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Cigarette smoking patterns preceding primary Sjögren's syndrome

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ABSTRACT

Background Cigarette smoking is a well-established risk factor for several autoimmune diseases, but its role in primary Sjögren's syndrome (pSS) remains unclear. Here, we investigated the association between cigarette smoking and subsequent development of pSS.

Methods Information on smoking habits was collected from lifestyle habit questionnaires of patients with pSS (n=815) and a matched control group (n=4425) for a case–control study. Differences in smoking exposure were analysed by conditional logistic regression. Potential interactions between smoking and risk-associated human leucocyte antigens (HLA) were assessed by multivariate regression.

Results The fraction of patients with pSS having ever smoked prior to diagnosis was lower than in controls (OR 0.67, 95% CI 0.55 to 0.81). Current smoking at diagnosis was also less prevalent in cases (OR 0.37, 95% CI 0.26 to 0.53). However, period prevalence of smoking during early adulthood was not statistically different from controls (OR 0.89, 95% CI 0.66 to 1.22) but markedly decreased over time. This was partly due to patients being more prone to stop smoking, starting already 30 years prior to diagnosis (OR 2.01, 95% CI 1.22 to 3.30). Smoking patterns were also stratified by autoantibody status, yielding similar estimates. No interaction effects between HLA-DRB1 haplotypes and smoking were observed.

Conclusion The observed smoking patterns indicate that individuals who develop pSS smoke equally much as the general population during early life but are then more prone to stop. The data can be interpreted as smoking conferring protective effects, or reflecting early symptoms of pSS that affect smoking habits, emphasising the slow, progressive development of the disease.

Key messages

What is already known about this subject?

- Exposure to cigarette smoke is a well-established risk factor for several autoimmune diseases. However, the role of smoking in the aetiopathogenesis of pSS has not been thoroughly investigated and lacks consistent findings.

What does this study add?

- Overall, smoking does not appear to increase the risk of developing pSS.
- Novel observations indicate that individuals who are later diagnosed with pSS are more prone to discontinue smoking already several decades prior to diagnosis compared to the general population.
- There appears to be no interaction effects between smoking and risk-associated human leucocyte antigens (HLA) haplotypes in pSS.

How might this impact on clinical practice?

- Our findings indicate that disease progression may start several decennia prior to becoming clinically overt, highlighting potential benefits from earlier detection and treatment of the condition.

INTRODUCTION

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease of multifactorial origin.[1 2] Tissue-specific inflammation of exocrine glands, primarily salivary and lacrimal glands, is a hallmark of the disease and results in dryness of the mouth and eyes. Exocrine dysfunction of mucosal epithelium including that of the nasal cavity, oropharynx and bronchi is common. A majority of patients also present with persistent fatigue and arthralgia, and subsets of patients develop systemic, organ-specific manifestations in, for example, the haematological, cutaneous, renal or neurological systems.[3 4] The presence of autoantibodies in serum targeting the Ro/SSA and La/SSB antigens demarks a patient subset with distinct major histocompatibility complex genotypes, whereas genetic features in patients with pSS without these autoantibodies have not been demonstrated to significantly differ from that of controls.[5–8] Treatment of pSS is mainly symptomatic since evidence-based treatment with a significant impact on the disease course is currently lacking.[3] Also, knowledge on factors suitable for preventive measures is insufficient.[9]

The precise nature of why pSS occurs remains elusive, but disease processes are thought to be initiated through a complex interaction between genetic and environmental factors. Reliable data on monozygotic twin concordance rates for pSS are lacking, but familial aggregation of the disease has been reported.[10] Data from other systemic autoimmune diseases indicate concordance rates of about 3–8% in dizygotic twins and 12–15% in monozygotic twins,[11–13] revealing that environmental factors most likely have a significant contribution to disease risk.

The most significant genetic associations with pSS are found within the human leucocyte antigen (HLA) locus.[14 15] This is of particular relevance since specific HLA haplotypes may interact with environmental factors such as smoking to increase the risk of seropositive rheumatoid arthritis (RA) and multiple sclerosis (MS).[16 17] Notably, the strong HLA class II association with pSS is only found in autoantibody-positive disease,[8] and specifically, HLA-DRB1*03 is associated with production of both anti-Ro/SSA and anti-La/SSB autoantibodies, while HLA-DRB1*15 is associated with anti-Ro/SSA only.[5]

Infections have repeatedly been proposed as an environmental risk factor for pSS,[18–20] but the roles of other environmental factors remain to be determined. Cigarette smoking, which is a well-established risk factor in autoimmune diseases such as RA and MS,[21 22] has not been thoroughly studied in pSS and reports present diverging data.[23–27] Further, the relevance of dose of smoking in pack-years and potential gene–environment interactions have not been assessed.

To better define the influence of cigarette smoking on the risk of developing pSS, we performed the present case–control study using a well-characterised and large Swedish cohort. We quantified the levels of smoking exposure and stratified disease subsets based on the presence or absence of autoantibodies and investigated potential interactions between smoking and HLAs associated with rheumatic disease.

MATERIALS AND METHODS

Study population and study design

Patient data in this report were collected within the project Genes and Environment in Sjögren's Syndrome (GESS), which is a study comprising prevalent pSS cases in Sweden. Patients fulfiling the American-European Consensus Group criteria[28] for pSS (n=815) diagnosed at the Departments of Rheumatology at the University Hospitals in Gothenburg, Malmö/Lund, Linköping, Örebro and Uppsala, as well as the Karolinska University Hospital in Stockholm, Sweden, were invited to participate in the study in 2017. Clinical parameters related to diagnosis, including autoantibody status, were collected through patient chart review. Control data for the same questions were collected within the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) I[29] and EIRA II[30] studies during 1996–2014, which are part of a population-based project comprising the Swedish population.

The index date was defined as the date of pSS diagnosis for cases and the date of responding to the questionnaire for controls. A maximum of n=15 unique controls were matched to each pSS case based on age at index date, calendar time at index date, sex and area of residency. In analyses stratified by specific HLA haplotypes, controls were additionally required to have at least one allele (ie, heterozygotic) of the haplotype of interest.

The studies were approved by the Regional Ethics Committee in Stockholm and all participants gave informed consent to participate.

Data collection

Information regarding historical and current lifestyle habits was collected through standardised questionnaires, including questions on smoking where respondents were requested to provide the years and amount of smoking (online supplemental table 1). The response rates were 74% for cases in GESS, 80% for controls in EIRA I and 70% for controls in EIRA II. Missing data were excluded. For controls, HLA-DRB1 genotypes were determined as previously described.[31] Cases were genotyped using the Illumina OmniExpressExome array, and HLA genotypes were imputed as previously described using tag SNPs and reference genomes.[32]

Definition of smoking exposure

Smoking exposure was defined as reporting having smoked on a regular basis prior to the index date. Smoking pack-years were estimated by multiplying the reported average smoking on a weekly basis by the length of a stated smoking period. Sensitivity tests including both records of regular and intermittent smoking were performed, in which the results were largely unaltered, and are therefore not included in the final analyses. Moreover, to account for potential reversed causality in instances where early symptoms of pSS might influence the likelihood of smoking, various latency periods were applied for smoking exposure that is only accounting for smoking in cases and controls occurring prior to the latency period.

Statistical analysis

ORs and 95% CIs of smoking exposure were estimated using logistic regressions conditioned on the matching strata. Never-smokers were used as reference group. In analyses comparing the likelihood of stopping current smoking, ever-smokers in respective time-band were used as reference group. Interaction effects between smoking exposure and HLA haplotypes, assessed on a multiplicative scale, were also estimated.

All analyses were performed using STATA/MP version 13.0 (StataCorp LP, College Station, TX, USA). Statistical significance was defined by an alpha level of 0.05.

RESULTS

Study population

Of the patients with pSS returning the questionnaire (n=606), 530 patients were matched to 4425 controls, and thus eligible for inclusion in further analysis. The median age at pSS diagnosis was 54 years (IQR: 43–61 years); 93% of the cases were female and 71% were Ro/SSA and/or La/SSB autoantibody positive. The median time between pSS diagnosis and year of responding the questionnaire was 10 years. The pSS individuals included for analysis were similar to the entire group of patients with pSS responding to the questionnaire (table 1).

Smoker status at index date

Thirty-seven per cent of the patients with pSS reported having ever smoked prior to pSS diagnosis date. Of the controls, 44% reported having ever smoked, resulting in

Table 1 Demographics of cases and controls

	pSS cases invited to questionnaire	pSS cases returning the questionnaire	pSS cases returning the questionnaire and matched to controls	Matched controls
No. of individuals	815	606	530	4425
% Females	93	93	93	89
Age at index date (years)				
Median (IQR)	53 (42–61)	54 (41–61)	54 (43–61)	54 (42–62)
≤24	25 (3%)	14 (2%)	13 (2%)	117 (3%)
25–39	137 (17%)	114 (19%)	93 (18%)	795 (18%)
40–54	272 (33%)	197 (33%)	169 (32%)	1360 (31%)
55–64	222 (27%)	184 (30%)	173 (33%)	1437 (32%)
≥65	137 (17%)	95 (16%)	82 (15%)	716 (16%)
Calendar year at index date				
1980–1985	7 (1%)	6 (1%)	0 (0%)	0 (0%)
1985–1990	37 (5%)	23 (4%)	0 (0%)	0 (0%)
1990–1995	59 (7%)	42 (7%)	13 (2%)	0 (0%)
1995–2000	131 (16%)	97 (16%)	94 (18%)	506 (11%)
2000–2005	144 (18%)	112 (18%)	110 (21%)	857 (19%)
2005–2010	196 (24%)	161 (27%)	156 (29%)	1809 (41%)
2010–2015	214 (26%)	159 (26%)	154 (29%)	1253 (28%)
2015–2020	3 (0%)	3 (0%)	3 (1%)	0 (0%)
Area of residence				
Bigger cities and Southern Sweden	609 (75%)	452 (75%)	406 (77%)	3 763 (85%)
Middle Sweden	194 (24%)	143 (24%)	115 (22%)	583 (13%)
Northern Sweden	12 (1%)	11 (2%)	9 (2%)	79 (2%)
Highest attained education				
Primary education (≤9 years)	–	134 (22%)	114 (22%)	1 053 (24%)
Secondary education (10– 12 years)	–	193 (32%)	172 (32%)	1 601 (36%)
Higher education	–	274 (45%)	241 (45%)	1 764 (40%)
SSA and SSB status at the date of pSS diagnosis				
SSA positive	563 (69%)	418 (69%)	363 (68%)	–
SSB positive	367 (45%)	269 (44%)	230 (43%)	–
SSA and/or SSB positive	578 (71%)	430 (71%)	375 (71%)	–
No. of years between pSS diagnosis and questionnaire response date				
Median (IQR)	12 (7–19)	11 (7–18)	10 (7–16)	–
No. of individuals with HLA data	–	409 (67%)	363 (68%)	2097 (47%)

HLA, human leucocyte antigen; pSS, primary Sjögren's syndrome; SSA, Ro/SSA autoantibodies; SSB, La/SSB autoantibodies.

an OR of 0.67 (95% CI 0.55 to 0.81) for ever-smoking. An even lower OR was observed for current smoking at the pSS diagnosis date (OR 0.37, 95% CI 0.26 to 0.53). Stratification of patients with pSS by Ro/SSA and La/SSB status resulted in similar ORs (table 2).

Period prevalence of smoking prior to pSS diagnosis

Next, to more thoroughly investigate smoking patterns preceding pSS diagnosis, period prevalence of smoking during the five decades preceding pSS diagnosis date was assessed separately. The fraction of ever-smokers during 49–40 years prior to pSS diagnosis date was not significantly different between cases and controls (OR: 0.89, 95% CI 0.66 to 1.20). However, the corresponding ORs for the following periods were consistently lower ($p<0.05$). Moreover, individuals who developed pSS were more likely to discontinue smoking compared to controls (figure 1).

Stratification with regard to Ro/SSA and La/SSB status revealed a similar pattern for patients with and without autoantibodies, with ORs of smoking prevalence decreasing with greater temporal proximity to the pSS diagnosis date. Notably, patients with pSS without Ro/SSA and La/SSB autoantibodies presented with the highest ORs for discontinuing smoking and with lower ORs for period prevalence of smoking during the three decades preceding diagnosis (figure 1).

Smoking exposure prior to pSS diagnosis was also stratified by age. Although largely not statistically significant, the ORs of smoking decreased with higher age (online supplemental table 2).

Table 2 Ever-, former-, current regular smoking and never-smoking at the time of pSS diagnosis date*

		Risk estimate		N exposed (%)†	
Patients with pSS	**Exposure**	**OR**	**95% CI**	**Cases**	**Controls**
All patients with pSS	Ever-smoker	**0.67**	(0.55 to 0.81)	194 (37)	1961 (44)
	Former smoker	0.81	(0.65 to 1.00)	154 (29)	1244 (28)
	Current smoker	**0.37**	(0.26 to 0.53)	38 (7)	717 (16)
	Never-smoker	Ref.		301 (57)	2027 (46)
SSA- and/or SSB-positive pSS	Ever-smoker	**0.70**	(0.55 to 0.89)	141 (38)	1365 (44)
	Former smoker	0.82	(0.63 to 1.06)	109 (29)	865 (28)
	Current smoker	**0.41**	(0.27 to 0.62)	30 (8)	500 (16)
	Never-smoker	Ref.		208 (55)	1429 (46)
SSA-/SSB-negative pSS	Ever-smoker	**0.58**	(0.40 to 0.85)	52 (35)	582 (45)
	Former smoker	0.77	(0.51 to 1.17)	44 (29)	370 (29)
	Current smoker	**0.28**	(0.13 to 0.59)	8 (5)	212 (16)
	Never-smoker	Ref.		90 (60)	577 (45)

*Intermittent smoking was not included in exposure variables; never-smokers were defined as individuals reporting having never smoked regularly or intermittently.
†Sums of former and current smokers lower than number of ever-smokers relate to missing data/inconsistent reporting of respondents.
pSS, primary Sjögren's syndrome; SSA, Ro/SSA autoantibodies; SSB, La/SSB autoantibodies; Ref., reference.

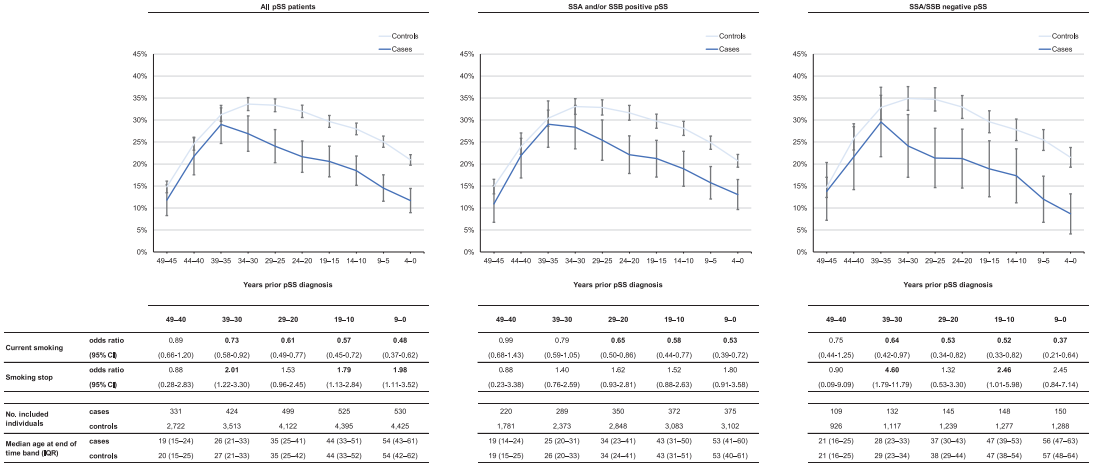


Figure 1 Period prevalence of smoking in relation to pSS diagnosis, stratified by SSA and SSB status. Error bars mark 95% CIs. pSS, primary Sjögren's syndrome; SSA, Ro/SSA autoantibodies; SSB, La/SSB autoantibodies.

Cumulative cigarette smoking pack-years prior to pSS diagnosis

To examine the potential dose–response relationships of smoking and pSS, ORs for reaching cumulative thresholds of smoking pack-years were calculated. The fraction of patients with pSS having cumulatively smoked ≥2, as well as 4, pack-years at pSS diagnosis was significantly lower compared to the control group. As latency periods were applied, ORs increased closer to 1. A similar pattern was observed both in Ro/SSA- and/or La/SSB-positive and -negative patients with pSS (figure 2). The aforementioned analyses were also performed for ≥10 or ≥20 pack-years, in which estimates were similar to the disclosed data.

Smoking patterns and HLA haplotype in relation to the risk of developing pSS

HLA profiles have been demonstrated to interact with smoking to increase the risk of developing several chronic inflammatory diseases,[16 17] and were therefore incorporated in the analyses as a last step. In our cohort, HLA DRB1*03 and DRB1*15 genotypes were significantly enriched in patients with pSS with Ro/SSA and/or La/SSB autoantibodies, whereas HLA-DRB1*01, *04 and *10 were less frequent (online supplemental tables 3 and 4). In patients without Ro/SSA and La/SSB antibodies, none of the investigated HLA haplotypes were significantly more or less frequent than in controls.

Stratified by HLA haplotypes, current smoking at pSS diagnosis date was significantly less prevalent in all assessed groups. However, ever-smoking was only significantly less common in patients with pSS with HLA-DRB1*03, although with OR<1 in patients with pSS with HLA-DRB1*15 and HLA-DRB1*01/04/10. Interestingly, the lowest prevalence and OR of current smoking at pSS diagnosis was observed in patients with HLA-DRB1*01/04/10 (table 3). Analyses of cumulative smoking pack-years prior to pSS diagnosis resulted in relatively similar estimates across the different groups. However, no estimates indicated a significantly lower cumulative dose of smoking in patients with pSS with HLA-DRB1*15 compared to controls (figure 3). Interaction effects of smoking exposure and HLA haplotypes were assessed in a multivariate logistic regression model, in which no significant modifying properties from smoking and HLA combinations were observed (figure 4).

DISCUSSION

In this case–control study encompassing clinically validated pSS cases and matched controls, we observed a lower frequency of smoking preceding pSS diagnosis compared with the population at large. Investigations of smoking patterns over time revealed that individuals who later develop pSS smoke as much as the general population early in life, but were then significantly more prone to discontinue smoking. Strikingly, this behavioural change was observed as early as three to four decades prior to diagnosis. Our study is the first to provide a detailed description of smoking patterns preceding pSS diagnosis, which may be of key importance to understanding the role of smoking in pSS, and partly confirms previous studies showing lower frequencies of current smoking among patients with pSS.[23 26 33]

A main finding of our study was the shift in smoking habits occurring approximately 30 years prior to diagnosis, a time during which the frequency of smoking markedly decreased among individuals later to be diagnosed with pSS relative to controls. This pattern can be explained by pSS cases being significantly more prone to stop smoking and/or not start smoking. Notably, this

	Exposure		Risk estimate		Fraction exposed	
pSS patients	Pack-years prior to latency period	Latency period	Odds Ratio	95% CI	Cases	Controls
All pSS patients	**≥ 2 pack-years**	**> 0 years**	**0.64**	(0.52-0.78)	32%	40%
		> 10 years	**0.66**	(0.53-0.82)	31%	38%
		> 30 years	**0.72**	(0.56-0.94)	22%	27%
		> 40 years	0.74	(0.49-1.11)	9%	12%
	≥ 4 pack-years	**> 0 years**	**0.61**	(0.49-0.77)	27%	37%
		> 10 years	**0.65**	(0.51-0.81)	26%	34%
		> 30 years	**0.74**	(0.55-0.99)	16%	21%
		> 40 years	0.88	(0.53-1.46)	6%	7%
SSA and/or SSB positive pSS	**≥ 2 pack-years**	**> 0 years**	**0.67**	(0.52-0.85)	32%	40%
		> 10 years	**0.69**	(0.54-0.89)	31%	38%
		> 30 years	0.81	(0.59-1.11)	21%	26%
		> 40 years	0.80	(0.49-1.32)	9%	13%
	≥ 4 pack-years	**> 0 years**	**0.64**	(0.49-0.83)	27%	36%
		> 10 years	**0.67**	(0.51-0.88)	26%	33%
		> 30 years	0.87	(0.61-1.25)	16%	20%
		> 40 years	0.94	(0.51-1.76)	6%	8%
SSA/SSB negative pSS	**≥ 2 pack-years**	**> 0 years**	**0.57**	(0.38-0.84)	31%	41%
		> 10 years	**0.60**	(0.40-0.89)	31%	40%
		> 30 years	**0.61**	(0.38-0.97)	23%	30%
		> 40 years	0.66	(0.32-1.36)	8%	12%
	≥ 4 pack-years	**> 0 years**	**0.56**	(0.37-0.84)	27%	38%
		> 10 years	**0.59**	(0.39-0.90)	27%	36%
		> 30 years	**0.55**	(0.32-0.94)	14%	22%
		> 40 years	0.82	(0.33-2.01)	5%	7%

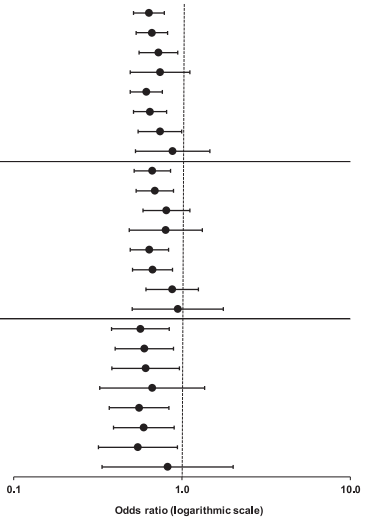


Figure 2 Cumulative pack-years of regular smoking prior to pSS diagnosis date, stratified by SSA and SSB status. Error bars demark 95% CIs. pSS, primary Sjögren's syndrome; SSA, Ro/SSA autoantibodies; SSB, La/SSB autoantibodies.

Table 3 Ever-, former-, current regular smoking and never-smoking at the time of pSS diagnosis date, stratified by HLA haplotype*

		Risk estimate		N exposed (%)¶	
HLA haplotype (present in cases and controls)	**Exposure**	**OR**	**95% CI**	**Cases**	**Controls**
HLA-DRB1*03†	Ever-smoker	**0.60**	(0.40 to 0.92)	55 (35)	240 (47)
	Former smoker	0.72	(0.46 to 1.13)	43 (28)	169 (33)
	Current smoker	**0.42**	(0.18 to 0.99)	11 (7)	71 (14)
	Never-smoker	Ref.		89 (57)	219 (43)
HLA-DRB1*15‡	Ever-smoker	0.87	(0.57 to 1.31)	58 (44)	254 (46)
	Former smoker	0.97	(0.62 to 1.51)	45 (34)	169 (31)
	Current smoker	**0.41**	(0.19 to 0.91)	12 (9)	85 (15)
	Never-smoker	Ref.		68 (51)	242 (44)
HLA-DRB1*01/04/10§	Ever-smoker	0.70	(0.46 to 1.06)	46 (39)	376 (48)
	Former smoker	0.95	(0.60 to 1.50)	39 (33)	244 (31)
	Current smoker	**0.27**	(0.11 to 0.66)	6 (5)	132 (17)
	Never-smoker	Ref.		67 (56)	339 (43)

*Intermittent smoking was not included in exposure variables; never-smokers were defined as individuals reporting having never smoked regularly or intermittently.
†n=155 cases, n=515 controls.
‡n=133 cases, n=554 controls.
§n=119 cases, n=782 controls.
¶Sums of former and current smokers lower than number of ever-smokers relate to missing data/inconsistent reporting of respondents.
HLA, human leucocyte antigen; pSS, primary Sjögren's syndrome; Ref., reference.

shift occurred prior to time points when self-reported symptom onset has been reported.[19] While these data allow for different ways of interpretation, we suggest that these behavioural changes may potentially reflect very early, mild disease symptoms and underlying pathological changes. Disease symptoms and the presence of disease-associated autoantibodies are known to precede diagnosis by many years.[34 35] Indeed, signs of autoimmune processes initiated several decades before diagnosis was described in a study by Theander *et al*, in which autoantibodies could be detected up to 20 years before pSS diagnosis.[35] We speculate that such early processes may be associated with unrecognised pathological changes of mucosal surfaces, which may in turn influence

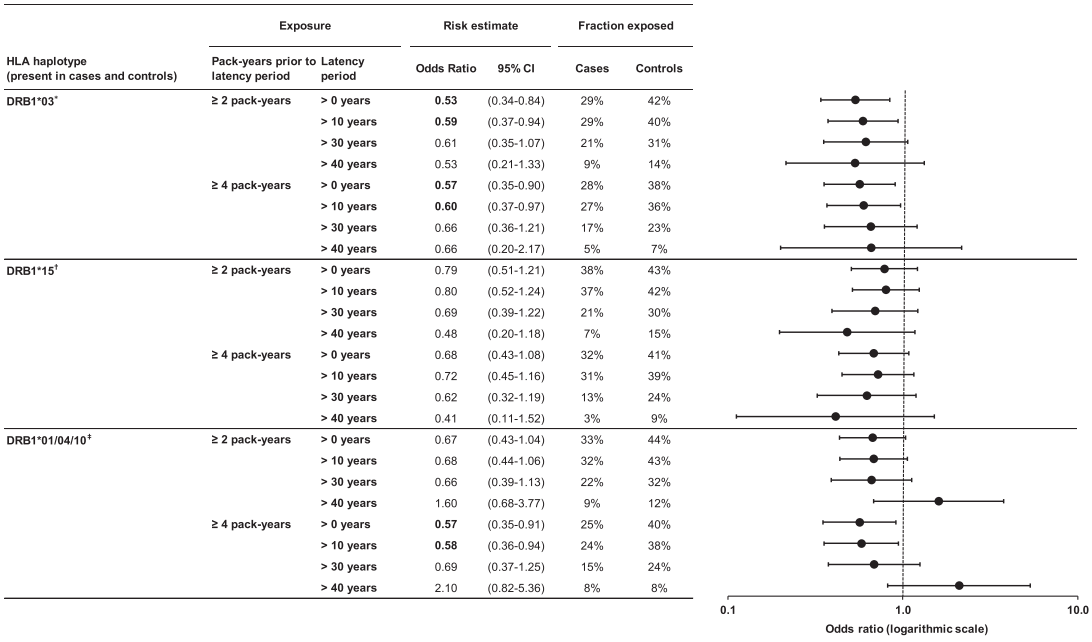
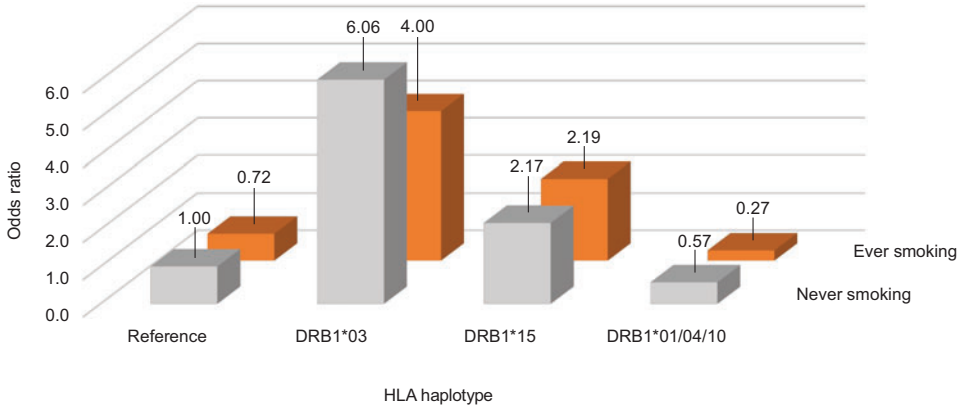


Figure 3 Cumulative pack-years of regular smoking prior to pSS diagnosis date, stratified by HLA haplotype. Error barks demark 95% CIs. HLA, human leucocyte antigen; pSS, primary Sjögren's syndrome. *n=155 cases, n=515 controls; †n=133 cases, n=554 controls; ‡n=119 cases, n=782 controls.



	Never smoking		Ever smoking		Smoking & HLA interaction term	
Exposure	**Odds Ratio**	**95% CI**	**Odds Ratio**	**95% CI**	**Odds Ratio**	**95% CI**
Reference	-		0.72	(0.34-1.50)	-	
DRB1*03	**6.06**	(3.89-9.45)	**4.00**	(2.16-7.40)	0.92	(0.46-1.81)
DRB1*15	**2.17**	(1.35-3.48)	**2.19**	(1.14-4.21)	1.40	(0.70-2.83)
DRB1*01/04/10	**0.57**	(0.35-3.48)	**0.27**	(0.13-0.56)	0.66	(0.31-1.38)

Figure 4 ORs of ever regular smoking and interaction effects with HLA-DRB1 alleles in patients with pSS with Ro/SSA and/or La/SSB autoantibodies compared to controls. The reference group consists of never-smokers and non-carriers of the investigated HLAs; HLA, human leucocyte antigen; pSS, primary Sjögren's syndrome.

the likelihood to continue smoking. However, subclinical signs of disease multiple decennia prior to diagnosis have not been described in the literature thus far.

An alternative interpretation of our data could be that smoking mechanistically acts to decrease the risk of pSS. However, current smoking has been associated with a higher risk of the immunologically related diseases systemic lupus erythematosus and RA,[29 36] perhaps making it less likely that it would have a protective effect in pSS and further supporting the interpretation of a behavioural change caused by early symptoms of pSS rather than a biologically protective effect of cigarette smoke.

Knowledge on the role of smoking in pSS is scarce, and most previous studies on smoking have been performed in prevalent cases, not specifically studying exposures prior to diagnosis.[23–26] However, consistent with our results, lower frequency of current smokers among prevalent pSS cases has been observed in several smaller studies.[23 26 33] Indeed, this observation has often been attributed to the fact that tobacco smoke may cause discomfort for patients due to dryness in the mouth, respiratory system and the eyes. Smoking habits prior to diagnosis were previously investigated in only one study by Olsson *et al*,[27] where prediagnostic data from a health survey conducted years before diagnosis in n=63 patients with pSS were used. Similar to our observations, individuals who later developed pSS were less likely to be current smokers but more likely to be former smokers, giving further support to the validity of this observation.

Stratification by the presence of Ro/SSA and/or La/SSB antibodies revealed similar patterns of smoking preceding pSS diagnosis in our study. Given the apparent differences in genetic risk variants, age distribution and clinical disease course comparing autoantibody-positive and -negative patients,[5 8 37 38] more pronounced differences between these two groups might have been anticipated. However, the observation that both subgroups stopped smoking at a higher degree than controls, that is, regardless if they developed Ro/SSA and/or La/SSB antibodies, further strengthens the hypothesis that early symptoms of pSS may cause this trend.

Smoking was also analysed in the context of risk-associated HLA carriage. The investigated HLAs were selected on the basis of previous studies showing that HLA-DRB1*03 is a risk factor for pSS and for the production of anti-Ro/SSA and anti-La/SSB autoantibodies,[5 14 39] while HLA-DRB1*15 is

associated with production of anti-Ro/SSA autoantibodies in pSS and interacts with smoking to increase the risk of MS.[5 40] Also, HLA-DRB1*01/04/10 was included as a marker of shared epitope, which interacts with smoking to increase the risk of seropositive RA.[31] Our data confirmed that HLA-DRB1*03 and HLA-DRB1*15 were significantly enriched only in autoantibody-positive patients.[5] Regardless of HLA haplotype, current smoking was less frequent among cases than controls at the time of pSS diagnosis. Slight differences in smoking patterns were observed in different HLA strata, potentially reflecting that the relationship between smoking and pSS differ depending on the genetic context. However, risk-associated HLA alleles were not found to modulate the effects of smoking in an interaction analysis, which is in contrast to previous studies in RA and MS where gene–environment interactions between HLA and smoking have been identified.[16 17] As smoking did not emerge as risk factor for pSS, this is perhaps not surprising.

The study has some limitations to consider. First, being a questionnaire-based case–control study, it is inherently vulnerable to recall bias. However, the facts that the questionnaire included questions on many potential environmental factors and that no specific emphasis was put on smoking, as well as smoking at large being relatively less prevalent in pSS cases, decrease the risk of this possibility having a major influence on the results. On the other hand, the different definitions of the index date for cases and controls, with a median time between index date (pSS diagnosis) and questionnaire-response date of 10 years for cases, may lead to differences in recall bias. Further limitations include that the impact of passive smoking exposure was not accounted for and that misclassification of smoking may be increased longer back in time. However, these errors are presumably similar between cases and controls, thus not amplifying any observed associations. Lastly, although the participation rate was high, selective participation may cause bias. Yet, reassuringly, demographical and serological variables in the assessed group of patients with pSS were similar to the entire group of patients invited to the questionnaire.

Key strengths of the study relate to only including patients with pSS fulfiling internationally accepted criteria,[28] and the contextually large number of included cases. To the best of our knowledge, this is by far the largest study undertaken to investigate behavioural and environmental patterns preceding pSS. Moreover, we were able to stratify patients based on Ro/SSA and/or La/SSB autoantibodies, the presence of which demark a genetically and clinically distinct subgroup.[5 8] Relatedly, the data enabled the assessment of combined effects from smoking and HLA genotype, which has previously not been investigated in pSS. Lastly, the frequency of autoantibodies and HLA haplotypes among the pSS cases mirrors that of previous studies to indicate that our material is indeed a valid representation of the pSS population as a whole.

CONCLUSION

In this case–control study, cumulative smoking exposure prior to pSS diagnosis was lower than compared to controls. However, observed smoking patterns indicate that individuals who later develop pSS smoke equally much as the general population in early life, but then are more prone to stop smoking. This shift occurs several decennia prior to the pSS diagnosis. We interpret the data to potentially reflect very early pathological changes, highlighting the slow, but progressive nature of pSS, and potential benefits from earlier diagnosis and treatment.

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