The European Journal of Psychiatry 36 (2022) 143—151

THE EUROPEAN JOURNAL OF PSYCHIATRY

www.elsevier.es/ejpsy

REVIEW ARTICLE

# Inflammatory biomarkers associated with depression, anxiety, and/or fatigue in primary Sjögren's syndrome — a systematic review

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Received 15 March 2021; accepted 13 April 2022
Available online 6 June 2022

**KEYWORDS**
Primary Sjögren's syndrome;
Fatigue;
Depression;
Anxiety;
Inflammation;
Biomarkers

**Abstract**
*Background and objectives:* Fatigue, depression, and anxiety are common burdens present in primary Sjögren's syndrome patients. Those symptoms have all been linked to inflammatory dysregulations. To explore the link between inflammatory biomarkers and fatigue, depression, and anxiety in pSS patients, we aim to do a systematic literature review.
*Methods:* The systematic review protocol and data extraction forms were designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Our protocol has been registered on Prospero (ID CRD42020161952). The Cochrane Library, PubMed, Scopus, and PsycInfo were used, from inception to December 2019.
*Results:* The literature search initially identified 445 articles. Finally, 12 articles were included in this systematic review. The population in studies was quite similar with mainly middle-aged women. Dates of publication extended from 2008 to 2019. Different scales were used to measure fatigue, depression, and/or anxiety. Measured inflammatory biomarkers were very diverse across studies. In consequence, results in the different included studies were disparate. Only one study explored the link between depression/anxiety and inflammatory markers: patients with depression and/or anxiety were compared to pSS patients.
*Conclusion:* Even if the association between fatigue, depression, and/or anxiety with inflammatory markers in pSS is of interest, there are a lot of discrepancies. Sickness behavior and IFN pathways seem to be important in the inflammatory physiopathology of fatigue in pSS, and

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https://doi.org/10.1016/j.ejpsy.2022.04.002

interest in depression. It also appears crucial to standardize clinical scales, inflammatory blood, and CSF tests in pSS patients to allow better generalization.


## Introduction

### Sjögren

Primary Sjögren's syndrome (pSS) is an auto-immune disease resulting from infiltration of certain glands, mainly lacrimal and salivary glands, by lymphocytes, leading to a decrease in tear and saliva production, and in turn to ocular and oral dryness. For almost half of patients, it is possible to find extra glandular systemic manifestations. This disease is associated with a heavy burden as pSS patients experience greater functional impairment than age-matched healthy controls.[1,2]

Using the European-American consensus group (EACG) criteria[3] for pSS, the prevalence among women is estimated at 0,1 — 0,7%.[4,5]

According to the previous criteria, diagnosis is met if there is the presence of ocular and oral dryness-related symptoms, focal lymphocytic signs in the accessory salivary gland biopsy, and anti-SSA/Ro and/or anti-SSB/La autoantibodies. Nowadays, pSS physiopathology is still not entirely understood.

### Fatigue

Fatigue is a common, but a complex and disabling symptom. Its descriptors include tiredness, weakness, lack of energy, and inability to concentrate.[6] In the general population, it affects 22 to 25% of people,[7,8] and in its chronic form (over 6 months of evolution) can lead to substantial economic costs.[9,10] Among patients with autoimmune disease, the prevalence of fatigue is much higher: in the range of 60—70%.[11,12]

Even if socioeconomic risk factors are found to predict fatigue, more and more evidence points toward genetic and molecular mechanisms that are activated during inflammation and cellular stress conditions.[13]

In pSS, fatigue is a highly represented symptom, its presence ranging from approximately 38—88% of patients.[14] It has been associated with healthcare consumption, and worse working status[15] and has been described as "an ever-present, fluctuating, and non-relievable lack of vitality being beyond one's own control".[16] Furthermore, fatigue has been shown as remaining essentially unchanged over the pSS course.[17] pSS is considered an efficient model to study the biological basis of fatigue.[18,19] Indeed, clear diagnostic criteria exist and provide a well-defined group. Moreover, no effective treatment is available, particularly no immunosuppressive medication that could alter immune and inflammatory pathways. Furthermore, fatigue does not appear to correlate well with disease activity suggesting it could be possible to study a separate mechanism for fatigue in chronic autoimmune disease.[20]

### Depression and anxiety

Depression is a frequent, disabling, and recurring disease.[21,22] In 2014, depression alone accounted for 76,4 million years lost to disability (YLD) worldwide which is 10,3% of the total burden of disease; in comparison: diabetes represented 22,5 million YLDs or 3,0% of the total burden. Depression and anxiety are comorbid in up to 70% of cases.[23] More and more studies are exploring inflammatory pathways to explain depression and anxiety pathophysiology.[24—27]

Already in 1988, Angelopoulos et al.[28] conducted a study exploring personality and psychopathology in patients with pSS and found that they present mainly with depression, somatization, anxiety, and obsessive-compulsive symptoms. Later, it was shown that pSS patients had significantly higher scoring rates for "possible" clinical anxiety (48%) and depression (32%) compared with control groups with rheumatoid arthritis (RA), and also reduced physical and mental well-being.[29] Anxiety was also found to be even more present than depression in patients with sicca symptoms with or without pSS, respectively 41,5% and 39,5% for anxiety, and 28,3% and 26,3% for depression.[30] Furthermore, in 2014, compared to UK general population, pSS patients have shown significantly impaired utility values that were significantly related to pain and depression scores.[2]

### Aim

As we can see, fatigue, depression, and anxiety are three disabling symptoms present in pSS, responsible for a major part of the reduced quality of life in this population. All three don't have established pathophysiology, but have been linked to inflammatory dysregulations. As said previously, pSS constitutes a good disease model to explore inflammatory pathways as it is not influenced by immunomodulatory treatments. In this context, we performed a systematic literature review to explore the link between inflammatory biomarkers and fatigue, depression, and anxiety in pSS patients.

## Methods

### Protocol and registration

The systematic review protocol and data extraction forms were designed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[31] Our protocol has been registered on Prospero (ID CRD42020161952).

### Literature search strategy

A systematic literature search was executed in The Cochrane Library, PubMed, Scopus, and PsycInfo, from inception to December 2019. The main search strategy was (depressive OR depression OR anxiety OR fatigue) AND (Sjogren's syndrome OR sicca) AND (inflammatory OR interleukin OR IL-1 OR IL-2R OR IL-6 OR CRP OR c-reactive protein OR cytokine OR TNF OR tumor necrosis factor). References of selected

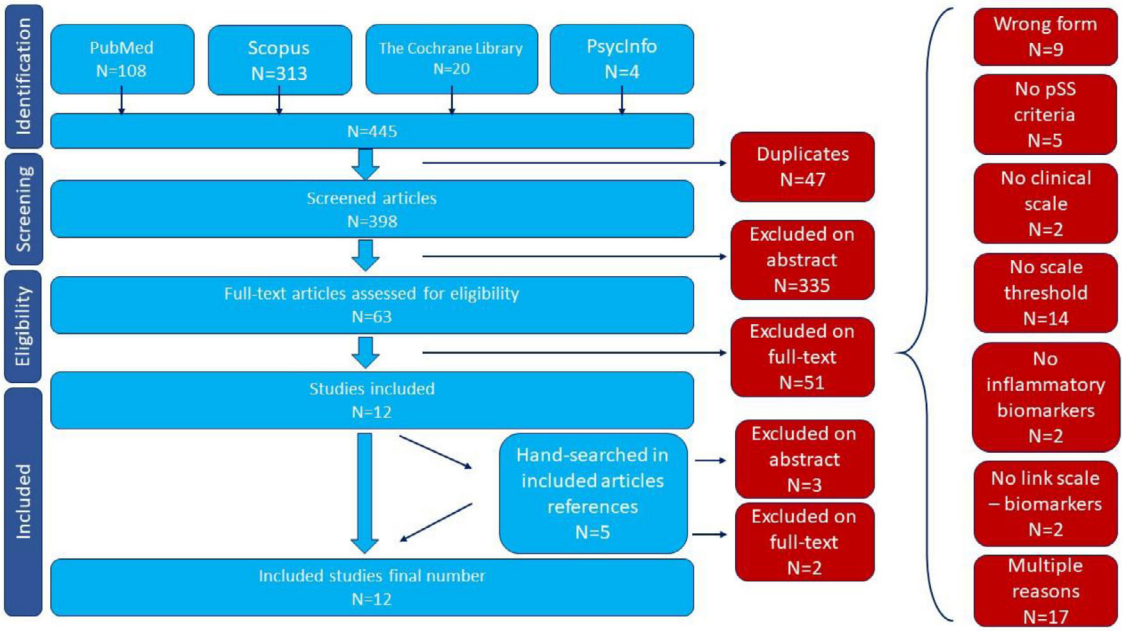


**Fig. 1** Flow chart.

articles were also searched to identify additional reports. Papers in English and French were accepted.

### Inclusion and exclusion criteria

The following criteria were used for screening literature. The study design included a cross-sectional study, case-control, and baseline data of a cohort study. Studies were required to have documented criteria in their study design in defining patients as having pSS according to validated criteria. Finally, studies had to include a standardized evaluation of depression, anxiety, and/or fatigue (scale).

Exclusion criteria were the following: studies using screening tools without at least one tool stating the cut-off threshold used to detect depression, anxiety, and/or fatigue; and meta-analyses, review articles, case studies, qualitative studies, conference papers, letters, and opinion pieces/editorials; studies without measures of inflammatory markers.

### Data extraction

Two review authors applied eligibility criteria and selected studies for inclusion in the systematic review: one screened papers and another checked decisions. In case of doubt, it was established that the paper would be submitted to the rest of the review group, and no similar case was encountered. The list of data extracted was: title of the paper, first author, year of publication, country of a team, mean age of the population, sex ratio, presence of pSS criteria, presence/type of fatigue and psychiatric scales, study groups, and inflammatory biomarkers (type and difference between groups). The same strategy as in the screening step was adopted for the data extraction among review authors.

## Results

### Studies selection

Figure 1 summarized the process of study inclusion. The literature search initially identified 445 articles. Among these, 47 duplicates were excluded. After an initial screening of the title and abstract, 335 articles were excluded. It left 63 articles to read in full length. Of these studies, 51 were excluded for the wrong form of design study (n=9), or the absence of pSS criteria (n=5), a clinical scale for fatigue, depression, and/or anxiety (n=2), the threshold in these scales (n=14), inflammatory biomarkers (n=2), a link between clinical scales and inflammatory biomarkers (n=2), or for combined previous reasons (n=17). We were able to obtain every abstract or full-text needed. Finally, 12 articles were included in this systematic review. A hand search of the references of those articles revealed 5 potential studies to include, amongst them, 3 were excluded on title and abstract, and the 2 remaining reads in full-text, were excluded, one for not linking clinical scales and inflammatory biomarkers, and the other for the absence of threshold in clinical scales. At last, 12 articles were included in this systematic review.

### Characteristics of included studies

Our extracted data is shown in Table 1. All the studies were in English and applied the 2002 American-European Consensus Group classification criteria for pSS diagnosis.[3] Dates of publication extended from 2008 to 2019. 10 studies were made by European teams, one from China and one from the USA. Population in studies was quite similar with mainly middle-aged women (mean age ranging from 55 to 59,6; 963 women for 1020 subjects [57 men], or 94,4% of participants). Different scales were used to measure fatigue, depression, and/or anxiety, which are summarized respectively in Table 2

**Table 1** Data extraction from include papers.

| | Country | Mean age (years old) | Sex Ratio | pSS criteria | Studied Groups |
|---|---|---|---|---|---|
| Segal et al. | USA | 58 | 90F/4M | AECG | 94 pSS: 63 fatigued/31 not fatigued |
| Harboe et al. | Norway | pSS: 56,9<br>HC: 58,2 | 46F/8M | AECG | 54 pSS<br>53 HC |
| Haldorsen et al. | Norway | 57 | 134F/7M | AECG | 141 pSS:100 with high Fatigue |
| Xie et al. | China | 53,8 | 79F/9M | AECG | 31 pSS<br>19 RA<br>18<br>anxiety/depression<br>20 HC |
| Karageorgas et al. | Greece | 58 | 100F/6M | AECG | 106 pSS:<br>32 fatigued/74 non fatigued |
| Bardsen et al. | Norway | 58,5 | 34F/6M | AECG | 40 pSS:<br>20 high fatigue/<br>20 low fatigue |
| Howard Tripp et al. | UK | pSS: 59,6<br>HC: 50 | pSS: 159F<br>HC: 28F | AECG | 159 pSS<br>28 HC |
| Jülich et al. | Germany | 55 | 42F/4M | AECG | 46 pSS |
| Bodewes et al. | Netherlands | 58 | 43F/2M | AECG | 45 pSS:<br>22 fatigued/23 non fatigued |
| Bardsen et al. | Norway | 56,1 | 41F/8M | AECG | 49 pSS |
| Larssen et al. | Norway | 58,5 | 17F/3M | AECG | 20 pSS: 10 high fatigue/10 low fatigue |
| Davies et al. | UK | 56,7 | pSS:120F<br>HC:30F | AECG | 120 pSS<br>30 HC |

AECG: 2002 American-European Consensus Group Classification criteria; F: Female; HC: Healthy Control; HDRS: M: Male; MFI: Multidimensional Fatigue Inventory; pSS: primary Sjögren Syndrome; RA: Rheumatoid Arthritis; UK: United Kingdom

and Table 3. Measured inflammatory biomarkers were very diverse across studies: 34 cytokines, 7 types of other inflammatory biomarkers (CRP, Erythrocyte Sedimentation Rate [ESR], lymphocytes, neutrophils, white cell count, immunoglobulins, and complement factor), Interferon (IFN) scores defined from certain genes expression, surface expression of P2 × 7R in peripheral blood mononuclear cells (PBMC), proteins in serum, proteins in CSF (Cerebro-Spinal Fluid) and heat shock proteins (HSP32, HSP60, HSP72, HSP90-$\alpha$).

## Discussion

Table 4

### Inflammatory markers

Studies included in our systematic review found disparate results. Globally, it was reported involvement of proinflammatory cytokines in fatigue in pSS patients such as IL-36a,[32] IFN-score[32] in serum, IL-1Ra in cerebrospinal fluid,[33,34] IFN-$\gamma$, IP-10,[18] TNF-$\alpha$, LT- $\alpha$,[18,35] and sIL2-R serum concentrations.[36] Association between other inflammatory markers and fatigue in pSS patients was also found for CRP, ESR, and lymphocytes. Association between fatigue in pSS patients and heat shock protein HSP90-$\alpha$ was presented by Bardsen 2016 et al.[37] As for Bodewes et al.[32] and Larssen et al.,[19] they showed an association between fatigue and respectively 16 serum proteins and 15 CSF proteins in pSS patients.

Only Xie et al.[38] explored the link between depression/anxiety and inflammatory markers, but instead of exploring that association in a pSS population, patients with depression and/or anxiety were compared to pSS patients. However, they found a similar IL-6 profile in these two groups compared to controls and a link for both populations with P2 × 7R expression on CD14-PBMC. They also showed higher levels of supernatant IL-1$\beta$ in the pSS group compared to the anxiety/depression group.

### Fatigue – inflammation - pSS

Several teams included in our study showed an association between cytokines and fatigue in pSS patients.[17,18,32–36] Cytokines play a role in the start of the initial inflammatory response which has been leading teams to hypothesize that maintenance of fatigue in chronic inflammatory diseases such as pSS could be explained by a potentially maladaptive immune response. Indeed, the hypothesis of a dysregulated sickness behavior explaining chronic fatigue in inflammatory diseases is mentioned in several studies.[18,19,33–37] Sickness behavior appears to be a well-conserved response across evolution as it is considered to be a survival advantage because it facilitates recovery.[39] It is a collection of symptoms such as anorexia, reduction of grooming, depression, social withdrawal, and fatigue, that appear in response to infection or inflammation. Its link to inflammation pathways has been shown, particularly with IL-1.[40] Several elements point to an association between IL-1 and fatigue. For

**Table 2** Fatigue scales used in included studies.

| | FSS | fVAS | FACIT-F | SF-36 | PRoF | MFI | Threshold |
|---|---|---|---|---|---|---|---|
| Segal et al. | x | x | | | X | | FSS: fatigue > or = 4 |
| Harboe et al. | x | x | | | | | |
| Haldorsen et al. | X Norwegian version | | | X Vitality Domain | | | FSS: fatigue > or = 4 |
| Karageorgas et al. | | | x | | | | Severe fatigue > 30 |
| Bardsen et al. | | x | | | | | |
| Howard Tripp et al. | | | | | x | | Minimal (0-1) Mild (2-3) Moderate (4-5) Severe (6-7) |
| Jülich et al. | | x | | | | | |
| Bodewes et al. | | | | | | X Dutch version | 25 percentiles highest (fatigued group) and lowest (non-fatigued group) |
| Bardsen et al. | | x | | | | | |
| Larssen et al. | | x | | | | | |
| Davies et al. | | | | | x | | |

fVAS: Fatigue Visual Analogic Scale ; FSS: Fatigue Scale Severity; FACIT-F : Functional Assessment of Chronic Illness Therapy-Fatigue; MFI: Multidimensional Fatigue Inventory; PRoF: Profile of Fatigue questionnaire; SF-36: Short-Form Health Survey.

example, injections of IL-1$\beta$ in cancer patients lead to fatigue among other symptoms[41] and administration of IL-receptor antagonists in patients with Rheumatoid Arthritis reduced fatigue,[42] which was also found in pSS patients.[43] Included studies found an association between higher levels of fatigue and higher levels of IL-1Ra in CSF of pSS patients[33,34] and lower levels of Il-1$\beta$ in pSS patients with increasing fatigue over 5 years.[17] However, other included studies didn't find an association between fatigue and the IL-1 pathway in pSS patients.[17,18]

Nevertheless, Davies et al.[35] suggest that the chronic inflammation coming from the continuous immune dysregulation (present in pSS), leads to transforming an initially adaptative behavioral response, sickness behavior, into a dysfunctional response, resulting in the persistence of fatigue through a dysregulated anti-inflammatory response.

Interestingly, Larssen et al.[19] found different expression patterns of proteins linked to sickness behavior symptoms (hemopexin, apolipoprotein A4, pigment epithelium-derived factor, secretogranin-3 and selenium-binding protein 1) according to a level of fatigue in the cerebrospinal fluid proteome of patients with pSS.

Another pro-inflammatory cytokine that has been linked to fatigue and pSS is the IFN. On one hand, it is hypothesized that IFN plays a major role in the physiopathology of pSS through induction of B cell hyperactivity.[44] On the other hand, IFN is linked to fatigue through its secondary effects as treatment.[45] IFN seems to be involved in fatigue through the induction of a gene coding for the enzyme indoleamine 2,3-dioxygenase (IDO) which in turn converts the precursor of serotonin (tryptophan) into kynurenine, reducing the levels of serotonin in the brain and create cerebral toxic effects with its metabolites.[46] In our study, multiple teams explored the role of IFN in fatigue in pSS patients,[14,17,18,35,47] results were not homogenous. Howard Tripp et al.[18] found an inverse relationship between fatigue and IFN-$\gamma$. However, Haldorsen et al.[17], et Davies et al.[35] did not find an association between fatigue and IFN-$\gamma$ or IFN-$\alpha$ (neither did Howard Tripp for the latter). Bodewes et al.[47] defined an IFN score by the relative expression of 5 genes linked to IFN: IFI44, IFI44L, IFIT1, IFIT3, and MXA, and found an association between higher levels of fatigue and higher levels of IFN score. Karageorgas et al.[14], who does not describe precisely how they calculated their IFN score but reference two other studies instead, did not explore fatigue with IFN score, but with IDO-1 peripheral blood transcript level and did not find a significant difference between fatigued and non-fatigued pSS patients.

## Depression and anxiety

None of the included studies explored the link between depression/anxiety and inflammatory markers in pSS patients. Only one included team, Xie et al.,[38] used depression/anxiety as the main interest and compared pSS patients to anxiety/depression patients according to their levels of inflammatory markers. Both groups had higher blood levels of IL-6 compared to healthy controls. They also linked the two groups with P2 $\times$ 7R expression on CD14-PBMC. P2 $\times$ 7R is considered a critical communication link between the nervous and immune systems.

In the other included studies, depression, and anxiety when it was measured (only in three other studies[14,18,35]), were either considered confounding factors or not included in comparative analysis. The majority of these studies found an association between depression and fatigue[14,18,33,34,36,37,48] (Haldorsen[17] too through SF-36 mental health domain). Moreover, depression has even been

**Table 3** Depression and anxiety scales used in included studies.

| | SF-36 | HADS | BDI | ZSRDS | CES-D | PHQ-9 | HDRS | HAMA | STAI | EPQ 29 | Treshold |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Segal et al. | | | | | x | | | | | | D > or = 16 |
| Harboe et al. | | | x | | | | | | | | D > 13 |
| Haldorsen et al. | X Mental Health Domain | | | | | | | | | | |
| Xie et al. | | | | | | | x | x | | | A: HAMA > 14<br>D: HDRS > 20 |
| Karageorgas et al. | | | | x | | | x | x | | | ZSRDS: D > 40%<br>STAI> 35%<br>EPQ: neuroticism > 12% |
| Bardsen et al. | | | X | | | | | | | | D: > 12 |
| Howard Tripp et al. | | x | | | | x | | | | | D > 5 |
| Jülich et al. | | | | | | | | | | | |
| Bodewes et al. | | | | | x | | | | | | |
| Bardsen et al. | | | x | | | | | | | | D: > 12 |
| Larssen et al. | | | x | | | | | | | | |
| Davies et al. | | x | | | | | | | | | |

A: Anxiety; BDI: Beck Depression Inventory; CES-D: Centers for Epidemiologic Studies Depression scale; D: Depression; EPQ 29: Eysenck Personality Questionnaire; HADS: Hospital Anxiety and Depression Score; HAMA: HAMilton Anxiety rating scale; HDRS: Hamilton Depression Rating Scale; PHQ-9: Patient Health Questionnaire 9; SF-36: Short-Form Health Survey; STAI: State-trait Anxiety Inventory; ZSRDS: Zung Self-Rating Depression Scale.

**Table 4** Fatigue, anxiety, depression and biomarker evolution.

| | Biomarkers Evolution |
|---|---|
| Segal et al. | Predictor of FSS fatigue and fVAS: Absolute lymphocyte count |
| Harboe et al. | Increasing fVAS scores → increasing CSF levels of IL-1Ra<br>Even stronger on non-depressed patients, whereas no association in the depressed pSS group<br>Association held in multiple regression with age and BDI |
| Haldorsen et al. | Cross-sectional: No association between fatigue and cytokines<br>Longitudinal: Decreasing vitality → higher IgG, RANTES<br>Increasing FSS → higher IL-17<br>Increasing fatigue (scale not mentioned) → lower CRP, IL-1$\beta$ |
| Xie et al. | pSS group → IL-1$\beta$ higher than in other groups<br>HC group without ATP stimulation → IL-6 lower than in other groups<br>RA group → IL-6 higher than pSS and anxiety/depression groups<br>After ATP stimulation, P2 × 7R expression on CD14− PBMC → positively correlated to scores of anxiety and depression |
| Karageorgas et al. | Fatigued patients → decreased type I IFN scores |
| Bardsen et al. | HSP90a differed between high- and low fatigue groups<br>In a multiple regression with BDI, age, sex, disease duration, CRP and the presence of anti-SSA/SSB → only HSP90a and BDI remained<br>No difference in HSP concentrations between the two BDI groups |
| Howard Tripp et al. | Increasing fatigue<br>→ Decreased IgG, IP-10, TNF-$\alpha$, LT-$\alpha$ and IFN-$\gamma$<br>→ Increased lymphocytes (within normal ranges) |
| Jülich et al. | High fVAS score ($\geq$ 8): lower sIL-2R |
| Bodewes et al. | 14 were upregulated in fatigued patients (MFI): SNAP25, 5 complement factors: C3, C3a, iC3b, C3d, C4b, IL36A, UCHL1, ENO1, GPD1, BMP6, GOT1, MAP2K1 and CLEC4M<br>2 downregulated: FTCD and EGF |
| Bardsen et al. | Associated with fatigue → IL-1Ra<br>In multiple regression for fVAS → depression, pain, and IL-1Ra held |
| Larssen et al. | Separation between high and low fatigue → 15 CSF proteins |
| Davies et al. | Inverse relationship with fatigue → TNF-$\alpha$ and LT-$\alpha$<br>Predictive power: The full model, including all seven cytokines, was able to correctly identify fatigue category in 85% of cases |

BDI: Beck Depression Inventory; CSF: CerebroSpinal Fluid; fVAS: Fatigue Visual Analogic Scale; HSP: Heat Shock Proteins PBMC: Peripheral Blood Mononuclear Cell; pSS: primary Sjögren Syndrome.

shown as a predictor of levels of fatigue: in Howard Tripp et al.[18] in association with IFN-$\gamma$, IP-10, and pain, in Segal et al.[48] with pain and helplessness, and Karageorgas et al.,[14] their multivariate analysis detected three independent determinants of fatigue, including depression, but the most associated was neuroticism, a fundamental personality trait characterized by anxiety and particular sensibility to stress. Anxiety traits and state is associated with fatigue in Karageorgas et al.[14] with a p<0,005.

From a clinical point of view, it suggests that defective coping strategies for stress such as neuroticism or

helplessness, with anxiety and depression, contribute greatly to fatigue in pSS patients. Bardsen et al.[37] highlight the fact that fatigue and depression questionnaires share a lot of similar inquiries. Even more, fatigue is one of the symptoms composing major depressive disorder according to DSM-5.[49] In this context, adding that it has been shown that a minority of pSS patients with depression had antidepressant treatment,[14] we can wonder if a great part of fatigued patients with pSS is not just unnoticed and untreated depressed patients. In that sense, Segal et al.[50] state that depression is one of the substantial unmet health needs for pSS patients.

Depression and fatigue can also be linked through inflammatory pathways. Previously, we presented the sickness behavior theory to explain fatigue in chronic diseases such as pSS, but it can also explain depression as it is one of the sickness behavior symptoms. The IL-1 pathway seems to play an important role once again. Indeed, Goshen et al.[51] worked on mice subjected to chronic mild stress (CMS), which is the validated model of depression in animals, and found increased IL-1$\beta$ levels in their brain. Moreover, they found that mice with deletion of the IL-1 receptor type I or with brain-restricted overexpression of IL-1 receptor antagonist did not display depression-like behavior after being submitted to CMS, nor neuroendocrine changes. Concerning anxiety, it has been shown that mice with ILRI suppression exhibited less anxiety-related behaviors.[26] In humans, it also has been shown that IL-1$\beta$ is increased in the blood of patients with major depression.[27] Furthermore, the activation of P2 $\times$ 7R is one of the steps on the pathway to change the IL-1$\beta$ into its proinflammatory form.[52] As was said previously, P2 $\times$ 7R expression is correlated to anxiety and depression scores, and increased in pSS patients,[38] providing other elements to link depression to sickness behavior in pSS.

Other findings link depression to fatigue through inflammation pathways. IFN pathways that are involved in fatigue also are explored in depression. For example, an IFN-$\alpha$ injection can induce a depressive episode.[53] Moreover, as said previously IFN can induce IDO gene producing IDO enzyme which activation reduces serotonin synthesis by reducing levels of tryptophan, serotonin's precursor, which is linked to depression; IDO can also convert serotonin precursor into kynurenine, leading to its metabolites production which has also been associated with depression.[46] Furthermore, among the 15 proteins in CSF highly contributing to the separation between high and low fatigue in pSS patients, Larssen et al.[19] found five proteins that were linked to depression through their biological function.

As it has been demonstrated in the different included studies, depression has a strong clinical link with fatigue, which can raise the question of a clinical overlap. Unfortunately, those previous studies didn't explore the link between depression and inflammation in pSS patients. However, other authors show inflammatory hypotheses behind depression and its role in sickness behavior that seems to be part of chronic inflammatory diseases' physiopathology such as pSS. Nevertheless, depression cannot on its own explain fatigue in pSS, as there are not-depressed but fatigued patients.

### Limits

We identified several limits in those studies. First, sample sizes were globally small (mean of 75 pSS patients, ranging from 20 to 159). Samples were composed of a majority of women (94,4%) generalizing to the rest of the population impossible. Nonetheless, combining results is complicated because of the variety of used scales: 6 different fatigue measures, 8 different depression measures, 3 different anxiety measures, and 1 personality questionnaire, across 12 studies. There was only one longitudinal study. Secondly, chosen biomarkers were very different across studies: 34 different cytokines measured in serum or CSF, IFN scores, HSP, CSF proteome, serum proteome, and surface expression of P2 $\times$ 7R in peripheral blood mononuclear cells. Moreover, cytokines variate easily in the blood and are influenced by a lot of factors.[24] Thirdly, known confounding factors of fatigue have not been taken into account, for example: sleep disturbance,[33] obesity, and effects of medication.[48]

### For future studies

Our systematic review showed that fatigue, depression, and anxiety are connected to pSS through inflammation. It appears crucial that research continues in this field, but it needs to be standardized to be able to narrow involved pathways.

Concerning scales, it appears interesting to differentiate auto-questionnaires and hetero-questionnaires. On one hand, auto-questionnaires are easy to enforce. To evaluate anxiety and depression, the HADS[54] is validated, easy to interpret, and widely used. Regarding fatigue, the MFI[55] also meet those criteria and explores different aspects of fatigue. On the other hand, to explore psychiatric diseases, hetero-questionnaires conducted by a psychiatrist allow for better detection. Using the anxiety and depression sections of the MINI appears as a good choice, as it is widely used, quickly conducted, and easily interpreted.

As we showed, numerous biomarkers are studied to explore fatigue, depression, anxiety, and pSS. At this point in research, where it is hard to individualize specific inflammatory biomarkers, it seems interesting to begin with routine inflammatory biomarkers (such as CRP, interleukins, IFN, TNF...) that allow the constitution of vast cohorts, reproducibility, and comparison. According to the literature, it seems that the following markers can be prioritized: IL-1b which is linked to fatigue,[41] pSS,[43] pSS and fatigue,[17] depression,[27,51] and anxiety,[26] IL-6 linked to depression[56,57] and pSS,[38] and IFN for its link to fatigue, depression, and anxiety through its link to IDO enzyme and serotonin (as explained before).

## Conclusion

Through this systematic review, we found that even if the association between fatigue, depression, and/or anxiety with inflammatory markers in pSS is of interest, there are a lot of discrepancies. What we can gather from our study, is that sickness behavior and IFN pathways seem to be important in the inflammatory physiopathology of fatigue in pSS. Moreover, depression seems to be able to explain a vast part

of fatigue from a clinical point of view supported by the sickness behavior hypothesis, but it also raises the question of a clinical overlap occurring between fatigue and depression. It could be potentially explained because fatigue is more often explored and accepted than depression, highlighted by the contrast between depression prevalence in pSS patients and the low rate of prescribed antidepressants in that population.

Nonetheless, we showed that the link between sickness behavior and IFN pathways in depression has been established by other studies on an inflammatory level. Unfortunately, included studies did not explore inflammatory biomarkers for depression in pSS patients. Another interesting matter raised by our study is that anxiety is frequent in pSS patients, even more than depression, and responsible for a certain amount of burden, but it is nearly not explored on a clinical level and even less on an inflammatory one.

Our systematic review highlights the strong link between fatigue, depression, and anxiety in pSS patients, from a clinical and inflammatory view. It shows the importance for the clinician to search and identify those symptoms which lead to a heavy burden in pSS patients. Moreover, it appears crucial to standardize clinical scales and inflammatory blood and CSF tests in pSS patients to allow better generalization. Furthermore, it opens new ways to explore treatments in pSS, such as antidepressants and anti-inflammatory treatments, but also cognitive behavioral therapy to work on coping strategies which seem to be failing in this population.

## Ethical considerations

None

## Funding

We have not received any financial support in this article

## Declaration of Competing Interest

No author has any interest in this article.

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