Environmental factors in the pathogenesis of primary Sjögren’s syndrome

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Primary Sjögren’s syndrome (SS) is a systemic autoimmune disease in which exocrine organs, primarily the salivary and lacrimal glands, are targets of chronic inflammation, leading to severe dryness of eyes and mouth. Fatigue and arthralgia are also common, and extraglandular manifestations involving the respiratory, nervous and vascular systems occur in a subset of patients. Persistent activation of the type I interferon system, and autoreactive B and T cells with production of disease-associated autoantibodies are central to the pathogenesis. Genetic polymorphisms that associate with an increased risk of SS have been described, though the risk-increase contributed by the respective variant is generally low. It is thus becoming increasingly clear that genetics cannot alone account for the development of SS and that other, presumably exogenous, factors must play a critical role. Relatively few studies have investigated exposure to potential risk factors prior to SS disease onset. Rather, many factors have been studied in prevalent cases. In this review, we summarize current literature on exogenous factors in the pathogenesis of SS including infections, hormones, smoking, solvents and additional compounds. We delineate for which factors there is current evidence of increased disease risk, and for which our present knowledge is confined to suggesting their role in SS pathogenesis. Finally, we outline future perspectives in the continued search for environmental risk factors for SS, a research area of great importance considering the possibilities for preventive measures.

Keywords: infection, Sjögren’s syndrome, smoking, SSA, SSB.

Introduction

Primary Sjögren’s syndrome (SS) is a systemic autoimmune disease characterized by immune-mediated destruction of exocrine glands. Predominantly, salivary and lacrimal glands are targeted, causing the disease hallmarks of severe dryness of the eyes and mouth, also denoted ‘sicca symptoms’. Apart from glandular symptoms, fatigue and arthralgia are often noted, and systemic complications involving extraglandular tissues, such as respiratory, vascular, neurological and renalmanifestations, affect one third of patients [1]. Sjögren’s syndrome also occurs in the presence of other autoimmune diseases and is then referred to as secondary Sjögren’s syndrome. The incidence of SS peaks around 50 years of age, with a considerable sex bias with female-to-male ratio reported at 9-14:1, which is stronger than in almost all other autoimmune diseases [2, 3]. The morbidity associated with SS should not be underestimated; in fact, high psychological distress and significantly reduced quality of life is common amongst patients [4, 5]. Moreover, overall mortality rates are increased, partly owing to increased risks of lymphoma and cardiovascular disease [6].

The involvement of adaptive immunity in SS pathogenesis is evident through observations of autoreactive B and T cells with production of the disease-associated autoantibodies anti-Ro/SSA and anti-La/SSB, formation of ectopic lymphoid structures and frequent hypergammaglobulinaemia. The contribution of innate immunity is apparent through observations of high type I interferon (IFN) system activation, systemically and in target tissue, in a majority of patients [7-9] (Fig. 1).

Susceptibility to SS has a definitive genetic component, with the strongest associations with the...
human leucocyte antigen (HLA) locus [10]. Associations of genetic variants in the IRF5 and STAT4 loci with SS also imply the importance of IFN signalling pathways in the disease pathogenesis. However, notably, the identified genetic risk variants only convey modestly increased risk. Although data on concordance rates of SS in twins are lacking, observations from other systemic autoimmune diseases generally indicate concordance rates around 12–15% in monozygotic twins and 3–8% in dizygotic twins [11–13], thus further demonstrating that factors other than genetic makeup are of major importance in autoimmune disease development. Together, these observations make clear that factors in the environment must play a pivotal role in SS pathogenesis.

Several factors complicate studies of environmental risk factors in SS. Patients usually experience their first clinical symptoms of SS long before the diagnosis is set (Fig. 2), and due to the nonspecific symptoms of dryness, arthralgia and fatigue, the reported mean delay of 6.2 years from symptom onset to diagnosis [14] may relate to both patient’s and doctor’s delay. Moreover, disease-associated autoantibodies can be found several years before the diagnosis, and even before the time of reported symptom onset [15]. This raises the question whether the same or different environmental factors are involved in the different stages of disease development in this chronic inflammatory condition (Fig. 2).

In this review, we cover biological, organic and inorganic chemical factors studied for their possible contribution to SS disease pathogenesis (Fig. 3). We analyse why infections are relevant as disease triggers, and we discuss studies that have
specifically focused on assessing exposure to possible environmental risk factors prior to SS diagnosis.

**Biological factors**

*Microbes in the pathogenesis of Sjögren's syndrome*

Investigations of biological agents driving the development of SS dominate the literature, and infections have long been considered a probable main environmental risk factor. Viral infections in particular fit well into proposed immunopathogenic models of how the disease may be triggered [16] (Fig. 4). Specifically, augmented activity in crucial parts of the defence against viruses in innate immune system, including Toll-like receptor (TLR) signalling and the type I interferon (IFN) system [17], infers the involvement of viral infections in SS. Several infections can also mimic glandular or extraglandular symptoms of SS, which may lead to confusion regarding diagnosis [18]. Further, some viruses of the Herpesviridae family exhibit tropism for the SS target tissues, that is salivary and lacrimal glands, making them attractive candidates as disease triggers [18]. Although the search for one specific infectious agent responsible for triggering SS has proven difficult, recent studies on the association between SS and infections in general have corroborated the notion that infections per se play

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**Fig. 2** Proposed model of the temporal contribution of environmental factors in the pathogenesis of autoantibody-seropositive primary Sjögren’s syndrome. (a) The green line indicates disease progression in a genetically susceptible individual over time. Different environmental factors (types A-C) that convey protection or risk are likely to be of importance at different stages of disease development. In some individuals, environmental factors type A may trigger development of autoantibodies in serum without the development of clinically overt disease. Environmental factors type C are of importance for the severity of manifest disease. (b) Environmental factors important at different stages of disease are likely overlapping and interact with each other. Genetic factors may both determine the baseline disease susceptibility and disease phenotype as well as interact with the different types of environmental factors.
an important role as an environmental risk factor for SS.

Epidemiologic studies on the association of infections in general with development of Sjögren’s syndrome

The association between infection and later development of autoimmune diseases, including SS, was investigated by Nielsen et al. in a nationwide registry-based study in Denmark including 4.5 million individuals followed from 1945 to 2000 [19]. For the 1977 SS cases identified, a relationship between previous hospitalization for infections and increased risk of SS was established. Incidence rate ratios (IRR) were the highest for infections that occurred <1 month before the diagnosis of SS (IRR 9.89, 95% CI 5.28–16.64), and decreased in a temporal manner to 10 years before diagnosis (IRR 2.16, 95% CI 1.94–2.41). Furthermore, a higher number of infections were associated with greater risk of SS. No difference in risk estimates was found between viral or other types of infections. The pattern observed for SS was similar to that made for other autoimmune diseases investigated. In the study, the SS cases were identified by ICD codes and the observation time occurred before implementation of the American-European Consensus Group (AECG) criteria [20] in 2002. Therefore, the accuracy of the SS diagnosis may be questioned and the results interpreted with caution.

Addressing the point of infections as risk factor in clinically verified SS, Mofors et al. recently published results from a study of 945 SS cases fulfilling AECG criteria and 9048 matched controls in Sweden [14]. Infections occurring within a latency period of 1 year prior to diagnosis were excluded to decrease the risk of reverse causality. Overall, a history of any infection was associated with an increased risk of SS (OR 1.9, 95% CI 1.6–2.3). Stratifying the analysis based on the presence of the SS-related autoantibodies anti-Ro/SSA and anti-La/SSB revealed that the association was
stronger for seropositive (OR 2.7, 95% CI 2.0–3.5) than seronegative SS (OR 1.9, 95% CI 1.4–2.7). By organ system, infections in the respiratory tract associated both with seropositive and with seronegative SS. Furthermore, a dose–response relationship between number of infections and increased risk for seropositive SS was observed. Notably, the data used for the analysis did not include records of infections diagnosed in primary care, wherefore the results from this study are applicable to more severe infections. A distinction between viral and bacterial infections was not made.

A smaller retrospective interview-based study also investigated the association between serious infections and SS. In this study by Ben-Eli et al., 91 prevalent SS cases diagnosed according to the AECG criteria and 211 controls underwent a structured interview including questions about infections prior to diagnosis that required hospitalization [21]. Patients were more likely than controls to report such infections, reaching an OR of 4.74 (95% CI 2.66–8.44). Main limitations of the study, also mentioned by the authors, relate to the small sample size and possible recall and selection bias.

Taken together, the studies on associations between infections in general and development of SS all point in the same direction (Table 1), and are in concordance with the long-standing hypothesis of a relationship between infections and SS development. Further strengthening the observations are results demonstrating temporal and dose–response relationships. Of importance, only more severe infections have been studied in an epidemiologic context, and it thus remains unexplored how milder, everyday infections influence the risk of SS, which is an important query for future studies. Moreover, it is important to note that epidemiologic studies only confirm association and do not prove causation. It may be that individuals more prone to SS development are also more susceptible to infections, and underlying genetic traits could predispose for both infections and SS development, although the scenarios of infections due to genetic susceptibility and as factors triggering autoimmunity certainly are not mutually exclusive. A further interesting hypothesis is that infections do not cause autoimmunity per se, but rather through immune activation accelerate the progression of autoimmune processes that have already begun many years before disease onset (Fig. 2). Indeed, it has been established that disease-related autoantibodies may be present many years before the SS diagnosis [15] and that various infections such as hepatitis B and hepatitis C, human immunodeficiency virus, parvovirus B19 and EBV may...
Table 1  *Studies on exposure to proposed risk factors before Sjögren’s syndrome diagnosis*

| Factor studied | SS diagnostic criteria | Participants (SS/controls) | Estimated risk (95% CI) | Author, year | Study design and factor definition | Comment |
|----------------|------------------------|-----------------------------|-------------------------|--------------|------------------------------------|---------|
| Infections     | Danish version of ICD-8, ICD-10 | 1977/4.5 million in total cohort | IRR 2.17 (1.98–2.38) | Nielsen *et al.*, 2016. [19] | Nationwide cohort; hospital admission for infection | Study population of 4.5 million individuals followed prospectively |
| Infections     | 2002 AECG criteria      | 945/9048                    | OR 1.9 (1.6–2.3)        | Mofors *et al.*, 2019. [14] | Case–control; hospital admission for infection | Infections occurring during a 1-year period before SS diagnosis was excluded |
| Infections     | 2002 AECG criteria      | 91/211                      | OR 4.74 (2.66–8.44)     | Ben-Eli *et al.*, 2019. [21] | Case–control; self-reported hospitalization for infection | Interview-based study in prevalent SS cases |
| Nontuberculous mycobacterial infection | ICD-9-CM, RCIPD | 5751/86265 | OR 11.24 (2.37–53.24) | Chao *et al.*, 2017. [58] | Population-based case–control; history of NTM infection | |
| *Helicobacter pylori* infection | ICD-9-CM, RCIPD | 5553/83295 | OR 1.80 (1.31–2.47) | Chao *et al.*, 2018. [60] | Population-based case–control; history of *H. pylori* infection | Individuals with a history of mycobacterial infection were excluded |
| Oestrogen      | 2016 ACR/EULAR criteria | 1320/1360                   | OR 0.5 (0.30–0.86)      | McCoy *et al.*, 2019. [84] | Case–control; composite oestrogen score ≥ 3 | SS cases were compared to sicca controls |
| Vitamin D      | ICD10                  | 8 605 952 in total cohort   | RR 2.1 (1.1–3.7)        | Ramagopalan *et al.*, 2013. [93] | Cohort; hospital admission for vitamin D deficiency | 12 SS cases |
| Stress         | 2002 AECG criteria      | 47/120                      | OR 6.45 (2.17–19.16)    | Karaiskos *et al.*, 2009. [100] | Case–control; >0 negative stressful life events | Interview-based. Events occurring during a 1-year period prior to SS symptom onset were studied |
| Current smoking | 2002 AECG criteria      | 63/252                      | OR 0.3 (0.1–0.6)        | Olsson *et al.*, 2017. [109] | Nested case–control; current of former smoking at inclusion | Prediagnostic data. The OR indicates risk of subsequent SS diagnosis |
| Former smoking |                        |                             | OR 4.0 (1.8–8.8)        |              |                                    |         |
| Silicone breast implants | ICD-9-CD | 467/123 255 in total cohort | OR 1.58 (1.26–1.97) | Watad *et al.*, 2018. [126] | Population-based cross-sectional; silicone breast implant recipient | Women with definite, probable and possible silicone breast implant were included in the exposure group |

ACR/EULAR, American College of Rheumatology/European League Against Rheumatism; AECG, American-European Consensus Group; ICD; International classification of diseases; IRR, incidence rate ratio; ns, not specified; OR, odds ratio; RCIPD, Registry for Catastrophic Illness Patient Database; RR, rate ratio; SS, Sjögren’s syndrome.
promote transient production of autoantibodies even in healthy individuals [22]. Studies of the association between infections in general and SS are of value since it has proven difficult to unambiguously identify single infectious agents triggering the disease. Considering available data, it is plausible that several different types of infections confer increased risk of SS by creating proinflammatory microenvironments that promote the triggering of autoimmunity (Fig. 4).

**Viruses implicated in Sjögren’s syndrome**

Viral infections that may promote SS development have been under investigation for decades. Hitherto, the Epstein–Barr virus (EBV) stands out as the most studied agent. Other investigated viruses in SS include cytomegalovirus (CMV), hepatitis C (HCV), Coxsackievirus and human T-lymphotropic virus type I (HTLV-1), which are discussed below. Additional studies have also been performed on discrete viruses such as the mumps virus, hepatitis B and human parvovirus B19 [23, 24].

**Epstein–Barr virus.** EBV is a human double-stranded DNA virus of the Herpesviridae family with a tropism for B cells and epithelial cells. The virus infects the majority of mankind during childhood or adolescent years, and after an initial lytic phase, a lifelong and latent infection is established in memory B cells, which can be reactivated through unknown triggers [25]. Interestingly, EBV-encoded proteins mimic B-cell receptor (BCR) and CD40 signalling, and can stimulate such pathways [26], which is of relevance in the context of B-cell hyperactivity in SS.

Several lines of evidence suggest the involvement of EBV in SS. The initial reports on quantitatively higher presence of EBV nucleic acids [27–29] and of higher serum titres of anti-EBV antibodies [30, 31] in SS patients compared to controls appeared some 30 years ago. More recently, a connection was reported between serological signs of past EBV infection and the presence of anti-Ro/SSA and anti-La/SSB autoantibodies [32]. Moreover, B-cell lines from SS patients were found to spontaneously produce large amounts of EBV compared to controls [33], and using a reporter cell line, the capacity to induce reactivation of EBV using saliva from patients with SS was demonstrated [34].

Mechanistically, EBV-encoded small RNA was found to bind the SS autoantigen La/SSB, subsequently activating TLR3 and resulting in production of type I IFN and proinflammatory cytokines [35]. Also, cross-reactivity between an autoantigenic epitope of Ro60 in human systemic lupus erythematosus (SLE) and the Epstein–Barr virus nuclear antigen-1 (EBNA1) was reported, indicating a possible route of molecular mimicry [36]. Interestingly, the presence of EBV was reported to be exclusive to salivary glands of SS patients that contain germinal centre (GC)-like structures [37]. In the GC, a significant proportion of perifollicular plasma cells infected with EBV displayed reactivity towards the SS autoantigen Ro52, providing a possible connection between EBV infection and perpetuation of autoimmunity.

Although studies are numerous, it remains to be determined whether any causal relationship exists between EBV infection and increased risk of SS.

**Cytomegalovirus (CMV).** Studies on CMV in SS are few, and observations mainly stem from murine models. Whereas one study found higher levels of anti-CMV IgM antibodies in patients with SS compared to controls [38], a later study reported a lower prevalence of anti-CMV IgG antibodies [32]. Interestingly, sialotropic murine CMV intraperitoneally injected into female autoimmune-prone NZM2328 mice induced a SS-like disease with chronic inflammation of salivary and lacrimal glands [39]. The model was suggested to resemble human disease as focal infiltrates in the submandibular glands persisted even after the virus had become undetectable by PCR.

Although CMV exhibits sialotropic characteristics and therefore constitutes an interesting candidate as an environmental factor in SS, evidence to support a clear connection is insufficient.

**Hepatitis C.** Like EBV and CMV, HCV is sialotropic and has been detected in salivary glands [40, 41]. According to the 2002 AECG and 2016 ACR/EULAR criteria [20, 42], HCV infection is an exclusion criterion for the SS diagnosis. When employing the 1993 preliminary classification criteria proposed by the European Community Study Group [43], HCV-infected individuals classified as SS were older at diagnosis, had a lower female: male ratio (3:1), and had lower frequencies of anti-Ro/SSA and/or anti-La/SSB autoantibodies compared to a SS reference cohort [44]. These observations suggest that individuals with chronic viral infections may present with signs and symptoms similar enough to be classified as
SS, further supporting a role for infections in the pathogenesis of this autoimmune disease. However, HCV infection does not appear to drive development of the typical clinical presentation of SS, and in cases where HCV-infected individuals fulfill the AECG criteria, it has been suggested that the term ‘SS secondary to HCV’ should be used [44].

The discussion whether HCV may act as an environmental trigger of SS is long-standing and has been extensively reviewed elsewhere [45, 46], but at this point lacks formal convincing evidence.

Coxsackievirus. Whilst one group found evidence of the presence of two serotypes of Coxackievirus in minor salivary glands of patients with primary SS but not in controls or secondary SS [47], another group was unable to replicate these results [48]. Notably, one study found a possible cross-reaction between antibodies to an epitope of the SS-associated Ro60 antigen and a peptide from the Coxackievirus 2B protein, which were reported to share 87% sequence homology [49].

Human T-lymphotropic virus type I (HTLV-I). HTLV-1 is a human retrovirus causing lifelong infection. The virus is endemic to certain geographical areas, with an especially high prevalence in Japan. In 1989, Green et al. reported that transgenic mice with the HTLV-1 tax gene developed an exocrinopathy resembling human SS [50]. The HTLV-1 tax gene has been reported to be expressed not only in salivary glands of patients with SS [51, 52], but also in salivary glands of patient with other inflammatory diseases [53]. Also, HTLV-1 has been shown to infect salivary gland epithelial cells [54].

Epidemiologic studies have further indicated a connection between HTLV-1 infection and SS. In the Nagasaki Prefecture, anti-HTLV-1 seropositivity was found to be 23% in SS patients and 3% in controls [55]. In that study, anti-HTLV-1 IgA antibodies in saliva were also detected in 5 out of 7 patients with SS. Another study found that mononuclear cell infiltration in labial salivary glands could be detected in ten out of ten consecutively recruited patients with HTLV-1-associated myelopathy (HAM), and six out of these received a SS diagnosis [56]. A study of Nagasaki atomic bomb survivors showed an anti-HTLV-1 antibody prevalence of 28% in patients with SS compared to 8% in non-SS controls [57].

Altogether, several studies have indicated an over-representation and possible role for HTLV-1 infection in prevalent SS cases, but thus far, no prospective studies on increased risk of developing SS in HTLV-1-infected individuals have been performed.

Bacteria and Sjögren’s syndrome Few individual bacteria have been proposed or investigated as factors in the pathogenesis of SS, although the previously mentioned epidemiologic study suggested bacterial infections in general as a risk factor for SS [19]. Studies on specific agents are summarized below.

Mycobacterial infection. One epidemiologic study investigated potential connections between tuberculosis (TB) and nontuberculous mycobacterial (NTM) infection in 5751 newly diagnosed SS patients and 86 265 matched controls in Taiwan [58] (Table 1). A significant association was observed between NTM infection and SS (OR 11.24, 95% CI 2.37–53.24), but not for TB infection. Another study only had one observation of mycobacterial infection in the investigated cohort, and thus, no conclusion could be drawn [14].

Helicobacter pylori. The link between H. pylori infection and SS remains controversial due to conflicting reports. A recent meta-analysis of nine studies of infection rates of H. pylori in prevalent SS cases showed a weak association reaching an OR of 1.24 (95% CI 1.03–1.50) [59]. Of note, six of the nine included studies had employed outdated SS classification criteria and two of the studies used biopsies for verification of infection whilst seven studies used serology. Thus, results from this meta-analysis should be interpreted with caution. Notably, a recent study reported higher prevalence of a history of H. pylori infection in incident SS cases compared to matched controls [60] (Table 1). Studies on mechanistic links between H. pylori infection and SS are lacking.

Commensal bacteria as factors in the pathogenesis of Sjögren’s syndrome. Trillions of bacterial cells inhabit various niches of the human body, and throughout evolution, humans and bacteria co-evolved to form symbiotic relationships. Amongst other contributions, commensal bacteria protect the host against pathogen overgrowth [61], synthesize digestible short-chain fatty acids from dietary components [62] and play a crucial part in maintaining immune homeostasis [63]. Novel sequence-
based technologies such as 16s rRNA sequencing enable high-throughput analysis of the human microbiome.

It has become increasingly evident that dysbiosis, a state of imbalance in the composition of microbrial communities, in which bacteria are the most commonly investigated components, may partake in driving disease states. Several studies have highlighted possible mechanistic links between the microbiome and autoimmunity. Recently, the autoimmunity-predisposed (NZW x BXSB) F1 hybrid mouse, and germ-free C57BL/6 mice mono-colonized with the gut microbe Enterococcus gallinarum were used to demonstrate translocation of this microbe to the liver and to other systemic tissues in the mice, resulting in promotion of autoimmunity [64]. Moreover, E. gallinarum-specific DNA was detected in liver biopsies from three patients with SLE but not in healthy controls, thus further supporting its relevance. One study tested the hypothesis that Ro60-reactive T cells may also be activated by peptides from the commensal microbiota using T-cell hybridomas from HLA-DR3 transgenic mice recognizing three regions of the SS-related autoantigen Ro60 [65]. The von Willebrand factor type A domain protein from the oral microbe Capnocytophaga ochracea was identified as a potent activator. Another study found that commensal bacteria of the skin, oral cavity and gut carry orthologs of Ro60, against which antibodies could cross-react with human Ro60 and therefore initiate and sustain autoimmunity [66]. Further, a study of caecal content transfer between male and female nonobese diabetic (NOD) showed that the gut microbiome influences differences in sex-specific susceptibility to autoimmunity by inducing testosterone-dependent protection [67]. Thus, a growing body of evidence suggests that commensal bacteria may be involved as triggers of autoimmunity.

Commensal or pathogenic microbiota could potentially function as environmental triggers for SS, but their role in the disease is only beginning to be understood. In SS, autoimmune inflammation impairs mucocutaneous barrier function and could thus contribute to favour dysbiosis and colonization with pathogenic species in the mouth and gastrointestinal tract, lungs, eyes and vagina. Hence, it is important to keep in mind that observations of dysbiosis in prevalent SS cases do not necessarily mean that these conditions existed prior to disease onset and conferred increased risk of disease.

The microbiome in prevalent Sjögren’s syndrome cases. So far, a few studies have explored the gut microbiome in SS patients. A study comparing patients with SS (n = 39) and SLE (n = 30) to population controls (n = 965) found that faecal microbiota in both patient cohorts was characterized by lower bacterial richness and lower Firmicutes/Bacteroidetes ratios compared to controls [68]. In another study, stool samples from 42 patients with SS and 35 age- and sex-matched controls were analysed for dysbiosis using a 16s rRNA-microbiota test [69]. Severe dysbiosis was significantly more prevalent in patients with SS than in controls (21% vs. 3%), and the patients with severe dysbiosis had higher ESSDAI scores, lower C4, and higher levels of faecal calprotectin. One study found no differences in the conjunctival microbiome of SS patients compared to controls, but significant differences in oral and stool microbiome composition, and a combined systemic and ocular SS severity index was inversely associated with faecal microbial diversity [70]. These studies indicate that a state of gut dysbiosis may be connected with higher disease activity in patients with SS.

Some studies have looked at the oral microbiome in patients with SS. Recently, van der Meulen et al. used 16S rRNA sequencing to investigate the buccal mucosa microbiome in SS patients (n = 37), non-SS sicca patients (n = 86) and healthy controls (n = 24) [71]. Whilst 19 taxa were associated with SS compared to controls, analysis of the microbiome could not distinguish patients with SS from sicca controls, which were both characterized by a higher Firmicutes/Proteobacteria ratio. Notably, a comparable ratio was observed in a study of Chinese patients with SS [72]. However, the authors found that disease status and salivary secretion rate explained comparable levels of the variation in bacterial composition [71]. Similarly, in a study of oral washings, the same group reported that salivary secretion rate had a stronger influence on the microbiome than SS disease status [73], which was also confirmed in a third study [68].

One small study could not identify significant differences in the vaginal microbiome of pre-menopausal patients with SS (n = 9) with vaginal dryness compared to controls (n = 8) [74].
Altogether, studies of the microbiota in patients with SS have primarily focused on the gut and oral microbiome in prevalent disease. Although most studies report states of dysbiosis in patients with SS, results are inconclusive. For instance, whilst several studies have reported lower oral Streptococcus relative abundance [70, 72, 75], another study found it to be higher [73]. Notably, most studies have included few patients with SS who may not accurately represent the entire SS population. Moreover, regional and ethnic differences in composition of the microbiome could be expected. Importantly, SS is a disease of mucosal sites and studies of microbial compositions in prevalent SS cases cannot reveal potential cause–effect relationships. Notably, a recent epidemiologic study could not verify any significant connection between a history of gastrointestinal infections and increased risk of SS [14]. It remains unclear whether reported alterations of the microbiota constitute a risk factor for SS or rather reflect downstream events following niche alterations that follow upon SS development.

**Vaccination in the context of Sjögren’s syndrome**

Vaccination represents one of the greatest achievements in the history of medicine, reducing morbidity and mortality in millions of individuals. Through vaccination, individuals mount protective immune responses against pathogens in ways similar to when contracting actual infections. Consequently, systematic studies of immune responses to microbial antigens in vaccines may elucidate dysregulated immunological pathways involved in SS pathogenesis.

Brauner et al. [76] monitored patients with SS and controls receiving a squalene-adjuvanted anti-H1N1 influenza vaccine. Treatment-naïve anti-SSA-seropositive SS patients responded with higher titres of vaccine-specific antibodies compared to controls, and the higher serological response in patients was accompanied by increasing titres of autoantibodies and other off-target antibodies including anti-EBV. *In vitro* experiments on isolated naïve B cells confirmed a higher tendency for patient cells compared to control cells to differentiate into antibody-secreting plasma cells upon endosomal TLR activation. Another study found similar rates of seroconversion and seroprotection in patients with SS compared to controls after unadjuvanted anti-H1N1 vaccination [77]. In that study, significant increases in anti-Ro/SSA and anti-La/SSB autoantibodies were observed in the patients at 1-year follow-up.

In a recent study of immune responses to viral antigens in a nonadjuvanted seasonal influenza vaccine, we observed development of higher vaccine-specific IgG antibody titres in anti-SSA-seropositive patients with SS compared to controls [78]. Titres of anti-Ro52 autoantibodies increased in patients after vaccination, whilst anti-EBV titres remained unchanged. In peripheral blood monocytes, a higher vaccine-specific IgG response was associated with higher IFN scores prior to vaccination and higher vaccination-induced NF-kB signalling. Specifically, the vaccination-induced expression of the *IKBKG/NEMO* gene was associated with a higher serological response. Altogether, the observed augmented responses to viral antigens in patients with SS add to the body of evidence suggesting viral infections as an environmental risk factor for SS.

An aspect of adjuvant-containing vaccines and SS is the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) proposed in 2011 [79]. The syndrome includes different conditions defined by common signs and symptoms (e.g. chronic fatigue, arthralgia, myalgia) arising after adjuvant exposure. A link between ASIA and SS was suggested owing to the similarities in clinical symptoms, the link between infections and development of SS, and case reports of SS arising after vaccination [80]. However, more research is needed to understand the connection between ASIA and SS.

Results indicating an increased risk of SS following infections raise questions about the safety and necessity of vaccinations. Brito-Zeron et al. reported infections as a leading cause of death in SS [6], thus stressing the importance to vaccinate patients with SS for protective immunity. On the other hand, a few case reports have indicated a possible triggering of SS by vaccination against hepatitis B [81] and H1N1 influenza [82]. Well-designed and large studies on the safety and efficacy of different vaccines in SS are lacking. The recently updated EULAR recommendations state that influenza and pneumococcal vaccination should be strongly considered for a majority of patients with autoimmune inflammatory rheumatic diseases, whilst live-attenuated vaccines may be considered with caution [83].
Information suggesting a relationship between vaccination and increased risk of SS stems solely from a few case reports. In all, there is little support that vaccinations could be a risk factor for SS. Most importantly, it is well established that the benefits of appropriate vaccination in autoimmune patients by far outweigh the risks [83].

**Hormones**

The large female bias of SS suggests that sex hormones may be an important component in SS aetiology. However, counterintuitively, several studies have suggested a protective role for female sex hormones in SS. McCoy et al. reported on female patients with SS (n = 1320) compared to sicca controls (n = 1360) with regard to age of menarche, age of menopause, reproductive history, use of female hormone therapy at time of enrolment and hysterectomy history [84] (Table 1). Composite oestrogen scores (CES) and cumulative menstrual cycling (CMC) years before onset of sicca symptoms were analysed. Compared to controls, patients with SS had significantly lower CES, displaying an inverse dose–response relationship between oestrogen exposure and risk of SS. The results were corroborated for CMC, but the dose–response relationship was not observed there. Furthermore, sicca controls had a significantly younger age of menarche and a higher proportion of current female hormone therapy. Intriguingly, high compared to low CES was significantly associated with lower ocular staining score and lower prevalence of hypergammaglobulinaemia, RF and anti-Ro/SSA autoantibodies in the SS patients [84].

Mouse studies have further implied the importance of sex hormones in SS development. After ovariection, autoimmune exocrinopathy resembling SS was observed in healthy C57BL/6 mice [85], and more severe autoimmune lesions in salivary and lacrimal glands were observed in two different SS mouse models [86, 87]. A severe autoimmune exocrinopathy resembling SS develops in aromatase-deficient mice that cannot synthesize oestrogen [88], and administration of an aromatase inhibitor was shown to exacerbate autoimmune lesions in an SS mouse model [89]. Moreover, treatment with oestradiol has been shown to significantly decrease salivary gland focus score in the MRL-lpr/lpr autoimmune mouse model [90]. Of relevance, the steroid hormone dehydroepiandrosterone (DHEA), which is a metabolic intermediate in the biosynthesis of androgens and oestrogens, was evaluated for treatment of fatigue, well-being and physical functioning in SS in a randomized placebo-controlled clinical trial [91]. However, DHEA was not found to have a superior effect on the primary outcome measures of the study compared to placebo.

Taken together, experimental and clinical data imply a link between female sex hormone levels and SS. The presence of anti-Ro/SSA and La/SSB autoantibodies is associated with a younger age at SS onset, wherefore it could be important to separately consider seropositive and seronegative SS when assessing the influences of sex hormones in future studies. Whether hormonal therapy or perhaps a lack thereof constitutes a risk factor for SS remains to be determined. Future studies should focus on longitudinally assessing hormone levels and hormonal therapy in relation to SS development.

**Vitamin D**

The major natural source of vitamin D is through ultraviolet radiation-dependent production in the skin. Vitamin D exerts a plethora of immunomodulatory effects, and low levels caused by lack of sun exposure or low dietary intake have been identified as an important risk factor for the autoimmune disease multiple sclerosis [92].

Few studies have been performed on the potential role of vitamin D in the development of SS. One study used records of hospital admissions and death registrations from 1999 to 2011 in England to study the risk of immune-mediated diseases comparing individuals admitted for vitamin D deficiency or related diseases (osteomalacia and rickets) and control cohorts [93]. Significantly increased risk for SS was reported for the vitamin D-deficient cohort (Table 1). However, the study had limited access to data on potential confounding factors and SS cases were identified by ICD codes, wherefore the authors state that the results should be regarded as speculative. By contrast, Baldini et al. [94] studied vitamin D levels in patients referred to a Rheumatology unit for dry eyes and/or dry mouth, and found that vitamin D levels did not differ between the patients who later received a SS diagnosis (n = 30) compared to those who did not (n = 46). Similarly, in two other studies comparing patients with SS and healthy controls, no difference in vitamin D levels was noted [95, 96].
Also, one study could not find any associations between vitamin D receptor gene polymorphisms/haplotypes and SS [97]. With regard to disease manifestations, one study reported low levels of vitamin D in patients with SS presenting with peripheral neuropathy or with lymphoma compared to patients without these manifestations [96].

Thus far, there is little support for a potential involvement of vitamin D in the pathogenesis of SS. Vitamin D levels are largely dependent on sun exposure, wherefore it would be interesting for future studies to investigate a possible relationship between sun exposure and later development of SS.

**Stress**

Acute and chronic psychological stress may induce perturbations of innate and adaptive immune responses, primarily thought to be mediated via the hypothalamic–pituitary–adrenal (HPA) axis [98]. Indeed, stressful life events prior to disease onset have been proposed as a risk factor for autoimmune diseases [99]. One study investigated major and minor stressful events, coping strategies and social support in the year prior to disease onset in patients with SS, patients with lymphoma and in healthy controls [100] (Table 1). Negative stressful life events were more common prior to disease onset in patients with SS compared to patients with lymphoma and healthy controls. Also, perceived social support and defective coping strategies were more common amongst patients with SS compared to the other groups.

**Organic chemical factors**

**Smoking**

Tobacco smoking has a wide range of detrimental health effects and contributes to increase the risk of many diseases, including chronic inflammatory diseases such as seropositive RA and Crohn’s disease [101, 102].

In SS, several studies on prevalent cases have shown a significantly lower frequency of current smokers amongst patients with SS compared to controls [103–105], or trends indicating a lower frequency of smokers [106, 107]. One study reported a significantly higher proportion of former smokers amongst patients with SS compared to controls [103], and one reported a similar trend [106]. A study utilizing prediagnostic data found current smoking to be associated with lower risk and former smoking to be associated with higher risk of subsequent SS diagnosis [108] (Table 1). An intuitive explanation for these observations is that the oral, respiratory and ocular irritation caused by tobacco smoke makes patients with SS more likely to discontinue smoking. However, intriguingly, two studies have reported lower prevalence of focal sialadenitis in minor salivary gland biopsies from smoking compared to nonsmoking patients with SS [105, 109]. Lower inflammatory activity with lesser leucocyte infiltration in salivary glands could at least hypothetically be linked to a lower prevalence of SS amongst smokers. Another explanation could be that individuals with a milder inflammation and possibly also milder disease symptoms have a higher tendency to continue smoking. Whereas a pattern indicating higher risk amongst former smokers together with lower risk amongst current smokers in SS is reminiscent of the role of current smoking as a protective factor for ulcerative colitis [110], it must be kept in mind that SS symptoms, even several years before the clinical diagnosis, may negatively affect the likelihood to smoke.

Few studies have investigated associations between smoking and disease severity or SS subphenotypes. One study found no significant differences regarding ESSPRI scores, ESSDAI scores or type I IFN signature comparing different smoking categories [111]. However, in that study, the category of current smokers only encompassed 5 patients, wherefore meaningful conclusions could not be drawn for this group. Nevertheless, the observations are in line with two other studies where no associations were found between smoking and extraglandular manifestations [103] or disease activity scores [105].

Additional studies are needed to accurately define the role of smoking in SS. A majority of the conducted studies have included prevalent SS cases and thus do not elucidate the role of smoking as a potential risk factor prior to diagnosis. Lessons from MS and RA show that smoking may interact with genetic risk variants to increase the risk of disease [112, 113], wherefore stratification with regard to SS-associated HLA alleles may be needed in future studies to fully understand the role of smoking in development of SS. Given the insidious onset of SS, often spanning several years
between first symptom and diagnosis, recall bias is an inherent challenge in these studies. Regardless, the negative effects of cigarette smoking are well established and substantial, wherefore a potential beneficial role of smoking for SS is of limited clinical value.

**Alcohol**

Studies in autoimmune diseases have indicated inverse relationships between alcohol consumption and risk of RA [114, 115] and MS [116].

One recent study examined the association of alcohol intake and SS. Ben-Eli et al. investigated alcohol consumption occurring at least once a week (yes vs. no) in prevalent SS cases \((n = 91)\) diagnosed according to AECG criteria compared to controls \((n = 211)\) [21]. In a model adjusted for age, sex and education, patients with SS were less likely to consume alcohol reaching an OR of 0.26 (95% CI 0.14–0.49), where 27.7% of SS patients vs. 58.2% of controls regularly drank alcohol. In analogy with lower prevalence of smoking in patients with SS, it is conceivable that oral discomfort from intake of alcoholic beverages may underlie the lower prevalence. However, interestingly, alcohol intake can suppress inflammation and reduce responses to antigens [117, 118], suggesting how alcohol mechanistically could mediate a lower risk of autoimmunity.

The role of alcohol as a risk factor in SS remains unknown as only studies of alcohol consumption in prevalent SS cases have been performed. Future studies should therefore focus on quantification of alcohol intake before the onset of disease, and it would be desirable to understand whether a dose–response between alcohol intake and development of SS exists.

**Solvents**

Research on the relevance of solvents as risk factors for autoimmunity began in the 1950s after case reports of autoimmune-like conditions occurring after exposure [119]. One study reported an association between AECG-diagnosed SS and occupational exposure to organic solvents; however, the authors were unable to distinguish between exposures before or after disease onset, and therefore, no conclusions regarding a causal role could be drawn [120].

### Inorganic chemical factors

#### Silica

Silica can be found in nature as quartz and sand, and is often used in manufacturing of glass, ceramics and cement. Whereas exposure to silica is considered a well-established environmental risk factor for development of RA, systemic sclerosis and SLE [119], few studies have explored the possible link between exposure to silica and SS. Prior to the implementation of modern SS diagnostic criteria in 2002, case reports of SS occurring after exposure to silica in scouring powder [121], by coal mining [122], and in a 72-year-old male dental technician [123] were described. In a more recent study however, occupational exposure to crystalline silica was not associated with SS [120]. Notably, in that study, the numbers of exposed individuals were quite low: \(n = 1/175\) for SS cases and \(n = 5/350\) for controls. In all, available data are insufficient to support a definitive role for silica in SS. Of note, females, who are the ones predominantly affected by SS, are probably less prone to work-related silica exposure.

#### Silicone

Silicones, which like silica contain the element silicon, are synthetically created polymers. Since many decades, silicones have been used in medical implants and considered to be biologically inert materials. However, this notion has been challenged as several immunological effects of silicones have been reported [124]. Numerous studies have investigated potential connections between silicone breast implants (SBIs) and development of autoimmunity, yielding inconsistent and conflicting results. A meta-analysis of seven studies investigating potential associations between SBIs and risk of SS indicated a significant association reaching an effect size of 2.92 (95% CI 1.01–8.47) [125]. However, the association was driven by two studies of self-reported disease, and the five other studies did not report statistically significant associations. A recent study on SBIs and risks of various autoimmune diseases identified by ICD-9 codes suggested an increased risk of SS in women with SBIs (OR 1.58, 95% CI 1.26–1.97) [126] (Table 1). Even though some studies have reported a link between SBIs and increased risk of SS, a majority of the conducted studies have not. Also, the accuracy of SS diagnosis should be questioned in the performed studies as some of them were
conducted before implementation of modern SS diagnostic criteria, other cases were identified by ICD codes, and some relied on self-reported disease.

Conclusions and future perspectives

Although many studies have investigated possible environmental factors in SS, limited conclusions may be drawn. Many of the performed studies have been conducted on prevalent SS cases, sometimes many years after diagnosis, and do not consider exposure before symptom onset, the phase during which causal environmental factors would logically act (Fig. 2). To identify factors that increase the risk of SS in genetically susceptible individuals, it will be important to design future studies to explore exposures that take place before the disease is manifest. Amongst the numerous biological and chemical factors studied (Fig. 3), the most substantial epidemiologic and mechanistic evidence currently exist for viral infections as factors increasing the risk of SS.

The substantial female sex bias in SS suggests that some environmental risk factors may be specific to women. One possibility is that the exposure to such factors is largely confined to women. However, it may also be that women are inherently more susceptible to certain risk factors. In future studies, risk factors important to consider would be circumstances and specifics of female-dominant contexts and occupations. Immunological pathways regulated by sex hormones, which may in turn interact with environmental factors, should be further explored.

Observations in other autoimmune diseases have revealed interactions between genetic risk variants and environmental risk factors [112, 113] and further that some environmental factors constitute a risk only for subtypes of disease [101]. Subphenotypic characterization of patients may thus be highly relevant to understand the aetiopathogenesis of SS. Indeed, stratification by autoantibody status revealed substantial differences regarding the risk conferred by infections in SS [14]. We therefore propose that future studies stratify patients with SS both according to autoantibody status and for genetic risk factors such as HLA risk alleles in the analysis of risk factors. Moreover, possible interactions between proposed environmental factors should be considered, as well as the possibility that different environmental factors may be important for the transition into autoimmunity and into clinically manifest disease, respectively.

In summary, the fact that genetic studies in SS have not uncovered variants conveying large increases of risk [10], together with the observation that monozygotic twin concordance rates of autoimmune disease are relatively low [11–13], reveals that other factors must play a critical role. Importantly, and in contrast to genetic factors, environmental factors are modifiable. Although numerous environmental factors have been suggested in SS, data are still inconclusive and no single causal environmental factor has been unambiguously identified, though data continue to support infections as an important risk factor for SS. By identifying the major risk factors, it is possible to minimize exposure, which would be expected to lead to decreased disease incidence rates or ameliorate disease severity. For chronic conditions such as SS, for which effective therapy is still lacking, this will be an important step forward.

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Conflict of interest statement

The authors declare no competing interests.

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