Review

The effect of smoking on Sjögren's disease development and severity: a comprehensive literature review

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ABSTRACT

Unlike other autoimmune diseases, little is known about the environmental risk factors for Sjögren's disease (SjD). Smoking is an important risk factor for rheumatoid arthritis but the relationship between smoking and SjD is more complex to understand. Current smoking seems to be negatively linked to SjD, whereas there is mixed data on past smoking. Smoking also seems to impact SjD outcomes, influencing comorbidities like hypertension or associated immune-mediated diseases, and, less clearly, extraglandular involvement, particularly pulmonary disease. Minor salivary gland biopsy findings indicate a lower frequency of positivity associated with smoking, with a potential dose-response relationship. However, smoking's uncertain effect on dryness symptoms complicates interpretation of data with reverse causation remaining a possibility. This review underscores the complexity of the smoking-SjD connection, raising questions about causality and potential protective effects on either SjD's development and/or classification criteria. Understanding these nuances may help unravel SjD pathogenesis and inform future therapeutic strategies.

Sjögren's disease and its known risk factors

Sjögren's disease (SjD) is a complex systemic rheumatic disease that mainly targets exocrine glands, with ocular and oral dryness present in around 98% of patients (1). Other common symptoms are fatigue, arthralgia and salivary gland swelling, but patients can exhibit systemic organ involvement as well. The aetiopathogenesis of SjD is poorly understood. An increasing number of genetic risk alleles have been identified, but even though monozygotic twin concordance rates in SjD have not been determined, these are typically not more than 30% in autoimmune diseases (2, 3). Environmental factors remain, nevertheless, poorly characterised.

The study of SjD environmental risk factors presents a number of difficulties. The typical diagnostic delay at 2-6 years represents an important issue (4, 5). Symptom onset is usually gradual with nonspecific symptoms such as dryness, arthralgia and fatigue which can complicate patients' recall ability. Furthermore, disease-associated autoantibodies can be detected years before symptom onset (6) and there may be different environmental risk factors at different stages in SjD development. Further, since making an accurate SjD diagnosis itself can be challenging, the available studies are either well-characterised SjD cohorts in specialist centres with small numbers that limit subgroup analyses and correction for confounders, or are larger population-based cohorts that lack a well-defined diagnosis. Dryness symptoms prevalence in the non-SjD population raises questions on the accuracy of these more loosely-defined diagnoses. Other methodological issues include the selection of controls, with some studies comparing SjD to 'healthy' controls and others to sicca patients *i.e.* patients with dryness symptoms and/or signs without SjD. The inclusion/exclusion criteria for this sicca group may also differ between studies.

Despite these obstacles, some evidence on environmental risk factors is available. A positive immune-mediated disease family history has been associated with SjD (7), which may reflect both genetic and environmental factors. Diet is another proposed risk factor, with adherence to a Mediterranean diet

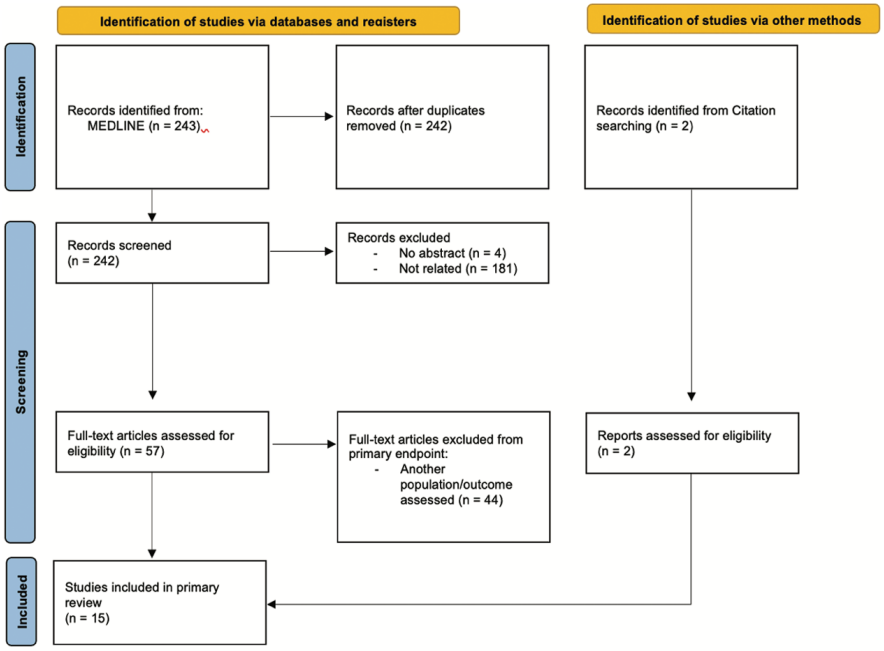

Fig. 1. PRISMA flow diagram of studies included through the review.

having previously been associated with a lower SjD likelihood (8).

Some infections have been associated with a higher risk of developing SjD (5, 9). In a recent 12-year prospective study, human papilloma virus infection was associated with a significantly higher risk of SjD (10), and Epstein-Barr Virus infection has previously been implicated in its pathogenesis (11, 12). Overall, a previous hospitalisation for an infection increases the risk of SjD, particularly closer to the diagnosis (13). Interestingly, the number of past infections also seems to correlate with development of SjD (5, 9, 13). Tonsillectomy has been associated with SjD in one study (14) and a history of tonsillectomy may be associated with a higher level of salivary gland inflammation in SjD patients (15).

Smoking and immune-mediated diseases

Smoking is a known environmental risk factor for multiple diseases and has been associated with some rheumatic diseases, most notably rheumatoid arthritis (RA) (16, 17). Current but not past smoking has also been linked to systemic lupus erythematosus (SLE), although less consistently in the literature (18, 19). Though the association of current smoking and SLE proved statistically significant in a meta-analysis, most studies included were not able to verify it. This questions the generalisation of the findings and highlights the potential challenge of extrapolating these conclusions across different demographic groups.

Conversely, smoking has been reported as having a potential protective effect on several other disorders such as ulcerative colitis (20) and Parkinson's disease (21) suggesting that smoking may have opposing directions of effect on the risk for different immune-mediated conditions (Table I). A small number of studies have reported a negative association between smoking and SjD. This is often assumed to be due to reverse causation (22, 23), but biological mechanisms underlying this smoking effect are not implausible.

Mechanisms by which smoking may influence the immune system

There are numerous proposed mechanisms whereby smoking may modulate the immune system, some of which may be highly relevant to SjD. For example, cigarette smoking may suppress induction of type 1 interferon (24) which is considered to have a key role in SjD pathogenesis (25). Similarly, studies in the field of ulcerative colitis suggest that nicotine may have an anti-inflammatory effect (26), possibly via a nicotinic acetylcholine receptor (27, 28). Smoking may also interfere with lymphocyte migration to salivary glands (29) as it is known to decrease leukocyte chemotaxis (30). Smoking can suppress B-cell differentiation processes at a very early stage (31, 32) and is also associated with a reduction in IgG levels (33). In fact, unlike IgE, the secretion of IgA, IgM and IgG has been found to be decreased both in serum and saliva of smokers, which may be a driver for periodontitis (34, 35). On the other hand, smoking has the ability to trigger an inflammatory reaction with increased release of tissue-destructive substances such as reactive oxygen species, collagenase, serine proteases and proinflammatory cytokines (30).

Our objective is to evaluate current knowledge on the association between smoking and SjD and the direction of causality.

Methods

This review was performed through a systematic search from MEDLINE considering literature up to July 2023, using the following search words: "((smoking) OR (tobacco) OR (cigarette) OR (smoke)) AND (Sjögren)". This search produced 243 articles, from which 13 articles were included in the main review after careful selection. An additional two articles were added from the screening of references cited in retrieved articles yielding 15 articles in total (Fig. 1). We evaluated the quality of evidence of studies with the Newcastle-Ottawa Scale (NOS) (36). The maximum NOS score is 9 points and studies achieving 0–3, 4–6 or 7–9 points were considered low, medium, and high quality, respectively. Some articles excluded from the main review (smoking as a risk factor for SjD) are referenced in subsequent sections of this manuscript.

Smoking as a risk factor for Sjögren's disease

Less research has been undertaken on smoking as a risk factor for SjD when compared with RA.

The majority of the few studies available have found a negative association

Table I. Association between smoking and other immune-mediated diseases.

Smoking as a protective factor	Disease	Smoking as a risk factor
	RA	Higher risk of developing RA in smokers; higher risk of rheumatoid factor and anti-CCP RA in smokers; risk related to smoking duration and intensity; smoking is associated with disease severity (16, 17, 57)
	SLE	Higher risk of developing SLE in current smokers; higher prevalence of dsDNA in current smokers (18, 59)
Lower risk of developing PsA in smokers amongst psoriasis patients (88, 89)	PsA	Higher risk of developing PsA in smokers in the general population[88,89]
	Crohn's	Higher risk of developing Crohn's disease in smokers; smoking is associated with disease severity (90)
Lower risk of developing ulcerative colitis in smokers; smoking is negatively associated with disease severity (90)	Ulcerative colitis	
	MS	Higher risk of developing multiple sclerosis; risk related to smoking intensity; smoking is associated with disease severity (91)
	Graves' disease	Higher risk of developing Graves' disease (particularly Graves' ophthalmopathy) in current smokers; risk related to smoking intensity; smoking is associated with disease severity/lower response to therapy (92)
Lower risk of developing hypothyroidism in smokers; lower prevalence of thyroglobin and thyroperoxidase autoantibodies in smokers (92)	Hashimoto's thyroiditis	
	Primary biliary cholangitis	Higher risk of developing PBC in smokers (93); smoking is associated with a risk of liver fibrosis amongst PBC patients (94)
Lower risk of developing Parkinson's disease in smokers (95)	Parkinson's disease	Smoking is associated with disease severity (95)
Lower risk of developing Behçet's disease in current smokers (96); smoking cessation can increase disease activity	Behçet's disease	Smoking is associated with disease severity (97)

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; PsA: psoriatic arthritis; MS: multiple sclerosis.

between smoking and the development of SjD. However, the available studies have varying methodology and lack homogeneity in both the approach to patient recruitment and SjD criteria, as well as in smoking status data details and collection (Table II).

Interestingly, and even though with a different methodology than that expected for this subject, US researchers trying to develop a screening questionnaire for SjD found that answering "No" to the question "Do you currently smoke cigarettes?" yielded a considerable likelihood of meeting ACR/EULAR 2016 SjD classification criteria (OR 2.83 95% CI 1.69–4.91) (37).

A recent meta-analysis, that included 5 studies on smoking and SjD, showed no statistical association between a history of smoking and SjD (pooled OR 1.39, 95%CI 0.76–2.53, p=0.290), but a statistically significant negative correlation between current smoking and SjD (pooled OR 0.49, 95%CI 0.29–0.83, p=0.008) (38).

In fact, from the 15 main studies included in our review, 8 found a negative association between current smoking and SjD (22, 39-45).

A population-based study from Malmö, Sweden (43) assessed both smoking and socioeconomic status and their association with the development of SjD. Sixty SjD patients fulfilling AECG classification criteria (46) and matched controls were analysed, and smoking at the time of the health survey was associated with a lower likelihood of having SjD (OR 0.3; 95% CI 0.1–0.6) (43). Conversely, former smokers had an increased risk of being diagnosed with SjD.

Furthermore, this study reveals interesting data on the group of patients that had a smoking history before SjD diagnosis (n=23). Although the numbers were small, the vast majority (n=20) stopped smoking more than 5 years preceding symptom onset, suggesting that dryness may not be the underlying reason behind the lower proportion of active smokers in Sjögren's cohorts (43). Other studies that evaluate the timeline of smoking cessation compared to SjD diagnosis seem to find similar results (39).

A North American study using a population-based cohort compared smoking status between 106 cases and 316 matched controls (44). This study defined SjD cases based on the opin-

ion of the assisting Rheumatologists. Smoking status was divided into never, former, or current smoking with data collected at time of diagnosis and one year prior. SjD patients were less frequently current smokers (OR 0.34, 95% CI 0.14–0.85, $p<0.021$) and more frequently former smokers compared to controls. The proportion of never smokers was similar between groups (44). Data collected at diagnosis and one year prior showed almost the same differences in smoking status between cases and controls, although no data on time of symptom onset was obtained.

In a cohort of positive anti-Ro/SSA individuals with self-reported skin symptoms, those with SLE had higher rates of smoking compared to SjD (47), with comparable data seen in Spanish SjD and SLE registries (48). Likewise, Stone *et al*. found that current smoking rates were significantly lower in SjD patients (4.6%) compared both to sicca (14.1%) and controls (16.8%), with SLE patients having the highest prevalence of active smokers (18.0%) (42).

The previously mentioned distribution of fewer current smokers but a higher prevalence of former smokers amongst SjD patients compared to controls was observed in two additional studies (39, 45). In one of these studies, however, when looking at smoking status divided into never and ever smokers, the frequency of ever smokers was significantly higher in SjD patients, as was the proportion of passive smokers. Interestingly, in this Turkish study, the number of smoking pack-years, and smoking duration were lower in SjD patients and a significant percentage of patients (34.9%) stopped smoking after dryness symptom onset (39).

In contrast to this, a multicentric Swedish study (22) with comprehensive data on smoking habits showed that SjD patients may smoke equally as much as controls during early adulthood by analysing the period prevalence of smoking. The main difference found was that Sjögren's patients were more likely to stop smoking, with the cessation of smoking beginning as early as 30 years prior to SjD diagnosis. This raises the question of whether the cessation of smoking is being driven either by dryness or by another factor in some way related to SjD that may be present a long time before the diagnosis. This SjD cohort had a significantly lower exposure (in pack-years) when compared to controls.

From the remaining 7 studies, 4 showed no difference in smoking status between cases and controls (7, 8, 29, 49) whereas the other 3 did not study smoking with current or past data but saw a lower prevalence of ever smokers in SjD (48, 50, 51).

Two of these studies have looked at smoking while assessing cardiovascular risk factors in SjD. In these, information about the smoking variable is mainly dichotomised into never and ever smokers. Both showed that smoking was less frequent in SjD compared to controls (41, 50). These results contrast with some of those previously mentioned, in which the higher risk from past smoking seemed to overcome the negative association of current smoking with SjD.

Amongst those studies that have failed to show a relationship between smoking and SjD, one study found no differences in smoking status distribution between cases and controls, however included both SjD and non-SjD stomatitis sicca patients as cases (29), which could potentially explain the lack of positive results. An Italian multicentric study that found the above-mentioned association between Sjögren's and a family history of an immune-mediated disease, found no connection between SjD and smoking (7). Similarly, a study looking at the prevalence of sleep apnoea in patients with SjD found no differences in smoking status between cases and controls (49). Furthermore, one study was not able to demonstrate differences in smoking status between SjD and sicca patients (8), in contrast to Gebreegziabher *et al*. (45). The population sizes of these last studies were, however, significantly smaller than the previous ones. Sub-analyses comparing current to never smokers, or former to never smokers, were therefore not performed.

To visualise the data, we present forest plots illustrating comparisons from the aforementioned studies. Specifically, when pooling all available studies using a randomised effects model, there is evidence supporting a negative correlation between both current and ever smoking and the development of SjD (Fig. 2 A, C). Regarding past smoking (Fig. 2 B), as previously noted, data appears less conclusive. When considering studies with sicca or SLE patients as the control group, past smoking is negatively correlated with SjD, but not when compared to healthy controls. These, however, do not account for study limitations and differences in methodology, such as selection of patients.

Limitations to the mentioned studies

There is an evident lack of knowledge on how the association between smoking and SjD works. There is no definitive evidence of causality and a lack of robust data on dose dependency as well as timeframe for the association, particularly considering current and past smoking may be associated with opposite SjD risk. Data on the relationship with past smoking is much more variable and therefore less certain.

Some population-based studies that analyse a greater number of subjects have less well characterised SjD diagnoses, but well characterised cohorts tend to be smaller and may lack the statistical power for sub-analyses. Furthermore, the choice of controls is also a limitation. The vast majority compares SjD patients to healthy controls with no information on dryness, which raises the question of reverse causation. There is only one study that included both healthy and sicca patients as controls (51), but used dry eye syndrome patients with no minor salivary gland biopsy (MSGB) as sicca, which could include undiagnosed SjD patients.

Likewise, only one study reported data on passive smoking (Table II). It showed that passive smoking was more frequent in SjD compared to controls, but other aspects of smoking data in this study differed from many studies included here (39). Information on passive smoking may be particularly useful when trying to assess never smokers, as a subgroup of non-exposed patients may be more reliable.

Table II. Characteristics and findings of the studies with data smoking and the likelihood of having Sjögren's syndrome.

Study		Population size‡	Cases	Controls	Smoking status groups				Findings	NOS		
					Never, past, current	Never, ever	Current, not currently	Passive		S	C	E/O
Manthorpe *et al*. (29),2000; Sweden	Case-control	355/3700	Copenhagen CC[85,98]; SjD and stomatitis sicca included as cases	HC (no information on dryness)	X				- No differences in smoking status - Ever smoking – lower risk of positive MSGB (amongst cases) - Ever smoking – less frequently positive anti-SSA/SSB (amongst cases)	****	**	
Priori *et al*. (7), 2007; Italy	Case-control	139/108	2002 AECG CC[46]	Orthopaedics inpatients, no history of immune mediated disease (no information on dryness)	X				- No differences in smoking status	***		*
Perez-De-Lis *et al*. (50), 2010; Spain	Case-control	312/312	2002 AECG CC[46]	HC (no information on dryness)		X			- Ever smoking – lower in SjD	****	**	
Karabulut *et al*. (39), 2011; Turkey	Case-control	207/602	2002 AECG CC[46]	HC (no information on dryness)	X	X		X	- Current smoking – lower in SjD; - Past, ever, and passive smoking – higher in SjD - Duration of smoking and pack years – lower in SjD - Smoking associated with ANA positivity (amongst cases)	***	**	**
Juarez *et al*. (99), 2014; UK	Case-control	538/410	2002 AECG CC[46]	HC (no information on dryness)			X		- Current smoking – lower in SjD	***	*	*
Bartoloni *et al*. (41), 2015, Italy	Case-control	788/4774	1993 CC[100] or 2002 AECG CC[46]	P opulation-based data (No information on dryness or diseases)			X		- Smoking – lower in SjD - Smoking – less frequently positive anti-SSA/SSB (amongst cases)	**	**	
Rúa-Figueroa *et al*. (48), 2016; Spain	Case-control	437/2523	2002 AECG CC[46]	SLE patients		X			- Ever smoking – lower in SjD	***	*	
Stone *et al*. (42), 2017; USA	Cohort	587/701	2002 AECG CC[46]	Sicca patients	X	X			- Ever smoking – lower in SjD [Current smoking – lower in SjD; Past smoking – non-significant] - Current smoking – lower risk of positive MSGB (both in entire cohort and amongst cases) - Current smoking – less frequently positive anti-SSA (entire cohort)	***	*	***
Olsson *et al*. (43), 2017; Sweden	Nested case-control	60/251	2002 AECG CC[46]	HC (no information on dryness)	X		X		- Current smoking – lower in SjD - Past smoking – higher in SjD - No differences in MSGB and anti-SSA (amongst cases)	****	**	*
Servioli *et al*. (44), 2019; USA	Nested case-control	106/308	physician based SjD diagnosis	HC (no information on dryness)	X				- Current smoking – lower in SjD; - Past smoking – higher in SjD - No significant differences in anti-SSA/SSB amongst cases	***	**	*
Ben-Eli *et al*. (51), 2019; Israel	Case-control	91/120+ 280+211	2002 AECG CC[46]#	DES (no MSGB done) + NHL + HC (no information on dryness)		X			- Ever smoking – lower in SjD (higher in lymphoma, intermediate and similar in DES and HC)	**	**	*
Machowicz *et al*. (8), 2020; UK	Cohort	78/48	2016 ACR/EULAR CC[101]	Sicca patients	X				- No differences in smoking status	****	**	***
Mofors *et al*. (22), 2020; Sweden	Case-control	530/4425	2002 AECG CC[46]	HC (no information on dryness)	X	X			- Ever smoking – lower in SjD [current smoking – lower in SjD; past smoking – non-significant]	****	**	**
Gebreegziabher *et al*. (45), 2022;	SICCA cohort Cohort	1538/1851	2016 ACR/EULAR CC[101]	Patients not meeting 2016 CC from SICCA cohort §	X				- Current smoking – lower in SjD [past smoking – non-significant] - Current smoking – less frequently positive MSGB and anti-SSA/SSB; less frequently objective ocular dryness (entire cohort)	****		**
Karabul *et al*. (49), 2022; Turkey	Case-control	44/88	2002 AECG CC[46]	Sleep polyclinic patients without SjD (no information on dryness)	X				- No differences in smoking status or pack-year units	***	**	**

‡ - considered number of cases and controls with smoking information; # - unclear if properly applied; § - unclear if sicca, clinical SjD that do not meet CC or both.
CC: classification criteria; SjD: Sjögren's disease; HC: healthy controls; MSGB: minor salivary gland biopsy; DES: dry eye syndrome; NHL: non-Hodgkin's lymphoma; NOS: Newcastle-Ottawa quality assessment Scale; S: selection; C: comparability; E: exposure; O: outcome.

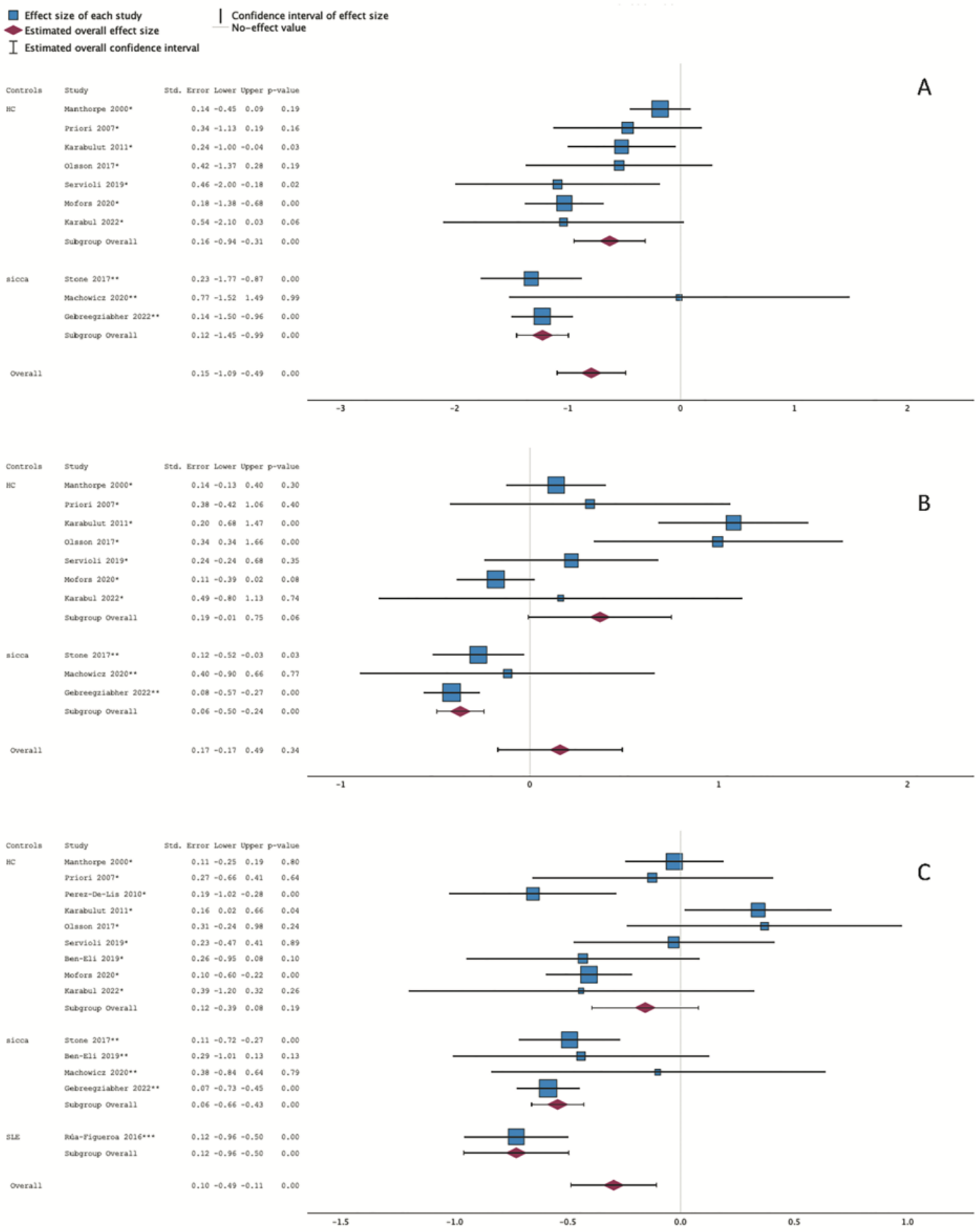

Fig. 2. Forest plots on current smokers (**A**), past smokers (**B**) and ever smokers (**C**) compared to never smokers; different studies had different control groups: *HC, **sicca, ***SLE. HC: healthy controls; SLE: systemic lupus erythematosus.
Plots were generated using a random effects model in SPSS.

Smoking and Sjögren's associated with other autoimmune rheumatic diseases

Considering SjD occurring in the context of other immune-mediated disorders (traditionally identified as secondary Sjögren's), there is little evidence on smoking as a risk factor.

Several studies have shown that smoking is associated with extraarticular involvement in RA, but most of them have not performed this analysis independently for SjD (52-54). In fact, the only study published to date shows that RA patients who currently smoke may have 80% lower odds of SjD (55). This population-based study did, however, rely on the presence of two ICD-9 codes for the diagnosis of SjD, which presents some limitations.

To the best of our knowledge no studies have examined the effects of smoking on the prevalence of SjD in SLE patients or other immune-mediated diseases.

Smoking and autoantibodies

The presence of some autoantibodies have been positively associated with smoking, such as anti-CCP (56), rheumatoid factor (57, 58), and double stranded DNA (dsDNA) autoantibodies. In fact, looking at an SLE cohort, Freemer *et al*. has found that SLE patients who are current smokers more frequently have anti-dsDNA compared to never (OR 4.0, 95% CI 1.6-10.4) and former smokers (OR 3.0, 95% CI 1.3-7.1) (59), consistent with the previously mentioned findings on smoking and risk of SLE.

Studies have shown variable results on the association between smoking and the prevalence of antinuclear (ANA), anti-Ro/SSA and anti-La/SSB autoantibodies. One study showed a significantly higher proportion of both anti-SSA and anti-SSB positive patients in never smokers compared to current smokers (29). Former smokers appeared to have values in between. In this same study, no differences were found between smoking status groups for ANA, rheumatoid factor or raised immunoglobulins. Similarly, other studies have demonstrated a lower prevalence of smokers in anti-SSA/SSB positive patients (41, 42, 45). Two of these studies however, evaluate anti-SSA according to smoking status in the entire cohort, including both cases and controls (42, 45). If there is indeed a negative association between smoking and SjD, the association with anti-SSA may therefore be influenced by the strong overlap between SjD and anti-Ro/SSA positivity.

On the contrary, there have been studies that were unable to link smoking and SjD-related autoantibodies. The previously mentioned American population-based study only showed a non-significantly higher prevalence of ANA and anti-SSA in never smokers, with a similar prevalence of both anti-SSB and rheumatoid factor between never and ever smokers (44). Moreover, the only other population-based study also could not find any associations between autoantibodies and smoking in SjD patients (43).

The Swedish study involving positive anti-Ro/SSA individuals with self-reported skin symptoms, showed that, irrespective of the underlying disease, non-smokers had higher titres of anti-Ro52 and anti-SSB (47).

Smoking and SjD outcomes

There is some evidence on the relationship of smoking status and other aspects of SjD. Regarding cardiovascular risk, a higher prevalence of both subclinical atherosclerosis and hypertension have been demonstrated in SjD patients (60). Although smoking has been reported as a risk factor for hypertension in SjD (61), similar to the general population, the influence of these traditional risk factors on atherosclerosis and cardiovascular events remains unclear (60). In fact, it has been hypothesised that smoking may only play a minor role in increasing cardiovascular risk for women with SjD (60, 62). Other comorbidities have been associated with smoking in SjD, namely immune-mediated diseases (63, 64), particularly Hashimoto's thyroiditis (65).

Furthermore, some evidence suggests an influence of smoking on SjD's extraglandular involvement. Smoking has been associated with lung involvement (66, 67). Another study associated male sex with interstitial lung disease in Sjögren's. They proposed that this could be driven by smoking, significantly more prevalent in males, but no adjustment was performed (68). Conversely, a French study that analysed 90 consecutive SjD patients with a systematic chest CT-scan, found similar smoking habits in SjD patients with and without cystic lung disease, although this subset of lung disease does not portray all lung involvement in SjD (69). Previous studies have found no association between lung involvement and smoking in SjD, although criteria for SjD were mainly based on subjective and objective dryness (70, 71). There have also been studies that found no significant association between smoking and extraglandular involvement (39), although, in this case, extraglandular involvement was considered as a whole and no particular analyses seem to have been performed for lung involvement. Nevertheless, smoking has been reported to be a mortality risk factor within patients with SjD-related interstitial lung disease (72).

The burden of systemic disease in SjD may be measured using ESSDAI (73, 74). Previous studies on ESSDAI have failed to find differences correlated to smoking (75, 76). One of these studies showed that ever smoking was associated with higher levels of TNF-α amongst SjD patients (75). No other differences were found between smokers and non-smokers when analysing cytokine, immunoglobulins and complement levels or assessing type I IFN signature (75, 76), although these studies had very few current smokers.

Another significant burden in SjD is dryness symptoms, which may be aggravated or possibly caused by smoking. This has been proposed as a potential bias on smoking as a risk factor for SjD, since patients may stop smoking if it exacerbates dryness. However, alongside the previously mentioned absence of a clear temporal association between symptom onset and smoking cessation, evidence on smoking as a dryness aggravator is not entirely consistent. In fact, a population-based study in the Netherlands with over 160,000 questionnaire participants found that current smoking had a strong negative association to dry eye and only former smokers had more fre-

quent dry eye (77). Similarly, a recent systematic review looking at the effect of smoking on eye disease concluded that smoking has a detrimental effect on the majority of anterior eye illness but not on dry eye (78). Another meta-analysis that included 10 studies on dry eye and smoking showed no significant correlation between current or past smoking and the risk of dry eye (79). A population-based assessment from Salisbury, USA, studied 2481 individuals, aged from 65 to 84 years, and saw no association between smoking and sicca symptoms, although with no assessment of SjD diagnosis (80).

Conversely, in a large, well-characterised cohort of patients with dry eye disease, smoking was associated with more severity in both subjective and objective dryness (81). Interestingly, smoking was mainly associated with more severe signs of meibomian gland dysfunction, as opposed to a diagnosis of SjD, and was associated with worse results on objective measures of ocular dryness including Schirmer tests, corneal fluorescein and lissamine green conjunctival staining and tear osmolarity. Ocular dryness symptoms were assessed using the Ocular Surface Disease Index (82), which was worse both in SjD patients and in overall smokers. No multivariate analyses was performed to evaluate whether Sjögren's and smoking had independent influences on ocular dryness (81). Results showing a lower likelihood of objective ocular dryness signs in active smokers have also been published (45).

ESSPRI is a patient-reported outcome evaluating dryness, pain and fatigue (83). When looking at SjD patients alone, patients with higher smoke exposure had higher total ESSPRI scores with significantly more dryness and pain (76). On the other hand, smoking hasn't always been associated with aggravated dryness. In fact, when looking at SjD patients, one study found no difference in smoking status between patients with an ESSPRI score above or below 5 (84).

Smoking and minor salivary gland histology

Interestingly, smoking may also influence MSGB findings. Manthorpe *et al*. evaluated both SjD and stomatitis sicca patients and found an association between smoking and a lower frequency of positive MSGB, although this may be confounded by the negative association between smoking status and SjD (29). Their findings also show a dose response between number of cigarettes smoked and focus score positivity prevalence (29).

MSGB from smoking SjD patients featured B-cells with a CD38 and CD79 pattern that mimics biopsies from healthy controls (26). Smoking seems to reduce periductal lymphocytic infiltration, seen in SjD patients that fulfilled the Copenhagen criteria (85). Interestingly, the study that found that smoking was associated with a lower likelihood of having a positive MSGB, saw no differences in salivary function tests between smokers and non-smokers (29). This latter study also examined the time between smoking cessation and time of biopsy in the former smokers' group to see whether it influenced MSGB results. There were no differences in this time interval between patients with a positive or negative MSGB (29). It would, however, be interesting to assess how smoking influences MSGB inflammation after smoking cessation, possibly by addressing the time analysis with focus score as a continuous variable and evaluating if tobacco pack-years influence MSGB results in former smokers.

There have been further studies on salivary gland biopsy features that have associated smoking with a lower odds of focal lymphocytic sialadenitis both amongst patients with SjD (42, 75), and when assessing both SjD and non-SjD sicca patients together (45, 86). Conversely, one study found no difference in MSGB features according to smoking status (75), possibly due to small population size. The only study assessing MSGB from healthy controls with no subjective ocular or oral dryness symptoms and in which SjD had been excluded, saw no correlation between smoking and focus score (87), however most subjects were not smokers and the population was small (54 subjects, of which 33 females).

Conclusion

The literature is still not completely clear on the association between smoking and SjD. There is strong evidence that active smoking is negatively associated with a diagnosis of Sjögren's but mixed results concerning previous smoking, with some evidence showing past smoking as a risk factor for disease development. An unresolved question is whether active smoking has a protective effect against development of Sjögren's or whether smoking contributes to a lack of fulfilment of classification criteria, particularly considering the data above on the relationship between smoking and dryness symptoms and autoantibodies. Data suggesting smoking is associated with lower salivary gland inflammation might also be consistent with the latter suggestion but needs to be interpreted cautiously given sample sizes and other methodological limitations. A further possibility is that smoking modulates the phenotype of an evolving connective tissue disease, analogous to the opposite smoking association seen with Crohn's and ulcerative colitis. It is therefore of interest that current smoking may be a risk factor for SLE although, as noted above, not all studies have consistently shown this.

The alternative hypothesis of reverse causation *i.e*. that patients stop smoking due to early dryness symptoms needs further assessment in prospective studies. Nevertheless, additional retrospective or cross-sectional studies evaluating dose-response, passive smoking, and temporal association between smoking cessation and SjD may increase understanding in the meantime. Likewise, the choice of non-SjD sicca patients as controls may help bypass the question of dryness symptoms being the trigger for quitting smoking.

If current smoking is indeed a protective factor on SjD development, then understanding the biological mechanism may shed light on aetiopathogenesis and possible future therapeutic approaches.

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