.2594 | 0.1641 | 0.5820 |
| IL-13 | 0.5307 | 0.0256* | 0.2987 | 0.1528 | 0.0867 |
| IL17A | 0.5135 | 0.0070* | 0.2209 | 0.1235 | 0.0326* |
| TNF-α | 0.5735 | 0.0080* | 0.2416 | 0.1094 | 0.0409* |
| G-CSF | 0.1388 | 0.0778 | 0.5520 | 0.0734 | 0.0856 |
| IFN-α | 0.6019 | 0.0097* | 0.1649 | 0.0793 | 0.0636 |
| IFN-γ | 0.0046* | 0.2944 | 0.6612 | 0.3362 | 0.6317 |
| SSPRO | 0.0767 | 0.7413 | 0.9609 | 0.3162 | 0.3969 |
| BRS | 0.5403 | 0.8771 | 0.7304 | 0.1052 | 0.6101 |

Analyses were done with Mann–Whitney U test to find associations between treatment and cytokines levels. [a] This variable includes any combination of treatment with immunosuppressors, DMARDs, corticoids or antimalarials, *Statistically significant. DMARDs: Disease modifying antirheumatic drugs.

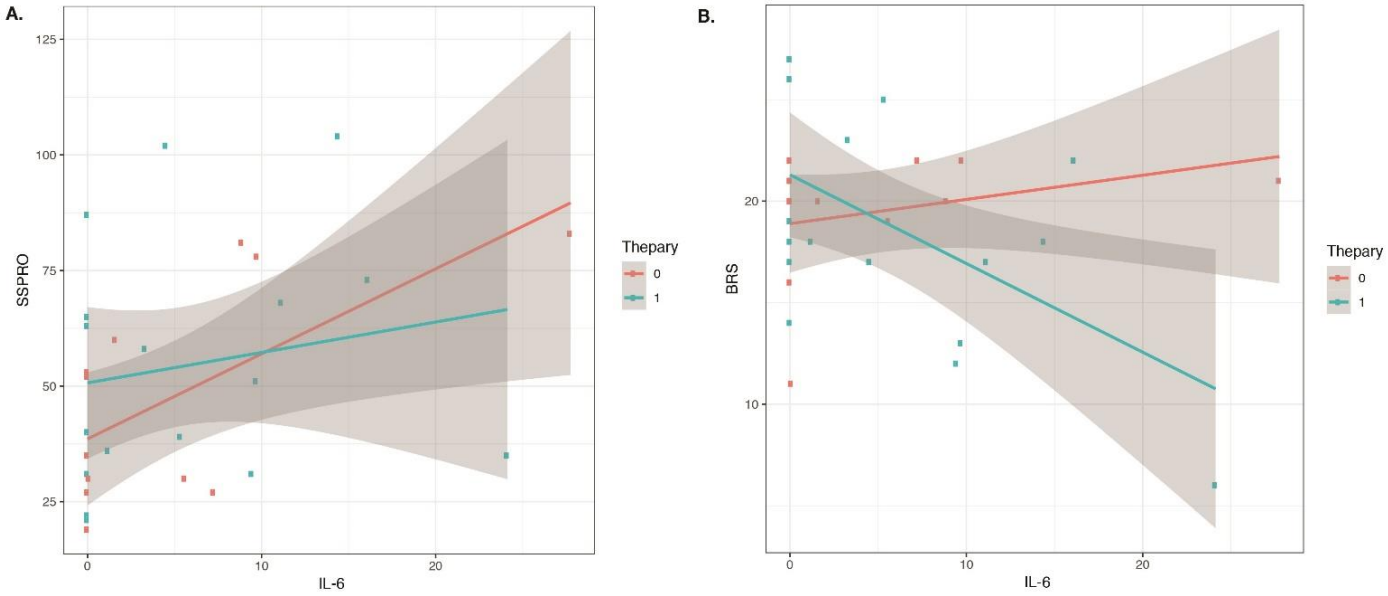


**Figure 7.** Joint effect of IL-6 and therapy on SSPRO scores, B. joint effect of IL-6 and therapy on BRS. Statistical analysis by means of linear regression with an interaction term. Therapy: includes any combination of treatment with immunosuppresors, DMARDs, corticoids or antimalarials. SSPRO: Scleroderma skin patient report outcome questionnaire; BRS: Brief Resilience Scale; DMARDs: Disease modifying antirheumatic drugs. Taken and adapted from (140).

# 8. DISCUSSION

## 8.1. RESILIENCE AND SOCIOECONOMIC FACTORS

In this study, we found an association of age and SES on resilience in all the ARDs assessed. In addition, a particular behavior was found in SSc, in which patients with recurrent physical activity (i.e., more than 30 minutes at least three times per week) showed a better capacity to face adversity, thus suggesting that resilience is different based on socioeconomically grouping and age. In addition, public health interventions including physical activity, could be major targets in management of resilience in rheumatic conditions.

The evidence about the role of age and duration of disease as modifiers of resilience in different rheumatic conditions is inconsistent. It was found that younger patients SLE (< 35 years old) exhibited the highest resilience scores (13), and it was negatively correlated with duration of disease (126). On the other hand, other observations of young individuals with SLE suggested that they may perceive physical and social abilities restriction, which may account for low resilience at the early stages of the disease (142). In the case of RA, studies of resilience are scarce. However, some authors have found that resilience in patients with RA is not influenced by age (14). In this study, the decision tree analysis revealed that individuals under 48 years old exhibited the lowest resilience levels when compare with those subjects with more than 48 years old. This data suggests that ability to coping with the illness could be influenced by the age, in which an older age together with different experiences across the lifetime could help to build resilience in patients with ARDs. However, the evaluation of those factors that may present in lifetime history was out of the scope of this work, and further analysis in this respect are mandatory.

Resilience is associated to gender, years of formal education, SES, and occupation in patients with chronic diseases (16). Psychiatric manifestations in women with low SES and a low level of education are common, especially after stressful life events (17). Recently, low SES was associated with higher symptoms of depression and anxiety through the effects of psychosocial resilience in SLE (128). These data are similar to our results since patients with low SES and SLE, SSc, and SS showed the lowest resilience scores. Overall, these observations call attention to the complex relations among multiple factors that play a key role in the development of resilient traits. Thus, resilience is a complex ability in which other factors, such as age and SES, play a crucial role in its development. In addition, the fact that older patients showed the highest resilience scores, settle the notion that resilience is a “continuum” associated to lifetime experiences in which the diagnosis of an ARD may not influence the outcomes.

Concerning occupational status, previous studies showed that unemployed patients with SLE did not have different resilience levels (13), and interestingly, resilience was positively correlated with the number of hours at work (126). In contrast, this study showed that BRS scores were not associated with the occupational status. Furthermore, prior studies showed that years of formal education was associated with a better response to adversity in chronic conditions, however, in patients with ARDs, a lack of association between year of formal education and resilience was found in this study. Thus, neither educational nor occupational status appear to be related to the ability to bounce back in Colombian patients with ARDs.

Exercise itself is a stressing phenomenon that increases the activity of the HPA axis and the sympathetic nervous system (118). However, regular, repeated, intermittent exposure to exercise, with enough time to recover in between, can lead to physiological ‘stress training’**,** which, in the end, helps patients to respond better to psychological and physical stress (118). In our study, patients with SSc, who exercise at least 30 minutes three times

per week, appeared to show highest resilience levels than those who did not (83). Conversely, earlier studies suggested that exercise strengthens systemic inflammation and oxidative stress in SSc (143), however, levels of cytokines were not different according physical activity in patients with ARDs. On the other hand, regular physical activity in SSc was associated with a higher ability to participate in social roles, and a lower prevalence of anxiety, fatigue and depression (144). Recently, it has been found that physical therapy in SSc significantly reduced pain, disability scores, and improved hand motility (145). Therefore, the hypothesis that physical activity, when not excessive, plays a positive role in improving resilience in patients with SSc deserves further validation, particularly under a clinical experiment that help to quantify the magnitude of the effect of exercise on resilience.

## 8.2. RESILIENCE AND CLINICAL DETERMINANTS

Allostatic load of disease is recognized as a critical factor for psychiatric and chronic diseases (20), which puts a high burden on QOL, particularly for those patients with poor social support networks (16). Physical disability and social dysfunction are directly associated with maladaptation to illnesses (130). This issue is secondary to different aspects of disease such as activity of disease, systemic compromise, comorbidities, and hospitalizations (103). In agreement with our results, Li *et al.* (14) described a lack of correlation between disease activity and a resilience score in RA patients. In addition, Ostojic *et al*. (91) found that severity of symptoms in SSc was not associated with development of depression or other psychiatric manifestations. This is similar to those patients with multiple sclerosis (MS) in which resilience is only associated with QOL, thus suggesting this trait has a unique role in nonphysical functional outcomes (131), and in some patients with MS, resilience may help to reduce depression/anxiety symptoms and improve QOL irrespective of the physical disability compromise (132).

Although some studies have suggested that resilience do not influence physical outcomes, it is clear that coping with the illness in some patients may have a considerable influence in physical domains in subjects with MS, such as chronic pain (133). In a qualitative approach for resilience in MS, it was found that physical fatigue was considered a key mediator to improve response to stress, together with negative thoughts, feelings, and social stigma (133). On the other hand, patients with RA, in which arthritis and arthralgia are tightly associated with QOL, resilience mediated the interaction between pain and negative effects (134). However, in this study, severity of symptoms nor PolyA (i.e., more than one autoimmune condition) influenced the ability to face adversity.

PolyA is frequent in patients with ARDs (146,147). PolyA has been associated with an earlier onset of disease, lung fibrosis and heart involvement, with particular distinctive pattern of autoantibodies in patients with SSc (148). In other rheumatic conditions, such as SLE, RA, and SS, the role of PolyA on outcomes is still unclear. However, it would be expected that more autoimmune conditions would be associated with more deleterious effects on the individual. In our study, patients with PolyA did not show lower resilience or worse severity of symptoms, and other autoantibodies were no associated with the capacity to face adversity.

It has been recognized that patients who face hardship could have learned from their experiences and may apply the acquired knowledge to coping with their illness (16). Our results may suggest that patients with ARDs facing worse clinical outcomes present better control of stress and develop an improved response to adversity. Furthermore, in studies on minority groups, factors such as spirituality and culturally relevant activities could have contributed to resilience (16). In this sense, a longitudinal study, aiming to identify whether long time experiences may influence the response to physical domains in ARDs, is pivotal to conduct training strategies in this subset of patients to improve QOL and outcomes.

## 8.3. RESILIENCE AND BIOLOGICAL FACTORS

This study reports the imbalance of cytokines in patients with SSc and resilience. Levels of IL-6 were associated with low resilience scores and a worse symptomatology, in patients with predominantly limited subphenotype. Furthermore, autoantibodies were not associated with resilience nor severity of symptoms in any of the ARDs studied.

Since ARDs, including SSc, are characterized by a pro-inflammatory state driven by cytokines, changes in behavior and response to stress are likely (103). Data regarding cytokine profiles and changes in behavior are controversial. Some reports have shown the role of these molecules in psychiatric illnesses such as MDD. In fact, both proinflammatory (i.e., Th1 and Th17) and regulatory (i.e., Th2) cytokines have been associated with changes in behavior (12,149). However, the heterogeneity of cytokine results across the studies has hindered finding a specific profile (149,150).

The cytokine hypothesis of depression states that several neuroendocrine processes are disturbed due to peripheral inflammatory cytokines (12). These molecules communicate with the central nervous system (CNS) through either neural pathways, vascular mechanisms or infiltration across circumventricular organs. In this sense, a neuroimmune communication process embracing the vagus nerve, and cytokine stimulating receptors in endothelial cells promoting inflammation in the CNS, has been proposed (112). This induces an imbalance between Th1 and Th2 profiles which might elicit a dysregulation of serotonin and glutamate leading to changes in behavior and stress response (12).

In the early stages of SSc, a predominance of Th1 and Th17 has been defined, whereas in later stages, when skin fibrosis occurs, a Th2 profile prevails (151). IL-6 and IL-13 have been associated with skin fibrosis (41,42), and IL-5 or IL-17 are associated with interstitial lung disease (43,44). These evidences indicate an unsuccessful regulatory process by

the immune system and a complex interaction among cytokines in SSc. Although a specific cytokine profile has not been associated with changes in behavior, the role of IL-5, IL-6, IL-10, and IL-13 has been previously reported, thus supporting their possible role in behavioral illnesses (150,152). This is in line with our results since these cytokines were associated with low BRS scores in SSc patients.

Noteworthy, the multivariate analysis revealed that IL-6 was associated with low BRS scores in presence of therapy. The IL-6 is considered a potent inflammatory mediator of the immune system and it has been associated with MDD development (153). In stress conditions, the IL-6 showed to negatively correlate with optimism, which is a critical factor for resilience (154). Maes *et al*.(155) provided evidence of increased levels of IL-6 in patients with treatment resistant depression (TRD). Twin studies have suggested that the association of IL-6 with depression is strongly genetically influenced (156). Thus, IL-6 blockade could be a therapeutic option for depression (157).

Some antidepressant therapies have shown to decreased levels of IL-6 and it was correlated with clinical improvement (158). On the other hand, some patients with TRD treated with either imipramine and venlafaxine, or in combination of 5-hidroxitriptamine (5-HT) and fluoxetine, exhibited increased levels of IL-6 (159). This is in line with our results, since those patients under treatment for SSc, showed a paradoxical effect of IL-6 on resilience. It has been proposed that the activation of the 5-HT4 and 5-HT7 receptors augmented the release of IL-1β, IL-6, IL-12p40 and IL-8/CXCL8 driven by LPS (160), suggesting that under treatment some patients may exhibit a paradoxical effect on cytokines. However, the role of immunomodulatory treatments on this mechanism has not been fully evaluated, and only a study found than those patients using methotrexate and leflunomide reported lower scores on suicidal ideation (161). Altogether, data indicate that IL-6 is a central cytokine on behavior and plays a key role on resilience in patients with SSc (Figure 10).

In addition, the role of IL-6 in skin fibrosis has been previously proposed, and some authors have found an association between its levels and the activity of disease (162), especially in those patients with diffuse subphenotype (163,164). Phase 2 trials (faSScinate clinical trial) with interleukin 6 receptor-α inhibitor (Tocilizumab) showed an improvement of the modified Rodnand skin score as well as benefits in predicted forced vital capacity after 96 weeks of treatment (165). Patients included in the faSScinate trial demonstrated improvement in QOL and fatigue (165), both of which have been previously associated with resilience in chronic diseases (22,166). In the current study, IL-6 was also associated with severity of symptoms in patients with limited SSc. Adding further evidence as a key factor on both SSc subphenotypes (i.e., limited and diffuse).

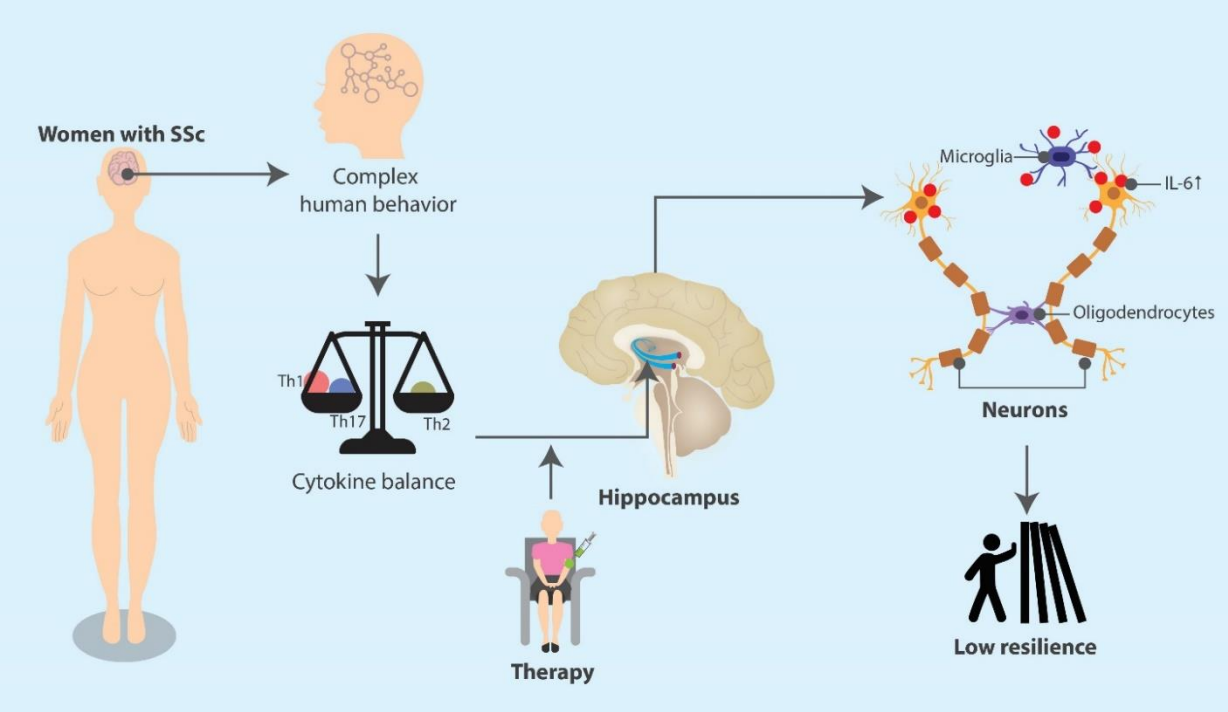


**Figure 10.** Cytokine imbalance in women with SSc. Immunomodulation may increase concentration of serotonin in the central nervous system, which, in turn, may activates microglia to produce pro-inflammatory cytokines in the hippocampus (i.e., IL-6). This imbalance impairs the ability to positively respond to acute stress, reducing resilience (see text for details). Taken and adapted from (140).

Although IL-6 has been associated with proinflammatory functions, exercise has been found to induce an increase in serum levels of IL-6 (167). This, in turn, acting as a myokine, induces the production of IL-10, a strong immunomodulatory cytokine (168). In the current study, cytokine levels did not significantly differ among groups based on a history of regular physical activity. Although an increase in systemic inflammation and oxidative stress secondary to physical activity in SSc has been reported (143), cumulative evidence suggests that physical activity is safe and tolerable, including in those patients with pulmonary involvement (169). Thus, physical activity should be promoted in patients with SSc since may improve resilience and may not induce a deleterious effect secondary to the increase of inflammatory cytokines.

## 8.4. SHORTCOMINGS AND LIMITATIONS

The possible shortcomings of our study must be acknowledged. Although coping, social support, self-efficacy, religious beliefs, and compliance have been associated with resilience; they were not evaluated in this work. According to our study design, we only aimed to evaluate the associations among resilience, sociodemographic variables, habits (e.g., exercise), PolyA and severity of disease. In addition, the fact that age was associated with resilience, suggest that the continuum of this trait is influenced by lifetime experiences which were not evaluated in this work. Thus, our study should prompt additional analysis to evaluate the associations among resilience and the above-mentioned characteristics in ARDs by a longitudinal-based study.

Another objective of this cross-sectional study was to describe the role of cytokines on resilience and severity of symptoms. Factors such as infectious diseases, and the time of the day in which the sample was obtain, could have affect the cytokines levels in these patients. However, individuals with infectious diseases in a week before the inclusion were

excluded, and serum sample was acquired between 7:00 AM to 8:30 AM, aiming to reduce the variability in cytokines induced by the circadian cycle.

An additional limitation of the present study is that the observed results may be due to the differences in sample size among the ARDs. Although the calculated minimal sample size per group in this study was 29 individuals, we include more individuals in each group, leading to differences the final sample size (i.e., 70 in SLE vs 32 in SS). However, such a possibility would be unlikely given the highly significant results seen as well as their consistent direction and magnitude within the different analyses.

The C Reactive Protein (CRP) and Erythrocyte Sedimentation Rate (ESR) are pivotal in the follow-up of ARDs. These biomarkers are included in disease activity scores such as the Disease Activity Index 28 (DAS28) and the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). These two factors, inflammatory biomarkers and clinical indexes, should be evaluated for their association with systemic inflammation (i.e., cytokines) that may help to explain their role in the development of resilient traits.

Since resilience levels were similar across ARDs, further studies on resilience in this group of patients should try to include subjects without chronic diseases (i.e., controls). This approach would help to find additional determinants associated with the ability to face adversity, including additional socioeconomic and biological factors. In addition, this may help to evaluate the different interactions among groups and aid to build better programs on resilience prior the onset of chronic conditions.

## 9. CONCLUSIONS

In conclusion, resilience in patients with ARDs is a continuum process asspciated to age, and SES. Interestingly, previous factors associated with resilience (e.g., occupation, education level) were not associated with BRS scores in this study, thus suggesting that these features do not play a key role in the development of resilience in ARDs. Our results could aid in setting up behavioral training programs in resilience since they have been proven to improve QOL, pain, and self-efficacy (22). However, since inheritable and environmental factors, including epigenetics (170), spirituality, and cultural activities may influence resilience (16), further studies that take these facets into account in ARDs are warranted.

In addition, programs for training in resilience, especially in those patients with SSc, should include the exercise (i.e., more than 30 minutes three times per week) as a major target to improve the ability to face adversity as well as other outcomes such as reduced disability scores, pain, and improve hand motility (145). Furthermore, in this group of patients, it would be interestingly to evaluate the role of targeted therapies to manage resilience. In fact, some studies showed that blockade of the IL-6 (i.e., Tocilizumab) influence QOL and fatigue (165), domains that are associated to resilience. Thus, Proof of concept studies aiming to evaluate the role of IL-6 blockade on resilience are warranted.

Whether resilience is population-specific is unknown. Gene-gene and gene-environment interactions underlying inter-individual variability in stress responses have been evaluated (107). Some studies have found associations with the telomere length and the appearance of elevates stress hormones and a poor response to stress (171). Thus, the genetic factors of resilience, including ancestry, deserve further evaluation (170). However, since inheritable and environmental factors, including epigenetics (170), spirituality, and cultural activities may influence resilience (16), further studies that take these facets into account in ARDs are necessary.

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# APPENDIX

**Appendix 1.** Variables table

| OBJECTIVE | VARIABLE | FACTOR | TYPE | LEVEL | RESULT | DEFINITION | OBSERVATIONS | REF. |
|---|---|---|---|---|---|---|---|---|
| 4.2.1 | Age | Independent | Quantitative continuous | Ratio | Older than 18 years old | Time elapsed between birth and the survey in years | At the start of the survey (younger patients than 18 years old must be excluded). | (172) |
| 4.2.1 | Socioeconomic status | Independent | Qualitative | Ordinal | 1. low (1 and 2),<br>2. intermediate (3)<br>3. high (4 and 6) | Classification of population with similar characteristics regarding wealth and quality of life. | Only the prior mentioned categories were accepted. | (48) |
| 4.2.1 | Occupation | Independent | Qualitative | Nominal | 1. employed<br>2. unemployed | Employed patients are considered as those with either manual exclusive, Intellectual exclusive or mixed job. Unemployed patients are considered as those as housewife, retired, and student or without work. | Only the prior mentioned categories were accepted. | (48) |
| 4.2.1 | Educational level | Independent | Quantitative continuous | Ratio | Years of formal education | Years of education in school, high school, university or technical institution. | Only answers in a numeric scale were accepted | (48) |
| 4.2.1 | Duration of disease | Independent | Quantitative continuous | Ratio | Years since diagnosis | Number of Years with Disease. | Only answers in a numeric scale were accepted | (48) |
| 4.2.1 | Polyautoimmunity | Independent | Qualitative | Nominal | 1: yes<br>2: No | Two or more autoimmune diseases in the same subject. | Chart reviews were be conducted to confirm the existence of secondary autoimmune diseases | (3) |
| 4.2.1 | Treatment | Independent | Qualitative | Nominal | 1: yes<br>2: No | The drugs taken by each patient that is included in the studied. | Chart reviews were be conducted to confirm the existence treatments | - |
| 4.2.1 | Physical Activity | Independent | Qualitative | Nominal | 1: yes<br>2: No | More than 30 minutes 3 times per week | Only the prior mentioned categories were accepted | (173) |
| 4.2.2 | Resilience | Dependent | Quantitative continuous | Ratio | A mean of total sum by the total number of questions answers in the brief resilience scale (BRS). 1 (lowest levels of resilience) y 6 (highest level of resilience) | Ability to recover after an adverse event | Every question of the BRS questionnaire were not be explained. (all questionnaires were audited to confirm their fulfillment) | (11) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 4.2.3 | RAPID 3 | Independent | Quantitative continuous | Ratio | 0 to 30 | Routine assessment of patient index data 3 | RAPID3 were be measured at the same moment of the survey | (60) |
| 4.2.3 | SLAQ | Independent | Quantitative continuous | Ratio | 0 to 61 | Systemic Lupus Activity Questionnaire | SLAQ were be measured at the same moment of the survey | (71) |
| 4.2.3 | SSPRO | Independent | Quantitative continuous | Ratio | 1 to 105 | Scleroderma Skin Patient Report Outcome | SSPRO were be measured at the same moment of the survey | (82) |
| 4.2.3 | ESSPRI | Independent | Quantitative continuous | Ratio | 3 to 30 | European League against Rheumatism Sjögren Syndrome Patient Reported Index | ESSPRI were be measured at the same moment of the survey | (100) |
| 4.2.4 | Cytokines | Independent | Quantitative continuous | Ratio | IL-2, IL-10, IL-6, IL-8, IL-9, IL-13, IL-12/23p40, G-CSF, IFNγ, IFNα, IL-4, IL-1β, TNFα, IL-5, and IL-17A en pg/ml | Proteins responsible for regulating cell function | Cytokines were be measured at the same moment of the survey. | (174) |
| 4.2.4 | Antibodies | Independent | Qualitative | Nominal | IgM RF, IgG CCP3, IgM and IgG ACA, IgM and IgG β2GP1, IgG dsDNA, IgG Tg and TPO, ANAs, anti-SSB/La, anti-SSA/Ro, anti-RNP, and Sm antibodies. | Glycoproteins produced by cells of the immune system. | Antibodies were be measured at the same moment of the survey. | (175) |

RF: Rheumatoid factor; CCP3: Anticyclic citrullinated peptide third-generation; ACA: Anticardiolipin Antibodies; β2GP1: β2glycoprotein Antibodies; dsDNA: Double-strand DNA antibodies; Tg: Thyroglobulin antibodies; TPO: Thyroid peroxidase antibodies; ANAs: Antinuclear antibodies; IFN: Interferon; TNF: Tumor necrosis factor; IL: interleukin; ESSPRI: European League against Rheumatism Sjögren Syndrome Patient Reported Index; SSPRO: Scleroderma Skin Patient Report Outcome; SLAQ: Systemic Lupus Activity Questionnaire; RAPID 3: Routine assessment of patient index data 3

**Appendix 2.** Format at CREA for inclusion of patients.


Appendix 2

(Double click the icon)

**Appendix 3.** Classification criteria for ARDs.


Appendix 3

(Double click the icon)

**Appendix 4.** Brief resilience scale (BRS) questionnaire.


Appendix 4

(Double click the icon)

**Appendix 5.** RAPID3, SLAQ, SSPRO and ESSPRI questionnaires.


Appendix 5

(Double click the icon)

**Appendix 6.** Article: “Resilience in women with autoimmune rheumatic diseases”


Appendix 6.pdf

(Double click the icon)

**Appendix 7.** Article: “Cytokine imbalance in patients with systemic sclerosis and resilience: the key role of interleukin-6”

Appendix 7.pdf

(Double click the icon)

**Appendix 8.** Informed consent.

Appendix 8

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