Seminars in Arthritis and Rheumatism 58 (2023) 152146

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Smoking and alcohol consumption are associated with peripheral musculoskeletal involvement in patients with spondyloarthritis (including psoriatic arthritis). Results from the ASAS-PerSpA study

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ARTICLE INFO

Keywords:
Spondyloarthritis
Arthritis
Enthesitis
Dactilytis
Smoking
Alcohol

ABSTRACT

Background: An inverse association between alcohol consumption and disease activity and functional impairment has been observed in patients with spondyloarthritis (SpA). However, neither this association nor the influence of smoking has been investigated in peripheral manifestations of SpA.
Objectives: The objective of this study was to analyze the association between smoking and alcohol consumption and the presence of peripheral musculoskeletal manifestations (arthritis, enthesitis or dactylitis) and to determine the specific location of these manifestations.
Methods: Patients from the worldwide cross-sectional ASAS-PerSpA study with a diagnosis of axial SpA (axSpA), peripheral SpA (pSpA) or psoriatic arthritis (PsA) according to their rheumatologist were included. Generalised linear mixed models used peripheral manifestation (or location) as a dependent variable, smoking status and alcohol consumption as fixed effects and country as a random effect. The interaction between smoking and alcohol was tested. Analyses were performed for each diagnosis (axSpA, pSpA and PsA).
Results: A total of 4181 patients were included. In axSpA patients, smoking was associated with a lower prevalence of any peripheral manifestation, and current alcohol consumption was associated with a lower prevalence of both current arthritis and current enthesitis. In pSpA patients, current alcohol consumption was associated with a lower prevalence of current arthritis or enthesitis. In PsA patients, a significant association was found for arthritis with smoking and for enthesitis with alcohol consumption, and current alcohol consumption was associated with a lower prevalence of current arthritis or enthesitis.
Conclusion: Taking into account the country, smoking and alcohol are associated with a lower prevalence of peripheral manifestations.

Introduction

The term spondyloarthritis (SpA) represents a group of heterogeneous rheumatic diseases of a chronic inflammatory nature that are interrelated and share a number of distinctive clinical manifestations, with predominant involvement of the axial skeleton, a typical pattern of peripheral arthritis, enthesitis, and extra-articular manifestations such as uveitis, psoriasis and inflammatory bowel disease [1]. The concept of SpA is evolving, and currently, the Assessment of Spondyloarthritis International Society (ASAS) group has proposed a classification of SpA patients based on the predominant symptoms: axial SpA (axSpA) and peripheral SpA (p-SpA), which includes psoriatic arthritis (PsA), among others [2]. In addition, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) has proposed specific criteria for the classification of PsA [3].

Peripheral manifestations appear in 64% of patients with SpA [4].

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https://doi.org/10.1016/j.semarthrit.2022.152146

Available online 30 November 2022

The presence of peripheral arthritis in SpA is common and may be its initial manifestation and the first reason for consultation. Mono- or oligoarticular, asymmetric and nonerosive involvement predominates in the lower limbs and shoulders and, exceptionally, affects the joints of the hands without producing deformities. Dactylitis can occur in all forms of SpA, although it is more frequent in PsA [5]. Peripheral enthesitis is more common at sites of increased physical stress and usually manifests with localised pain, stiffness, and increased tenderness with or without inflammation. The most common is that of the Achilles tendon [6].

It has been established that smoking represents a risk factor for the development of some rheumatic diseases, such as rheumatoid arthritis (RA) and PsA, contributing to higher disease activity and worsening the response to treatments due to its effect on the immune system [7,8]. In patients with SpA, smoking seems to also influence both the incidence and severity of SpA, since smoking is associated with manual occupations, unemployment, lower physical activity, body mass index and other lifestyle and socioeconomic factors [9]. Although the role of smoking in promoting radiographic progression in axSpA seems to be clear [10–12], only a few studies have examined the association between smoking and peripheral manifestations. A recent study in the COMOSPA registry suggested a lower prevalence of both peripheral arthritis and dactylitis among smokers [4]. In the British Society for the Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS) cohort, ex-smokers (but not current smokers) showed a small and nonsignificant reduced risk for peripheral arthritis [13]. They observed that smoking was associated with an adverse disease profile in axial SpA, including worse fatigue, sleep, anxiety and depression, and a higher odds of psoriasis, but they also found a paradoxical association between current smoking and reduced odds of uveitis. This was supported by findings from the French DESIR cohort, where peripheral arthritis was significantly associated with nonsmoking in patients with recent axSpA [14]. However, none of these studies evaluated the association between smoking status and the location of peripheral manifestations in patients with SpA and PsA.

Moderate alcohol consumption in the general population has been reported to be beneficial to health and is associated with reduced inflammation [15,16]. In RA, alcohol consumption is positively associated with radiographic progression [17]. On the other hand, alcohol consumption has been associated with increased disease susceptibility to psoriasis and psoriatic arthritis [18]. In axSpA, a direct association between alcohol consumption and radiographic progression on the spine has been reported [19]. Similarly, Zhao S et al. reported favourable axSpA disease activity and function in association with alcohol consumption, although this study was a cross-sectional analysis, and the relationship between alcohol consumption and biological effects was missing [20]. In terms of peripheral manifestations of SpA, a recent study in the COMOSPA registry suggested a lower prevalence of peripheral arthritis in association with alcohol consumption [4]. However, neither the quantity of alcohol nor the location of such peripheral manifestations have been investigated in patients with SpA. The present study, which is a large series designed specifically to evaluate peripheral manifestations, gives us a unique opportunity to answer these interesting questions.

On the other hand, peripheral manifestations in patients with SpA could be caused by a different pathophysiological mechanism in different patients, and association studies could help to elucidate whether there is indeed a different underlying mechanism in patients with axial and peripheral involvement. The recently described relationship between both toxic habits and epigenetic alterations (such as DNA methylation) does nothing more than underline the interest in studying the possible influence of these mechanisms on the clinical expression of diseases [21].

To clarify this, we proposed to evaluate the association between smoking status and alcohol consumption and the prevalence of peripheral articular manifestations (i.e., arthritis, enthesitis or dactylitis) and the specific location of such manifestations in patients with SpA with a diagnosis of axSpA, pSpA or PsA.

Methods

Study design

This is an ancillary analysis of the ASAS-PerSpA study. ASAS-PerSpA is a multinational cross-sectional study with 24 participating countries worldwide performed under the umbrella of the ASAS society. This worldwide study was described in detail elsewhere [22].

Patients

The ASAS-PerSpA study included consecutive adult patients (i.e., at least 18 years old) with a diagnosis of axSpA, pSpA or PsA who were able to understand and complete questionnaires and were included from July 2018 to February 2020 [22]. For this specific ancillary analysis, patients with available data for both smoking status and alcohol consumption and with a diagnosis of axSpA, pSpA or PsA according to their treating rheumatologist were included.

Collected data

To assess the influence of alcohol consumption, patients were classified into three groups according to alcohol use: never, history but cessation and current alcohol (either <3 units or ≥ 3 units). To assess the influence of smoking, patients were classified into three groups according to smoking status: never smoker, history but cessation (either >3 years or ≤ 3 years) and current smoker. For smokers, the number of packs/year was recorded.

Data on the prevalence of peripheral arthritis with objective signs of synovitis (e.g., confirmed by a rheumatologist or ultrasonography), enthesitis confirmed by specific investigations (e.g., sonography, X-rays, magnetic resonance imaging (MRI) or bone scintigraphy) and dactylitis at any time during the course of the disease according to the rheumatologist were collected, as well as the location of these peripheral symptoms. For peripheral arthritis, patients were classified as having it predominantly in the lower limbs or in the upper limbs; for enthesitis, patients were classified as having it predominantly in the upper limbs or predominantly in the lower limbs; and for dactylitis, the condition was classified as predominantly in the fingers or predominantly in the toes. Patients affected in both locations were excluded.

In addition, information on the presence of "current" peripheral arthritis or enthesitis during the physical examination at the study visit was collected. Current peripheral arthritis was assessed using the 66 swollen joints index [23], while current enthesitis was evaluated using the Mander Enthesitis Index (MEI) [24]. In this index, each enthesis is scored between 0 (no pain) and 3 (wince or withdrawn); thus, we gave the presence of enthesitis a score >1 at each location.

Statistical analysis

Univariate logistic regression for each peripheral manifestation (arthritis, enthesitis and dactylitis) was conducted using "alcohol ever" (i.e., history but cessation or current alcohol consumption) and "smoking ever" (i.e., history but cessation or current smoking) as independent variables. Additionally, multivariate generalised linear mixed using country as a random effect (which could be associated with a different phenotype depending on the geographic region) was conducted. The interaction between smoking and alcohol consumption was also tested. Analyses were adjusted by sex and the use of potential hepatotoxic conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (methotrexate and leflunomide) as confounders. All analyses were performed separately for each diagnosis (axSpA, pSpA and PsA).

The same univariate analysis and multivariate generalised linear

mixed models were conducted using the location for each peripheral manifestation as the dependent variable; among patients with peripheral arthritis: lower limbs vs. upper limbs; among patients with enthesitis: upper limbs vs. lower limbs; and among patients with dactylitis: involvement of toes vs. fingers. Patients with both lower and upper limb involvement or both toe and finger involvement were excluded from this subanalysis. Analyses were adjusted by sex and the use of potential hepatotoxic conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (methotrexate and leflunomide) as confounders. The analysis was performed separately for each diagnosis (axSpA, pSpA and PsA).

A similar analysis was conducted to evaluate the association between "current" peripheral manifestations on physical examination at the moment of the study visit and "current" habits of smoking and alcohol consumption. Thus, similar univariate logistic regressions and multivariate generalised linear mixed models were conducted using "current" peripheral manifestations (current arthritis and current enthesitis) as dependent variables and "current" alcohol consumption and smoking habits as independent variables. Analyses were adjusted by sex and the use of potential hepatotoxic conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (methotrexate and leflunomide) as confounders. All analyses were performed separately for each diagnosis (axSpA, pSpA and PsA).

Finally, to evaluate the influence of packs per year for smoking patients, a multivariable analysis using country as a random effect was performed, including the effect of ever alcohol consumption and 15 or more packs per year. Analyses were adjusted by sex and the use of potential hepatotoxic conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) (methotrexate and leflunomide) as confounders. The analysis was performed separately for each diagnosis (axSpA, pSpA and PsA).

All contrasts were bilateral and considered significant when the p value <0.05. Data were processed and analysed using R-Studio version 1.3.1073 (Boston).

Results

Description of the population

A total of 4181 patients with SpA (with a diagnosis according to the rheumatologist of 2717 axSpa, 432 pSpA and 1032 PsA) were included in the analysis, 61.2% of whom were men. A total of 43.2% had or were smokers, and 41.1% had ever been alcohol consumers. The demographic and clinical characteristics of the included patients are shown in Table 1.

Analysis with axSpA

Association between peripheral musculoskeletal manifestations and both alcohol and smoking

In axSpA patients, the univariate analysis assessing the association of alcohol consumption and smoking with any peripheral manifestation (arthritis, enthesitis or ever dactylitis) found a significant association with ever smoking (OR 0.79, 95% CI (0.67–0.96)). Patients who had ever suffered arthritis showed an inverse significant association with smoking (OR 0.78, 95% CI (0.64–0.96)) (Table 2).

The multivariate generalised linear mixed models using country as a random effect showed a decreased prevalence of any peripheral manifestation ever in smoking patients (OR 0.79, 95% CI (0.66–0.94)) (Fig. 1). Regarding the presence of arthritis, smoking patients also had a decreased prevalence. The group of patients with enthesitis presented an interaction between alcohol consumption and smoking. When assessing these factors in participants with dactylitis, smokers were less prevalent (OR 0.69, 95% CI (0.47–1)).

Table 1
Description of the population.

	$N = 4181$ (%)	Male $N =$ 2558	Female $N =$ 1623	p value
Age, mean (SD)	44.6 (13.8)	43.6 (14.1)	46.2 (13.2)	<0.001
Sex (male)	2558 (61.2%)	–	–	–
BMI, mean (SD)	26.4 (5.4)	26.1 (4.8)	27.0 (6.2)	<0.001
Smoking ever	1807 (43.2%)	1274 (49.8%)	533 (32.8%)	<0.001
Current smoker	867 (20.75)	594 (23.2%)	273 (16.8%)	<0.001
Number pack-year, mean (SD)	6.2 (11.7)	7.6 (13.0)	4.1 (9.0)	<0.001
Alcohol ever	1718 (41.1%)	1311 (51.3%)	407 (25.1%)	<0.001
Current alcohol	1364 (32.65)	1027 (40.1%)	337 (20.8%)	<0.001
Disease duration, mean (SD)	14.5 (11.4)	14.9 (11.5)	13.8 (11.1)	0.001
Diagnosis delay, mean (SD)	6.4 (8.7)	6.2 (8.4)	6.8 (9.1)	0.009
Axial SpA diagnosis	2717 (65.0%)	1856 (72.6%)	861 (53.0%)	<0.001
pSpA diagnosis	432 (10.1%)	202 (7.9%)	230 (14.2%)	<0.001
PsA diagnosis	1032 (24.7%)	500 (19.5%)	532 (32.8%)	<0.001
HLA-B27 positive	1990/2955 (67.3%)	1401/1888 (74.2%)	589/1067 (55.2%)	<0.001
Radiographic sacroiliitis	2399/3894 (61.6%)	1704/2416 (70.5%)	695/1478 (47.0%)	<0.001
Arthritis ever	2089 (50.0%)	1149 (44.9%)	940 (57.9%)	<0.001
Current arthritis	870/4177 (20.8%)	449/2555 (17.6%)	421/1622 (26.0%)	<0.001
Enthesitis ever	703 (16.8%)	357 (13.9%)	346 (21.3%)	<0.001
Current enthesitis	725 (17.3%)	347/2555 (13.6%)	378/1622 (23.3%)	<0.001
Dactylitis ever	646 (15.5%)	339 (13.2%)	307 (18.9%)	<0.001
Any peripheral involvement ever	2384 (57.0%)	1316 (51.4%)	1068 (65.8%)	<0.001
Current arthritis or enthesitis	1338/4177 (32.0%)	685/2555 (26.8%)	653/1622 (40.3%)	<0.001
Psoriasis	1195/4180 (28.6%)	603 (23.6%)	592/1622 (36.5%)	<0.001
IBD	163 (3.9%)	91 (3.6%)	72 (4.4%)	0.153
Uveitis	690 (16.5%)	450 (17.6%)	240 (14.8%)	0.017
ASDAS-CRP, mean (SD)	2.5 (1.1)	2.4 (1.1)	2.7 (1.1)	<0.001
BASDAI, mean (SD)	3.9 (2.4)	3.5 (2.3)	4.5 (2.5)	<0.001
BASFI, mean (SD)	3.0 (2.7)	2.7 (2.6)	3.4 (2.7)	<0.001
ASAS-HI, mean (SD)	6.6 (4.6)	5.8 (4.4)	7.7 (4.6)	<0.001
Hepatotoxic drugs	1474 (35.5%)	756 (29.6%)	718 (44.2%)	<0.001

Data are shown as N (%).
BMI: body mass index; SpA: spondyloarthritis; pSpA: peripheral spondyloarthritis; PsA: psoriatic arthritis; IBD: inflammatory bowel disease; ASDAS-CRP: ankylosing spondylitis disease activity score with C-reactive protein; BASDAI: bath ankylosing spondylitis.
Disease Activity Index; BASFI: Bath Ankylosing Spondylitis functional index; ASAS-HI: ASAS Health Index; SD: standard deviation.

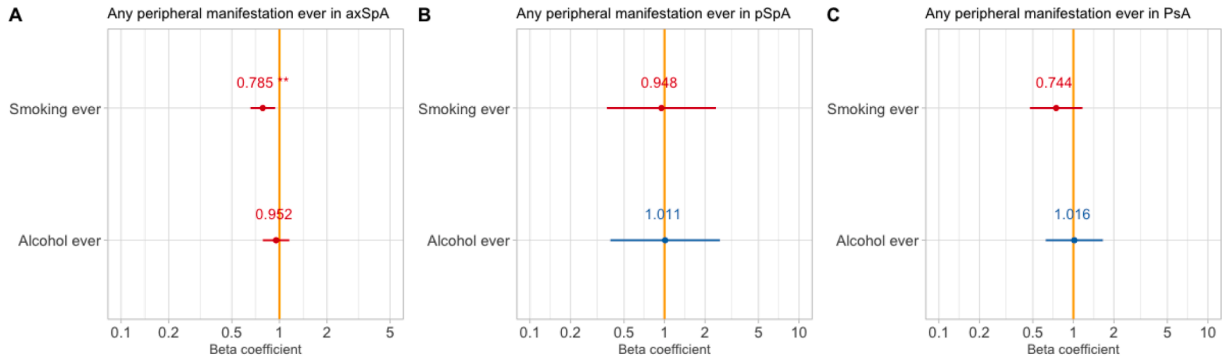
Association between the location of peripheral musculoskeletal manifestations and both alcohol and smoking

When analysing the association between alcohol consumption and smoking habits with the specific location of peripheral manifestations in axSpA patients, no association was found.

Table 2
Association between peripheral musculoskeletal manifestations and alcohol and smoking in axSpA patients.

Any peripheral manifestation ever	Yes = 1048	No = 1669	OR (95% CI) univariate	p value	OR (95% CI) multivariate	p value
Alcohol ever	419 (40.0%)	669 (40.1%)	0.99 (0.85–1.17)	0.957	1.07 (0.89–1.35)	0.383
Smoking ever	408 (38.9%)	777 (46.6%)	**0.73 (0.63–0.86)**	**<0.001**	**0.79 (0.67–0.96)**	**0.017**
Sex male	670 (63.9%)	1186 (71.1%)	**0.72 (0.61–0.85)**	**<0.001**	**0.67 (0.55–0.82)**	**<0.001**
MTX or LEF	304 (29.0%)	126 (7.5%)	**5.00 (4.00–6.29)**	**<0.001**	**4.97 (3.90–6.36)**	**<0.001**
Arthritis ever						
	Yes = 821	**No = 1896**	**OR (95% CI) univariate**	**p value**	**OR (95% CI) multivariate**	**p value**
Alcohol ever	328 (40.0%)	760 (40.1%)	0.99 (0.84–1.18)	0.948	1.11 (0.89–1.38)	0.376
Smoking ever	306 (37.3%)	879 (46.4%)	**0.69 (0.58–0.81)**	**<0.001**	**0.78 (0.64–0.96)**	**0.021**
Sex male	536 (65.3%)	1320 (69.6%)	**0.82 (0.69–0.98)**	**0.026**	**0.75 (0.61–0.92)**	**0.006**
MTX or LEF	270 (32.9%)	160 (8.4%)	**5.32 (4.28–6.62)**	**<0.001**	**5.52 (4.34–7.04)**	**<0.001**
Enthesitis ever						
	Yes = 351	**No = 2366**	**OR (95% CI) univariate**	**p value**	**OR (95% CI) multivariate**	**p value**
Alcohol ever	128 (36.5%)	960 (40.6%)	0.84 (0.67–1.06)	0.143	1.13 (0.77–1.64)	0.516
Smoking ever	157 (44.7%)	1028 (43.4%)	1.05 (0.84–1.32)	0.652	1.28 (0.92–1.76)	0.140
Alcohol*smoking					**0.56 (0.34–0.93)**	**0.022**
Sex male	202 (57.5%)	1654 (69.9%)	**0.58 (0.46–0.73)**	**<0.001**	**0.65 (0.51–0.84)**	**<0.001**
MTX or LEF	95 (27.1%)	335 (14.1%)	**2.25 (1.72–2.92)**	**<0.001**	**2.04 (1.53–2.71)**	**<0.001**
Dactylitis ever						
	Yes = 164	**No = 2553**	**OR (95% CI) univariate**	**p value**	**OR (95% CI) multivariate**	**p value**
Alcohol ever	73 (44.5%)	1015 (39.8%)	1.22 (0.88–1.67)	0.229	1.38 (0.94–2.01)	0.097
Smoking ever	57 (34.8%)	1128 (44.2%)	**0.67 (0.48–0.93)**	**0.019**	**0.69 (0.47–1.00)**	**0.050**
Sex male	105 (64.0%)	1751 (68.6%)	0.82 (0.59–1.24)	0.224	0.73 (0.51–1.06)	0.096
MTX or LEF	57 (34.8%)	373 (14.6%)	**3.11 (2.21–4.36)**	**<0.001**	**2.90 (2.01–4.16)**	**<0.001**

Univariate and multivariate analysis.
OR: odds ratio; CI: confidence interval.
MTX: methotrexate; LEF: leflunomide.



axSpA: axial spondyloarthritis; pSpA: peripheral spondyloarthritis; PsA: psoriatic arthritis

***p<0.001, multivariate analysis*

Fig. 1. Association between peripheral musculoskeletal manifestations and alcohol and smoking in axSpA, pSpA and PsA patients.

Association between the presence of peripheral musculoskeletal manifestations at the time of the study visit and both current alcohol and smoking consumption

At the time of the study visit, 32.65% of patients consumed alcohol, and 20.75% were current smokers. The univariate analyses showed that current alcohol consumption was associated with a lower prevalence of both current arthritis (36.3% vs. 40.4% (OR 0.6, 95% CI (0.45–0.8))) and current enthesitis (38.9% vs. 44.6% (OR 0.57, 95% CI (0.44–0.71))), while current smoking was associated with a lower prevalence of current arthritis (34.2% vs. 44.8% (OR 0.5, 95% CI (0.35–0.71))) (Table 3).

No interaction was found between smoking and alcohol consumption in any of these models.

Analysis with pSpA

Association between peripheral musculoskeletal manifestations and both alcohol and smoking

In pSpA patients, the univariate and multivariate analyses assessing the association of alcohol consumption and smoking with any peripheral manifestation (arthritis, enthesitis or ever dactylitis) found no significant association (Fig. 1).

Association between the location of the peripheral musculoskeletal manifestations and both alcohol and smoking

In pSpA patients, when analysing the association between alcohol consumption and smoking habits with the specific location of peripheral manifestations, no association was found.

Table 3
Association between current peripheral musculoskeletal manifestations and current alcohol and smoking in axSpA patients.

Current arthritis or enthesitis	Yes = 628	No = 2086	OR (95% CI) univariate	p value	OR (95% CI) multivariate	p value
Current alcohol	200 (31.8%)	855 (42.4%)	**0.54 (0.44–0.67)**	**<0.001**	0.83 (0.64–1.06)	0.126
Current smoking	244 (38.9%)	941 (45.1%)	**0.70 (0.56–0.88)**	**0.002**	0.94 (0.72–1.21)	0.626
Sex male	386 (61.5%)	1467 (70.3%)	**0.67 (0.56–0.81)**	**<0.001**	**0.62 (0.50–0.77)**	**<0.001**
MTX or LEF	143 (22.8%)	287 (13.8%)	**1.85 (1.47–2.31)**	**<0.001**	**1.80 (1.40–2.31)**	**<0.001**
Current arthritis						
	Yes = 281	**No = 2433**	**OR (95% CI) univariate**	**p value**	**OR (95% CI) multivariate**	**p value**
Current alcohol	102 (36.3%)	983 (40.4%)	**0.60 (0.45–0.80)**	**<0.001**	**0.72 (0.51–1.01)**	0.055
Current smoking	96 (34.2%)	1089 (44.8%)	**0.50 (0.35–0.71)**	**<0.001**	0.76 (0.51–1.01)	0.156
Sex male	185 (65.8%)	1668 (68.6%)	0.88 (0.68–1.15)	0.354	0.85 (0.64–1.14)	0.276
MTX or LEF	89 (21.7%)	341 (14.0%)	**2.84 (2.15–3.74)**	**<0.001**	**2.64 (1.94–3.57)**	**<0.001**
Current enthesitis						
	Yes = 455	**No = 2259**	**OR (95% CI) univariate**	**p value**	**OR (95% CI) multivariate**	**p value**
Current alcohol	177 (38.9%)	1008 (44.6%)	**0.57 (0.44–0.71)**	**<0.001**	0.96 (0.63–1.10)	0.786
Current smoking	133 (29.2%)	952 (42.1%)	0.80 (0.62–1.03)	0.084	1.03 (0.68–1.22)	0.871
Sex male	266 (58.5%)	1587 (70.3%)	**0.60 (0.48–0.73)**	**<0.001**	0.54 (0.42–0.67)	<0.001
MTX or LEF	89 (19.6%)	341 (15.1%)	1.37 (1.05–1.76)	0.018	1.27 (0.99–1.77)	0.115

Univariate and multivariate analysis.
OR: odds ratio; CI: confidence interval.
MTX: methotrexate; LEF: leflunomide.

Association between the presence of peripheral musculoskeletal manifestations at the time of the study visit and both current alcohol and smoking consumption

Current alcohol consumption was associated with a lower prevalence of current arthritis or enthesitis (36.8% vs. 45.9% (OR 0.48, 95% CI (0.31–0.72))) and current enthesitis alone (12.7% vs. 47.9% (OR 0.2, 95% CI (0.09–0.41))) (Table 4).

The multivariate generalised mixed model analysis showed no significant associations (Table 4).

Analysis with PsA

Association between peripheral musculoskeletal manifestations and both alcohol and smoking

The univariate analysis of PsA patients found a significant association in patients with arthritis and smoking (OR 0.56, 95% CI (0.39–0.80)) and in those who had ever presented enthesitis with alcohol consumption (OR 0.69, 95% CI (0.51–0.93)) (Table 5).

The multivariate generalised linear mixed models using country as a random effect also showed a decreased prevalence of arthritis ever in smoking patients (OR 0.63, 95% CI (0.41–0.95)), but no association of alcohol consumption or smoking with any peripheral manifestation (arthritis, enthesitis or dactylitis ever) (Fig. 1).

Association between the location of peripheral musculoskeletal manifestations and both alcohol and smoking

When analysing the association between alcohol consumption and smoking habits with the specific location of peripheral manifestations in PsA patients, no association was found.

Association between the presence of peripheral musculoskeletal manifestations at the time of the study visit and both current alcohol and smoking consumption

Current alcohol consumption was associated with a lower prevalence of current arthritis or enthesitis (38.6% vs. 48.6% (OR 0.61, 95% CI 0.47–0.79)), current arthritis alone (40.2% vs. 45.9%, OR 0.69, 95% CI (0.53–0.9)) and current enthesitis alone (31.9% vs. 46.3% (OR 0.49, 95% CI 0.34–0.71)) (Table 6).

However, the multivariate generalised mixed model analysis showed no significant associations with the presence of peripheral musculoskeletal manifestations at the moment of the study visit and both current alcohol consumption and smoking in patients with PsA.

Finally, the multivariable analysis to assess the influence of the number of packs per year performed separately for smokers among

Table 4
Association between current peripheral musculoskeletal manifestations and current alcohol and smoking habits in pSpA patients.

Current arthritis or enthesitis	Yes = 212	No = 220	OR (95% CI) univariate	p value	OR (95% CI) multivariate	p value
Current alcohol	78 (36.8%)	101 (45.9%)	**0.48 (0.31–0.72)**	**<0.001**	0.70 (0.42–1.17)	0.176
Current smoking	54 (25.5%)	74 (33.6%)	0.73 (0.42–1.27)	0.269	1.16 (0.61–2.19)	0.641
Sex male	88 (41.5%)	114 (51.8%)	0.66 (0.45–0.96)	0.032	0.68 (0.44–1.06)	0.089
MTX or LEF	96 (45.3%)	112 (50.9%)	0.80 (0.55–1.16)	0.242	0.89 (0.57–1.38)	0.591
Current arthritis						
	Yes = 179	**No = 253**	**OR (95% CI) univariate**	**p value**	**OR (95% CI) multivariate**	**p value**
Current alcohol	75 (41.9%)	104 (41.1%)	0.71 (0.46–1.08)	0.113	0.85 (0.51–1.41)	0.527
Current smoking	49 (27.4%)	79 (31.2%)	0.89 (0.50–1.55)	0.680	1.20 (0.64–2.23)	0.571
Sex male	81 (45.3%)	121 (47.8%)	0.90 (0.61–1.32)	0.597	0.85 (0.55–1.30)	0.450
MTX or LEF	80 (44.7%)	128 (50.6%)	0.80 (0.54–1.16)	0.227	0.90 (0.59–1.38)	0.621
Current enthesitis						
	Yes = 79	**No = 353**	**OR (95% CI) univariate**	**p value**	**OR (95% CI) multivariate**	**p value**
Current alcohol	10 (12.7%)	169 (47.9%)	**0.20 (0.09–0.41)**	**<0.001**	0.42 (0.13–1.06)	0.090
Current smoking	13 (16.5%)	115 (32.6%)	0.56 (0.23–1.22)	0.175	1.06 (0.30–2.42)	0.911
Sex male	23 (29.1%)	179 (50.7%)	0.40 (0.23–0.67)	<0.001	0.59 (0.21–1.11)	0.134
MTX or LEF	43 (54.4%)	165 (46.7%)	1.36 (0.83–2.23)	0.217	1.26 (0.71–2.58)	0.494

Univariate and multivariate analysis.
OR: odds ratio; CI: confidence interval.
MTX: methotrexate; LEF: leflunomide.

Table 5
Association between peripheral musculoskeletal manifestations and alcohol and smoking in PsA patients.

Any peripheral manifestation ever	Yes = 931	No = 101	OR (95% CI) univariate	p value	OR (95% CI) multivariate	p value
Alcohol ever	403 (43.3%)	48 (47.5%)	0.84 (0.56–1.27)	0.415	1.00 (0.59–1.69)	0.997
Smoking ever	437 (46.9%)	57 (56.4%)	0.68 (0.45–1.03)	0.071	0.76 (0.48–1.22)	0.254
Sex male	457 (49.1%)	43 (42.6%)	1.30 (0.86–1.98)	0.214	1.20 (0.73–1.95)	0.481
MTX or LEF	784 (84.2%)	52 (51.5%)	5.03 (3.27–7.72)	<0.001	5.06 (3.11–8.22)	<0.001
Arthritis ever						
	Yes = 884	**No = 148**	**OR (95% CI) univariate**	**p value**	**OR (95% CI) multivariate**	**p value**
Alcohol ever	379 (42.9%)	72 (48.6%)	0.79 (0.56–1.12)	0.190	0.99 (0.62–1.58)	0.950
Smoking ever	405 (45.8%)	89 (60.1%)	**0.56 (0.39–0.80)**	**0.001**	**0.63 (0.41–0.95)**	**0.029**
Sex male	435 (49.2%)	65 (43.9%)	1.34 (0.87–1.76)	0.234	1.09 (0.71–1.68)	0.696
MTX or LEF	753 (85.2%)	83 (56.1%)	**4.50 (3.09–6.54)**	**<0.001**	**5.06 (3.23–7.93)**	**<0.001**
Enthesitis ever						
	Yes = 241	**No = 791**	**OR (95% CI) univariate**	**p value**	**OR (95% CI) multivariate**	**p value**
Alcohol ever	89 (36.9%)	362 (45.8%)	**0.69 (0.51–0.93)**	**0.016**	0.77 (0.53–1.12)	0.162
Smoking ever	108 (44.8%)	386 (48.8%)	0.85 (0.64–1.14)	0.278	0.80 (0.58–1.11)	0.179
Sex male	102 (42.3%)	398 (50.3%)	0.72 (0.54–0.97)	0.030	0.86 (0.61–1.20)	0.366
MTX or LEF	195 (80.9%)	641 (81.0%)	0.99 (0.69–1.44)	0.966	1.05 (0.70–1.58)	0.807
Dactylitis ever						
	Yes = 382	**No = 650**	**OR (95% CI) univariate**	**p value**	**OR (95% CI) multivariate**	**p value**
Alcohol ever	165 (43.2%)	286 (44.0%)	0.97 (0.75–1.25)	0.801	1.06 (0.77–1.49)	0.713
Smoking ever	175 (45.8%)	319 (49.1%)	0.88 (0.68–1.13)	0.311	0.96 (0.72–1.27)	0.749
Sex male	190 (49.7%)	310 (47.7%)	1.09 (0.84–1.40)	0.525	1.04 (0.78–1.39)	0.782
MTX or LEF	330 (86.4%)	506 (77.8%)	1.81 (1.29–2.57)	<0.001	1.70 (1.18–2.47)	0.005

Univariate and multivariate analysis.
OR: odds ratio; CI: confidence interval.
MTX: methotrexate; LEF: leflunomide.

Table 6
Association between current peripheral musculoskeletal manifestations and current alcohol consumption and smoking in PsA patients.

Current arthritis or enthesitis	Yes = 498	No = 533	OR (95% CI) univariate	p value	OR (95% CI) multivariate	p value
Current alcohol	191 (38.6%)	259 (48.6%)	**0.61 (0.47–0.79)**	**<0.001**	0.93 (0.68–1.30)	0.617
Current smoking	233 (46.8%)	260 (48.8%)	1.28 (0.94–1.79)	0.119	1.24 (0.88–1.75)	0.217
Sex male	211 (42.4%)	289 (54.2%)	0.62 (0.48–0.79)	<0.001	0.66 (0.50–0.86)	0.003
MTX or LEF	411 (82.5%)	424 (79.5%)	1.21 (0.89–1.66)	0.223	1.01 (0.72–1.43)	0.962
Current arthritis						
	Yes = 410	**No = 621**	**OR (95% CI) univariate**	**p value**	**OR (95% CI) multivariate**	**p value**
Current alcohol	165 (40.2%)	285 (45.9%)	**0.69 (0.53–0.90)**	**0.006**	0.92 (0.67–1.25)	0.579
Current smoking	193 (47.1%)	300 (48.3%)	1.28 (0.93–1.75)	0.132	1.31 (0.92–1.85)	0.129
Sex male	183 (44.6%)	317 (51.0%)	0.77 (0.60–0.99)	0.044	0.79 (0.59–1.04)	0.095
MTX or LEF	350 (85.4%)	485 (78.1%)	1.64 (1.78–2.30)	0.004	1.51 (1.06–2.18)	0.025
Current enthesitis						
	Yes = 191	**No = 840**	**OR (95% CI) univariate**	**p value**	**OR (95% CI) multivariate**	**p value**
Current alcohol	61 (31.9%)	389 (46.3%)	**0.49 (0.34–0.71)**	**<0.001**	1.02 (0.64–1.60)	0.948
Current smoking	86 (45.0%)	407 (48.5%)	1.10 (0.73–1.62)	0.645	0.90 (0.56–1.44)	0.651
Sex male	58 (30.4%)	442 (52.6%)	0.39 (0.28–0.55)	<0.001	0.44 (0.30–0.66)	<0.001
MTX or LEF	115 (81.2%)	680 (81.0%)	1.01 (0.68–1.53)	0.949	0.69 (0.44–1.10)	0.123

Univariate and multivariate analysis.
OR: odds ratio; CI: confidence interval.
MTX: methotrexate; LEF: leflunomide.

patients with axSpA, pSpA and PsA found no association with the presence of any peripheral manifestation or current arthritis or enthesitis and having smoked 15 or more packs per year.

Discussion

The present work has evaluated for the first time, to our knowledge, the association between smoking status and alcohol consumption and the prevalence of peripheral articular manifestations such as arthritis, enthesitis, and dactylitis and the specific location of such manifestations in a large multinational registry of patients with a diagnosis of SpA. In this study, we found, for axSpA patients, that smoking was associated with a lower prevalence of any peripheral manifestation, while in pSpA patients, current alcohol consumption was associated with a lower prevalence of current arthritis or enthesitis. In PsA patients, smoking was associated with a lower prevalence of ever and alcohol consumption was associated with a lower prevalence of enthesitis, while current alcohol consumption was associated with a lower prevalence of current arthritis or enthesitis. No association was found between alcohol consumption and smoking habits with the specific location of peripheral manifestations in axSpA, pSpA or PsA patients.

The ASAS-PerSpA initiative aimed to compare the prevalence, characteristics and treatments of peripheral musculoskeletal manifestations in patients with a diagnosis of the spectrum of SpA across the world, and we performed an ancillary analysis of 4461 patients. Since the database is multinational, we performed an analysis adjusted by country, given that differences have been found in several previous studies that showed a greater prevalence of peripheral arthritis and enthesitis in patients from Latin America than in patients from Europe and the Middle East [25,26]. In addition, a lower prevalence of HLA-B27 in the Middle East and North Africa was found, and a higher prevalence was found in Asian countries. IBD was more prevalent among patients in

the Middle East and North Africa and less prevalent in Asia [22]. These data suggest that differences between regions can cause differences in the interpretation of certain SpA features with regard to making a clinical diagnosis, and indeed, other differences in the prevalence of peripheral manifestations were found, such as higher root joint involvement in Asian participants, the highest prevalence of tarsitis and enthesitis in Latin American SpA patients, and less frequent cases of enthesitis in European and North American patients.

Univariate logistic regressions for each peripheral manifestation were conducted using both smoking and alcohol consumption as independent variables and considering "never alcohol" as the reference to test the level of the association between alcohol consumption and the development of arthritis, enthesitis and dactylitis. The same logistic regression was computed by testing the interaction between alcohol consumption and smoking status. This interaction was tested for two reasons: first, because a clear association between alcohol consumption and smoking behaviours is likely to be detected in the general population [27,28]; and second, because an inverse association between smoking and peripheral arthritis in SpA patients has been previously reported in several studies of large registries of patients with SpA [4,14].

Under these premises, we found in the multivariate analysis for axSpA patients that smoking habits are associated with a lower prevalence of any peripheral manifestation, similar to a study by Zhao et al. published in 2019 that demonstrated a lower prevalence of arthritis among current smokers in comparison to patients who have never smoked. They analysed 2031 axSpA patients from the British Society for Rheumatology Biologics Register for Ankylosing Spondylitis. Logistic and linear models were used to quantify the associations between disease characteristics according to smoking status and quantity and adjusting for important confounding variables [13]. A history of alcohol consumption was associated with a lower likelihood of presenting enthesitis in axSpA, pSpA and PsA patients. These findings could be because patients with more severe disease tend to avoid toxic habits, and studies on the molecular mechanisms underlying this relationship would undoubtedly be necessary. Also, male sex seemed to be associated with a lower prevalence of enthesitis, as previously indicated by Wright et al. in 2020 [29], meanwhile use of potential hepatotoxic drugs increased the likelihood of enthesitis". Similarly, Lankester et al., using the UK Biobank, found a harmful and/or null effect of alcohol on cardiometabolic health and suggested that even moderate alcohol consumption should not be promoted as a part of a healthy diet and lifestyle [30]. On the other hand, cardiovascular risk factors and subclinical atherosclerosis are found more frequently in patients with SpA than in healthy populations [31], and some studies have suggested that cardiovascular risk associated with PsA and axSpA could be underestimated despite the use of guideline-recommended risk scores [32]. Furthermore, the impact of elevated C-reactive protein (CRP) and thus inflammation on increased cardiovascular risk mortality has been demonstrated [33], and smoking habits have been widely associated with cardiovascular risk [34]. Treating inflammation in patients with SpA and recommending smoking cessation as part of SpA patients' treatment could lead to a reduction of coronary artery disease and atherosclerosis and, therefore, of death, due to cardiovascular causes [35,36].

Finally, to study the impact of alcohol and smoking in a shorter period of time, we analysed whether current alcohol consumption and smoking at the time of the study visit influenced the prevalence of peripheral manifestations at the time of the study visit. Similar previous studies have found that current smokers had lower odds of acute anterior uveitis than either never or ex-smokers but higher odds of psoriasis, although they did not find statistically significant differences for arthritis, enthesitis or dactylitis [13] as we did.

This study has some limitations. First, the cross-sectional design of the ASAS-PerSpA study may introduce some recall bias regarding the peripheral manifestations. Second, the design of this study does not allow us to evaluate cause-effect relationships. Thus, a longitudinal study design may be more useful to confirm the effect of smoking and alcohol on peripheral musculoskeletal manifestations. It would have been interesting to adjust the analyses for some potential confounding factors, such as CRP levels. One important strength of this study is the large sample of SpA patients recruited from several geographic areas, which covers the whole spectrum of the disease and increases the generalisability and external validity of these results. In addition, only peripheral manifestations confirmed by a rheumatologist or by specific complementary examinations were considered in this analysis, precluding the inclusion of arthralgia or nonenthesis tender points, which could bias the results. Additionally, we adjusted the analyses by confounder variables such as sex and the use of hepatotoxic drugs.

Conclusion

We have shown that, surprisingly, among patients with a diagnosis of SpA, smoking and alcohol consumption are associated with a lower prevalence of peripheral manifestations. Future longitudinal and molecular studies are required to understand better the effect of smoking and alcohol on peripheral musculoskeletal manifestations in patients with SpA and the underlying mechanisms.

Ethics approval and consent to participate

This study was conducted according to the guidelines for Good Clinical Practice and was approved by the "Comité de protection des personnes - Ile de France III" under the code 3584-NI and by the ethical committees of all countries. Written informed consent was obtained from all subjects before enrolment.

Consent for publication

Not applicable. The study did not involve any individual person's data in any form.

Availability of data and material

Data are available upon reasonable request. Researchers willing to use data collected during the study should contact the first author of the main ASAS-PerSpA manuscript, who will send a study proposal template to be completed by the applicant. Thereafter, the steering committee of the ASAS-PerSpA study will approve (or not) the proposal and proceed to the data sharing.

Funding

No funding was provided for the current analysis. The ASAS-PerSpA study was conducted under the umbrella of ASAS with an unrestricted grant from Abbvie, Pfizer, Lilly, Novartis, UCB, Janssen and Merck. The funders did not have any role in the design or conduct of the study; collection, management, analysis or interpretation of the data; preparation, review or approval of the manuscript, or decision to submit the manuscript for publication.

Authors' contributions

López-Medina conceived and designed the study. López-Medina, Ladehesa-Pineda and Ortega-Castro contributed to data collection. López-Medina, Ladehesa-Pineda, Puche-Larrubia and Granados contributed to the data analysis and interpretation of the results. Ladehesa-Pineda took the lead in drafting and writing the manuscript. Collantes-Estévez and Dougados made critical revisions of the manuscript. All authors provided critical feedback, helped shape the manuscript and gave final approval of the version to be published.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Acknowledgements

We would like to acknowledge all of the patients and investigators who participated in this research. We would like to thank the ASAS-PerSpA Steering-Committee members, Clininfo, and the pharmaceutical companies supporting this initiative.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2022.152146.

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