Systematic review and meta analysis

The impact of smoking on prevalence of psoriasis and psoriatic arthritis

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Abstract

Objectives. In this systematic literature review and meta-analysis, we aimed to investigate the impact of cigarette smoking on the prevalence and incidence of psoriasis and psoriatic arthritis (PsA).

Method. We performed a systematic literature review using the MEDLINE, EMBASE and Cochrane Central Register databases. The literature included publications from January 1980 to July 2019. The studies that provided clear information on the number of patients with ever smoking data were included in the meta-analysis.

Results. The systematic literature review identified 52 and 24 articles for the prevalence of smoking in psoriasis and PsA, respectively. Of these, 16 articles on psoriasis and three and four (general population and psoriasis, respectively) articles on PsA met the criteria and were included in the meta-analysis. The prevalence of ever smoking was increased in psoriasis compared with the general population (OR: 1.84; 95% CI: 1.4, 2.3). For PsA the prevalence of ever smoking was reduced in psoriasis patients (OR: 0.70; 95% CI: 0.60, 0.81), but not changed compared with the general population (OR: 1.10; 95% CI: 0.92, 1.32).

Conclusion. This meta-analysis showed that ever smoking increases the risk of psoriasis in the general population, but may reduce the risk of PsA in psoriasis patients. The latter may be also due to the collider effect. Whether smoking cessation neutralizes the risk of developing psoriasis requires a well-defined smoking data collection for the past history and this is currently unavailable in the literature.

Key words: psoriasis, psoriatic arthritis, smoking, meta-analysis

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> **Rheumatology key messages**
> - Smoking is higher in psoriasis patients compared with the general population.
> - There is decreased prevalence of smoking in psoriatic arthritis patients compared with psoriasis.
> - Differences across studies can be multifactorial, such as heterogeneity of psoriatic arthritis study design and collider bias.

Introduction

Psoriasis is a chronic, inflammatory, autoimmune skin disease, affecting 2–4% of the general population [1]. Various studies suggest that cigarette smoking may trigger the development of psoriasis through oxidative, inflammatory and genetic mechanisms, and a meta-analysis including publications up to 2013 indicated an association between psoriasis, current smoking and former smoking [2, 3].

Psoriatic arthritis (PsA) is a progressive, destructive, complex inflammatory arthritis that develops in up to one-third of patients with psoriasis [4]. The evidence of the association between smoking and the development of PsA among psoriasis patients is unclear and controversial. Some studies detected an inverse association whereas others found a positive association or no effect between smoking and the development of PsA [5–10].

In this systematic review and meta-analysis, we aimed to investigate the impact of cigarette smoking on the

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prevalence of psoriasis and PsA in the general population as well as the development of PsA among psoriasis patients.

Methods

Search and selection strategy

A systematic literature review was performed using a predefined PICO (population, intervention, comparator and outcome) strategy on MEDLINE, EMBASE and Cochrane Central Register databases, and details regarding the search strategy are given in Supplementary material, 'Search strategy', available at *Rheumatology* online. Additionally, the references of all included articles were manually scanned. To be eligible for inclusion, studies had to meet the following criteria: case–control, cross-sectional and cohort study design with assessment of the effect of smoking on psoriasis or PsA development in comparison with a control group, with case numbers (percentages) given in detail for each group. We excluded articles with incomplete data, reporting bias, duplication, case reports, review articles, consensus reports and languages other than English. The literature was screened from January 1980 to July 2019 for PsA. For psoriasis, the search was performed from June 2013 to July 2019 as another meta-analysis was published by Armstrong *et al.* on psoriasis, using the same methodology for the data from January 1980 to June 2013 [3]. The studies that were identified through that meta-analysis were included in our analysis and tables.

Since there may be difficulties in measuring smoking, meta-analysis was only performed on ever smoking. To be included in the meta-analysis, studies had to have full data for smoking with number of cases and clear data on ever smoking. For articles that had missing data on the latter, the corresponding authors were contacted by e-mail. Studies that were captured through literature review but failed to be included in the meta-analysis are presented in Tables 1 and 2. When multiple papers were identified using the same cohort, only studies with the highest number of patients were included. The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42019140491).

General data extraction

The titles and abstracts were independently screened by two reviewers (U.G.G, G.A.). All abstracts with a discrepancy were carried to a full-text review. The full texts were reviewed independently by the same investigators. Any disagreement at this stage was resolved by the third investigator (S.Z.A). Articles that did not fulfill the inclusion criteria were identified and the reason for exclusion was documented. The control group for the psoriasis arm was subjects without psoriasis. For PsA two control groups were identified, (i) psoriasis and (ii) the general population. The following data were extracted: publication year, study period, country, study design, number of cases and controls, age, gender, and measure of association (univariate and multivariate). The number of both cases and controls was obtained from full texts and odds ratios were calculated by two reviewers independently.

Quality assessment

The National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) tool for quality assessment of Observational Cohort and Cross-Sectional Studies were used to assess the quality of all included studies [83]. The studies were divided into three groups as fair, poor and good by two reviewers independently and the disputes were evaluated by the third reviewer.

Meta-analytic methods

The odds ratios (ORs) and 95% CI for the dichotomous outcome of interest were computed by using a random effects method. All computation was performed with the software Comprehensive Meta-Analysis Version 3.3.070 (Biostat, Inc., Englewood, NJ, USA). Statistical heterogeneity was tested by the Q-test (χ^2) and I^2 statistic. An I^2 value ranges from 0 to 100% and the highest values represents strong heterogeneity [84]. A funnel plot was not utilized to assess the bias of publication since it is suggested to have low power for detecting asymmetry with good accuracy if the number of included studies is below 10, which was the case with our meta-analysis. P-values lower than 0.05 were considered significant [85].

Results

The initial literature search identified 884 psoriasis and 791 PsA articles. After reviewing all abstracts and full texts, 27 and 24 articles met the inclusion criteria for prevalence of psoriasis and PsA, respectively (Supplementary Figs S1 and S2, available at *Rheumatology* online). Four additional articles were identified with manual scanning of references for PsA. In addition, 25 articles that were identified by Armstrong *et al.*'s previous meta-analysis were included. For the prevalence of smoking in psoriasis and PsA, the results of 52 and 24 articles are given in Tables 1 and 2, respectively. Of these, 16 articles on psoriasis and three to four (general population and psoriasis) articles on PsA had given clear data on ever smoking and therefore were included in the meta-analysis.

For the incidence of psoriasis and PsA, our search identified one and three studies, respectively, and these were combined with the three studies identified by Armstrong *et al.* on incident psoriasis (Table 3) [3].

The prevalence of psoriasis in the general population according to smoking status

The details of the studies on the risk of psoriasis in the general population are given in Table 1 and Supplementary Table S1, available at *Rheumatology*

TABLE 1 Psoriasis and prevalence of smoking

Study	Sample size, n		Number of patients who smoke, n		Measure of association, OR (95% CI)	
	Psoriasis	No psoriasis	Psoriasis	No psoriasis	Multivariate[a]	Univariate[b]
Goolam Mahyoodeen (2019) [11]	103	98	Ever smoker: 61	Ever smoker: 26	Ever smoker: 3.87 (1.97, 7.63)	Ever smoker: 4.02 (2.22, 7.30)
Ferguson (2019) [12]	5069	489 728	Current smoker: 825 Ex-smoker: 2688 Ever smoker: 3511 Non-smoker: 1556	Current smoker: 51 318 Ex-smoker: 239 828 Ever smoker: 291 146 Non smoker: 198 582		Current smoker: 1.66 (1.54, 1.79) Ex-smoker: 1.18 (1.11, 1.24) Ever smoker: 1.54 (1.45, 1.63)
Shalom (2018) [13]	118 680	118 680	Ever smoker: 45 469	Ever smoker: 41 044		Ever smoker: 1.17 (1.16, 1.19)
Alhomoud (2017) [14]	100	100	48	36		Smoker: 1.64 (0.93, 2.89)
Atas (2017) [15]	33	27	30	10	Ever smoker: 148 (4.2, 5141)	Ever smoker: 17.00 (4.11, 70.39)
Chandravathi (2017) [16]	150	50	30	3		Smoker: 3.91 (1.14, 13.45)
Girisha (2017) [17]	156	156	65	53		Smoker: 1.38 (0.87, 2.19)
Koku Aksu (2016) [18]	300	177	Current smoker: 130 Past smoker: 80 Ever smoker: 210 Never smoker: 90	Current smoker: 56 Past smoker: 31 Ever smoker: 87 Never smoker: 90	Never smoker: 1 Current smoker: 2.3 (1.49, 3.63) Past smoker: 2.48 (1.47, 4.19)	Current smoker: 1.65 (1.12, 2.44) Past smoker: 1.71 (1.08, 2.72) Ever smoker: 2.41 (1.64, 3.55)
Yousefzadeh (2017) [19]	138	138	Current smoker: 50	Current smoker: 45		Current smoker: 1.17 (0.71, 1.93)
Zink (2017)[c] [20]	102	NR	49%	30%		NR[d]
Meziane (2016) [21]	150	300	27	28	Smoker: 1.4 (0.2, 11)	Smoker: 2.13 (1.20, 3.77)
Cohen (2016)[c] [22]	351	12031	Ever smoker: 57.5%	Ever smoker: 44.10%		NR[d]
Farshchian (2015) [23]	55	55	32	9	Smoker: 2.20 (1.1, 3.2)	Smoker: 7.11 (2.91, 17.36)
Irimie (2015) [24]	142	167	Current smoker: 36 Female: 9 Male: 20	Current smoker: 31 Female: 101Male: 149		Current smoker: 1.49 (0.86, 2.56)
Owczarczyk-Saczonek (2015) [25]	62	861				Smoker: 2.14 (1.27, 3.61)
Parisi (2015) [26]	47 390	200 433	Current smoker: 13 344 Ex-smoker: 18 814 Ever smoker: 32 158 Never smoker: 15 232 Unknown: 1133	Current smoker: 80 541 Ex-smoker: 73 056 Ever smoker: 153 597 Never smoker: 46 846 Unknown: 7744		Current smoker: 0.58 (0.57, 0.60) Ex-smoker: 1.15 (1.12, 1.17) Ever smoker: 0.64 (0.63, 0.66)
Takeshita (2015) [27]	1321	11 959	Current smoker: 1054 Former smoker: 127 Ever smoker: 1181 Never smoker: 462	Current smoker: 2176 Former smoker: 4228 Ever smoker: 6404 Never smoker: 5555		Current smoker: 17.75 (15.40, 20.46) Former smoker: 0.19 (0.16, 0.23) Ever smoker: 7.32 (6.12, 8.75)
Helmick (2015)[c] [28]	275	10 401	Current smoker: 30.2% Former smoker: 28.5% Non-smoker: 41.3%	Current smoker: 26.6% Former smoker: 19.2% Non-smoker: 54.1%	Current smoker: 1.5 (1.1, 1.9) Former smoker: 1.7 (1.2, 2.4) Never smoker: 1	NR[d]
Gonzaga (2015)[c] [29]	129	5472	Tobacco use: 3.30%	Tobacco use: 22%		NR[d]
Dowlatshahi (2013) [30]	267	8009	Current smoker: 85	Current smoker: 1773		Current smoker: 1.64 (1.26, 2.14)
Halimi (2014) [31]	53	55	23	11	Smoker: 3.03 (1.30, 7.14)	Smoker: 3.06 (1.30, 7.21)

(continued)

TABLE 1 Continued

Study	Sample size, n		Number of patients who smoke, n		Measure of association, OR (95% CI)	
	Psoriasis	No psoriasis	Psoriasis	No psoriasis	Multivariate[a]	Univariate[b]
Kokpol (2014) [32]	199	199	Current smoker: 59 Ex smoker: 25 Ever smoker: 84 Non-smoker: 115	Current smoker: 39 Ex smoker: 44 Ever smoker: 83 Non-smoker: 116		Current smoker: 1.73 (1.09, 2.75) Ex-smoker: 0.51 (0.30, 0.87) Ever smoker: 1.02 (0.69, 1.52)
Ma (2014) [33]	291	445	107	73	Smoker: 2.96 (2.09, 4.08)	Smoker: 2.96 (2.09, 4.18)
Behrooz Shokouhi (2014) [34]	47	42	16	19	Smoker: 1.60 (0.68, 3.77)	Smoker: 0.62 (0.26, 1.47)
Tseng (2013) [35]	184	324	Current smoker: 64 Former smoker: 17 Ever smoker: 81 Non-smoker: 103	Current smoker: 80 Former smoker: 33 Ever smoker: 113 Non-smoker: 211	Current smoker: 1.56 (0.87, 2.78) Former smoker: 0.67 (0.30, 1.50)	Current smoker: 1.63 (1.10, 2.41) Former smoker: 0.90 (0.48, 1.66) Ever smoker: 1.47 (1.01, 2.13)
Van der Voort (2014)[c] [36]	118	2174	Current smoker: 14.9% Former smoker: 50.9% Never smoker: 34.1%	Current smoker: 8.2% Former smoker: 55.0% Never smoker: 36.8%	Current smoker: 0.99 (0.96, 1.01) Former smoker: 0.88 (0.67, 1.15)	NR[d]
Jensen (2013)[c] [37]	238	3136	Current smoker: 24.4%	Current smoker: 22.4%		NR[d]
Armesto (2012)[e] [38]	661	661	232	190		Smoker: 1.34 (1.06, 1.69)
Shapiro (2012)[e] [39]	1079	1079	Current smoker: 234	Current smoker: 174	Current smoker: 1.38 (1.10, 1.73)	Current smoker: 1.44 (1.16, 1.79)
Armstrong (2011)[e] [40]	805	2098	Current smoker: 113 Ex smoker: 310 Ever smoker: 423 Never smoker: 382	Current smoker: 260 Ex smoker: 745 Ever smoker: 1005 Never smoker: 1093	Current smoker: 1.43 (1.01, 2.02) Former smoker: 1.22 (0.95, 1.55)	Current smoker: 1.15 (0.91, 1.46) Former smoker: 1.14 (1.96, 1.35) Ever smoker: 1.20 (1.02, 1.42)
Al-Mutairi (2010)[e] [41]	1484	1141	Current smoker: 762 Ex smoker: 341 Ever smoker: 1103 Never smoker: 381	Current smoker: 371 Ex smoker: 177 Ever smoker: 548 Never smoker: 593		Current smoker: 2.19 (1.87, 2.57) Ex-smoker: 1.62 (1.33, 1.99) Ever smoker: 3.13 (2.66, 3.69)
Gerdes (2010)[e] [42]	1097	6963	509	2295	Current smoker: 2.05 (1.77, 2.39)	Current smoker: 1.76 (1.55, 2.0)
Takahashi (2010)[c,e] [43]	151	154	NR	NR		NR[d]
Driessen (2009)[e] [44]	107	396	Current smoker: 50 Ex smoker: 31 Ever smoker: 81	Current smoker: 114 Ex smoker: 119 Ever smoker: 233		Current smoker: 2.17 (1.40, 3.36) Ever smoker: 2.18 (1.34, 3.54) Ex-smoker: 0.95 (0.59, 1.52)
Jankovic (2009)[e] [45]	110	200	Current smoker: 42 Former smoker: 20 Ever smoker: 62 Never smoker: 48	Current smoker: 72 Former smoker: 34 Ever smoker: 106 Never smoker: 94		Current smoker: 1.10 (0.68, 1.78) Former smoker: 1.08 (0.59, 1.99) Ever smoker: 1.15 (0.72, 1.83)
Jin (2009)[e] [46]	178	178	57	31	Smoker: 2.07 (1.12, 3.82)	Smoker: 2.23 (1.36, 0.68)
Wolk (2009)[e] [47]	373	373	82	138	Current smoker: 1.7 (1.1, 2.6)	Current smoker: 0.48 (0.35, 0.66)
Wolkenstein (2009)[e] [48]	350	1058	Current smoker: 72 Former smoker: 125 Ever smoker: 197	Current smoker: 197 Former smoker: 309 Ever smoker: 506	Current smoker: 1.46 (1.11, 1.94)	Current smoker: 1.13 (0.84, 1.53) Former smoker: 1.35 (1.04, 1.74) Ever smoker: 1.40 (1.10, 1.79)

(continued)

TABLE 1 Continued

Study	Sample size, n		Number of patients who smoke, n		Measure of association, OR (95% CI)	
	Psoriasis	No psoriasis	Psoriasis	No psoriasis	Multivariate[a]	Univariate[b]
Xiao (2009)[e] [49]	Mild Ps: 1619 Severe Ps: 1473	1521	Mild Ps: 309 Severe Ps: 376 Total Ps: 685	241	Mild Ps smoker: 1.31 (1.04, 1.65) Severe Ps smoker: 1.42 (1.12, 1.79)	Mild Ps smoker: 0.80 (0.67, 0.96) Severe Ps smoker: 0.97 (0.82, 1.15) Total Ps smoker: 1.77 (1.51, 2.08)
Bo (2008)[c,e] [50]	1144	17 600	Current smoker: 4739 Former smoker: 5581	NR	Men Current smoker: 1.49 (1.11, 2.00) Former smoker: 1.67 (1.29, 2.16) Women Current smoker: 1.48 (1.15, 1.91) Former smoker: 1.55 (1.21, 1.99)	NR[d]
Naldi (2008)[e] [51]	560	690	Ever smoker: 357	Ever smoker: 350	Ever smoker: 1.8 (1.3, 2.7)	Ever smoker: 1.71 (1.36, 2.15)
Cohen (2007)[e] [52]	340	6643	118	1648		1.61 (1.28, 2.03)
Gelfand (2006)[e] [53]	130 976	556 995	36 701	438 299	Current smoker: 1.31 (1.29, 1.34)	Current smoker: 0.11 (0.10, 0.11)
Sommer (2006)[e] [54]	581	1044	264	219		Smoker: 3.14 (2.52, 3.91)
Herron (2005)[e] [55]	557	4080	205	530		Smoker: 3.90 (3.21, 4.74)
Naldi (2005)[e] [56]	550	690	Current smoker, cigarettes per day <1–10: 99 (17.7) 11–20: 114 (20.4) ≥21: 40 Current smoker: 253 Former smoker: 103 Ever smoker: 356	Current smoker, cigarettes per day ≤15: 130 16–24: 64 ≥25: 21 Current smoker: 215 Former smoker: 83 Ever smoker: 298	Current smoker, cigarettes per day <1–10: 16 (1.2, 2.2) 11–20: 1.7 (1.1 2.5) ≥21: 1.7 (1.0, 3.2) Former smoker: 1.9 (1.3, 2.7)	Current smoker: 2.43 (1.86, 3.16) Former smoker: 2.56 (1.81, 3.62) Ever smoker: 2.47 (1.93, 3.16)
Zheng (2004)[e] [57]	189	333	Male: 53 Female: 0	Male: 49 Female: 2	Male smoker: 2.62 (1.53, 4.49)	Male smoker: 2.37 (1.53, 3.68)
Zhang (2002)[e] [58]	789	789	Male: 215 Female: 9	Male: 126 Female: 5	Ever smoker male: 2.33 (1.74, 3.11) Ever smoker female: 1.86 (0.56, 6.43)	Ever smoker male OR: 1.98 (1.54, 2.53) Ever smoker female: 2.09 (0.69, 6.26)
Naldi (1999)[e] [59]	404	616	Current smoker, cigarettes per day ≤15: 95 16–24: 56 ≥25: 24 Current smoker: 175 Former smoker: 75	Current smoker, cigarettes per day ≤15: 130 16–24: 64 ≥25: 21 Current smoker: 215 Former smoker: 83	Current smoker, cigarettes per day ≤15: 1.4 (1.0, 2.0) 16–24: 1.7 (1.1, 2.7) ≥25: 2.1 (1.1, 3.9) Former smoker: 1.5 (1.1, 2.2)	Total smoker: 1.99 (1.55, 2.53) Current smoker: 1.68 (1.27, 2.22) Former smoker: 1.87 (1.29, 2.69) Ever smoker: 1.73 (1.34, 2.24)

(continued)

TABLE 1 Continued

Study	Sample size, n		Number of patients who smoke, n		Measure of association, OR (95% CI)	
	Psoriasis	No psoriasis	Psoriasis	No psoriasis	Multivariate[a]	Univariate[b]
Poikolainen (1994)[c,e] [60]	55	108	Ever smoker: 250 NR	Ever smoker: 298 NR	Before onset of psoriasis (20 cigarettes per day): 3.3 (1.4, 7.9) After onset of psoriasis (20 cigarettes per day): 2.6 (1.1, 6.5)	NR[d]
Mills (1992)[e] [61]	108	108	Current smoker: 49	Current smoker: 25	Current smoker, cigarettes per day <15: 1.1 (0.6, 1.8) ≥15: 2.1 (1.1, 4.0) Former smoker: 1.1 (0.6, 2.0)	Current smoker: 2.79 (1.55, 5.02)
Naldi (1992)[e] [62]	215	267	Current smoker, cigarettes per day <15: 54 ≥15: 47 Current smoker: 101 Former smoker: 33 Ever smoker: 134	Current smoker, cigarettes per day <15: 66 ≥15: 30 Current smoker: 96 Former smoker: 38 Ever smoker: 134		Current smoker: 1.77 (1.19, 2.62) Former smoker: 1.46 (0.85, 2.52) Ever smoker: 1.68 (1.17, 2.43)

[a]OR (95% CI) numbers that were given in the articles. [b]OR (95% CI) numbers were calculated by investigators from given results. [c]Articles that gave only percentages. [d]Due to insufficient data, the OR could not be calculated. [e]Studies that were included from the meta-analysis by Armstrong *et al.* Identified numbers were extracted from full texts. NR: not reported; OR: odds ratio; Ps: psoriasis.

TABLE 2 PsA and prevalence of smoking

Study	Control group information	Sample size (n)		Number of smokers (n)		Measure of association, OR (95% CI)	
		PsA	No PsA	PsA	No PsA	Multivariate[a]	Univariate[b]
Ferguson (2019) [12]	General population and psoriasis	904	Psoriasis: 5069 General population: 489 728	Current smoker: 94 Ex smoker: 453 Ever smoker: 547 Non smoker: 357	General population Current smoker: 51 318 Ex smoker: 239 828 Ever smoker: 291 146 Non smoker: 198 582 Psoriasis Current smoker: 825 Ex smoker: 2688 Ever smoker: 3513 Never smoker: 1556		General population Current smoker: 0.99 (0.80, 1.23) Ex-smoker: 1.05 (0.92, 1.19) Ever smoker: 1.05 (0.92, 1.20) Psoriasis Current smoker: 0.60 (0.48, 0.75) Ex-smoker: 0.89 (0.77, 1.03) Ever smoker: 0.68 (0.59, 0.79)
Kaine (2019) [63]	General population	14.900	35.037	826	1.399		Smoker: 1.41 (1.2922, 1.5415)
Kibari (2019) [64]	General population	3161	31 610	Ever smoker: 904	Ever smoker: 8742	Ever smoker: 1.05 (0.97, 1.14)	Ever smoker: 1.05 (0.97, 1.14)
Yan (2019) [65]	Psoriasis	128	107	44	35		Smoker: 1.077 (0.62, 1.85)
Gulati (2018) [66]	General population	151	755	62	215		Current smoker: 1.74 (1.21, 2.50)
Yan (2018) [67]	Psoriasis	175	497	6	30	Smoker: 0.29 (0.06, 1.01)	Smoker: 0.52 (0.21, 1.27)
Queiro (2019)[c] [68]	Non-inflammatory rheumatic and skin problems	340	600	Current smoker: 26%	Current smoker: 21%	Smoker: 1.4 (1.0-1.8)	NS[d]
Ibanez-Bosch (2017) [69]	General population	53	53	Current smoker: 14 Ex smoker: 24 Ever smoker: 38 Never smoker: 15	Current smoker: 8 Ex smoker: 16 Ever smoker: 24 Never smoker: 29		Current smoker: 2.02 (0.77, 5.32) Ex-smoker: 1.91 (0.86, 4.25) Ever smoker: 3.06 (1.37, 6.85)
Tsuruta (2017) [70]	Psoriasis	55	276	Ever smoker: 24	Ever smoker: 113		Ever smoker: 1.12 (0.62, 2.00)
Wibetoe (2017) [71]	RA, AxSpA	721	RA: 1961 Axial Spa: 835	Current smoker: 126	Current smoker Among RA: 419 Among AxSpA: 162		Current smoker Among RA: 0.77 (0.62, 0.97) Among AxSpA: 0.87 (0.67, 1.13)
Krajewska-Włodarczyk (2018)[c] [72]	Psoriasis	44	51	Current smoker: 18%	Current smoker: 10%		NS[d]
Gulati (2016) [73]	General population	338	50 468	Current smoker: 76	Current smoker: 8270		Current smoker: 1.4801 (1.15, 1.9128)
Nas (2015)[c] [74]	Psoriasis and RA	173	Psoriasis: 67 RA: 138	Current smoker: 35.30%	Psoriasis current smoker: 31.3% RA current: 10.1%		NS[d]
Papagoras (2014)[c] [75]	AS and Healthy population	56	Healthy population: 71 AS: 56	Current smoker: 28.60%	Healthy population current smoker: 18.30% AS current: 60.7%		NS[d]

(continued)

TABLE 2 Continued

Study	Control group information	Sample size (n)		Number of smokers (n)		Measure of association, OR (95% CI)	
		PsA	No PsA	PsA	No PsA	Multivariate[a]	Univariate[b]
Bhole (2012)[c] [76]	Psoriasis, RA, and General population	644	Psoriasis: 448 RA: 350 General population: 115 787	Ever smoker: 44%	Ever smoker Psoriasis: 48% RA: 60% General population: NR		NS[d]
Velez (2012)[c] [77]	Psoriasis	107	161	Ever smoker: 31.80%	Ever smoker: 39.20%		NS[d]
Eder (2012) [7]	Psoriasis	728	404	Never smoker: 396 Current smoker: 162 Past smoker: 170 Ever smoker: 332 1–9 cigarettes per day: 68 10–19 cigarettes per day: 52 ≥20 cigarettes per day: 97	Never smoker: 174 Current smoker: 108 Past smoker: 122 Ever smoker: 230 1–9 cigarettes per day: 79 10–19 cigarettes per day: 61 ≥20 cigarettes per day: 66	Current smoker: 0.57 (0.41, 0.81) Ex-smoker: 0.81 (0.56, 1.12)	Current smoker: 0.78 (0.59, 1.04) Ever smoker: 0.63 (0.50, 0.81) Ex-smoker: 0.70 (0.54, 0.93)
Eder (2011) [78]	Psoriasis	159	159	Ever smoker: 64	Ever smoker: 89	Ever smoker: 0.6 (0.36, 0.89) Full regression: 0.47 (0.29, 0.77)	Ever smoker: 0.52 (0.33, 0.82)
Husted (2011)[c] [79]	Psoriasis	611	449	Current smoker: 12%	Current smoker: 24.40%		NS[d]
Tey (2010) [10]	Psoriasis	134	266	Current smoker: 31 Non-smoker: 103	Current smoker: 72 Non-smoker: 194		Current: 0.81 (0.50, 1.32)
Tam (2008) [80]	General population	82	82	Current smoker: 8	Current smoker: 0		Current smoker: 18.82 (1.06, 331.81)
Tam (2008) [81]	General population	102	82	Current smoker: 9	Current smoker: 8		Current smoker: 0.90 (0.33, 2.4336)
Kimhi (2007) [82]	General population	47	100	16	28		Smoker: 1.32 (0.63, 2.79)
Pattison (2007) [6]	Psoriasis	98	163	Ever smoker: 57	Ever smoker: 102	Ever smoker: 0.68 (0.39,1.17)	Ever smoker: 0.83 (0.50, 1.39)

[a]OR (95% CI) numbers that were given in the articles. [b]OR (95% CI) numbers were calculated by investigators from given results. [c]Articles that gave only percentages. [d]Due to insufficient data, the OR could not be calculated. AS: ankylosing spondylitis; AxSpA: axial spondylartritis; NS: not specified; OR: odds ratio; PsA: Psoriatic arthritis; RA: rheumatoid arthritis.

TABLE 3 Smoking and incident psoriasis and PsA

Study	Country	Study population	Study design and period	Smoking ascertainment	Sample size	Smokers that developed PSA or psoriasis	Non-smokers that developed PSA or psoriasis	Measure of association (95% CI)
Dai (2019) [86]	China	Psoriasis	Prospective cohort, 2001–2015	NHIS database	Current: 12 985 (21.6) Former: 2816 (4.7) Non-smoker: 44 335 (73.7)	Current: 80 Former: 17 Incident rates per 100 000 person-years Current: 66.88 Former: 82.48	145 Incident rate per 100 000 person-years: 36.57	Current smoker Univariable HR: 1.83 (1.40, 2.41) Multivariable HR: 1.47 (1.04, 2.07) Former smoker Univariable HR: 2.48 (1.50, 4.11) Multivariable HR: 1.16 (0.68, 1.99)
Li (2012) [87]	USA	Psoriasis	Prospective cohort 1996–2008 (NHS) 1991–2005 (NHS II) 1986–2006 (HPFS)	Questionnaire	Current: 309 Former: 977	Current: 309 Former: 977	1124	Current smoker Age adjusted RR: 1.95 (1.68, 2.27) Multivariate adjusted RR: 1.94 (1.64, 2.28) Former smoker Age adjusted RR: 1.43 (1.31, 1.56) Multivariate adjusted RR: 1.39 (1.27, 1.52)
Huerta (2007) [88]	UK	Psoriasis	Prospective cohort, nested case–control analysis, 1996–1997	OXMIS/read	Psoriasis cases: 3994 Non-psoriasis controls: 10 000	Patients without psoriasis who smoke: 2008	Patients with psoriasis who smoke: 1013	OR: 1.37 (1.25, 1.50) Adjusted OR: 1.45 (1.31, 1.59)
Setty (2007) [89]	USA	Psoriasis	Prospective cohort, 1991–2005	Questionnaire	Current: 9023 Former: 17 730 Non-smoker: 51 779	Current: 131 Former: 262	494	Current smoker Age adjusted RR: 1.82 (1.50, 2.21) Multivariate adjusted RR: 1.78 (1.46, 2.16) Former smoker Age adjusted RR: 1.40 (1.20, 1.62) Multivariate adjusted RR: 1.37 (1.17, 1.59)
Nguyen (2018) [8]	UK	PsA	Population-based cohort, 1995–2015	Medical records	General population Current smoker: 1 856 542 Ex-smoker: 1 035 203 Non-smoker: 3 759 554 Psoriasis Current smoker: 78 004 Ex-smoker: 43 205 Non-smoker: 104 004	General population Current smoker: 2180 Ex: 1178 Psoriasis Current: 1492 Ex: 789	General population Non-smoker: 3699 Psoriasis Non-smoker: 2288	Unadjusted HR Among general population Current smoker: 1.23 (1.17, 1.30), Ex-smoker: 1.32 (1.24, 1.41) Among Psoriasis Current smoker: 0.89 (0.83, 0.95), Ex-smoker: 1.00 (0.92, 1.08) Adjusted HR Among general population Current smoker: 1.23 (1.16, 1.29) Ex-smoker: 1.30 (1.21, 1.38) Among psoriasis Current smoker: 0.88 (0.83, 0.94)

TABLE 3 Continued

Study	Country	Study population	Study design and period	Smoking ascertainment	Sample size	Smokers that developed PSA or psoriasis	Non-smokers that developed PSA or psoriasis	Measure of association (95% CI)
Li (2012) [9]	USA	PsA	Longitudinal cohort, 1991–2005	Questionnaire	Current smoker: 129 032 person-years Past smoker: 30 9749 person-years Non-smoker: 865 189 person-years	Past smoker: 46 Current smoker: 35	Never smoker: 76	Ex-smoker: 1.03 (0.95, 1.12) Among all participants, multivariate-adjusted RR Past smoker: 1.54 (1.06, 2.24), Current smoker: 3.12 (2.07, 4.69) Among psoriasis, multivariate-adjusted RR Past smoker: 1.39 (0.89, 2.16), Current smoker: 1.62 (1.00, 2.63)
Green (2020) [90]		PsA	Cohort, 1998–2014	NR	Smoker: 50 172 Non-smoker: 38 452	758	644	Among psoriasis Unadjusted OR Ex-smoker: 0.92 (0.77, 1.1) Current smoker: 0.95 (0.78, 1.15) Adjusted OR Ex-smoker: 0.83 (0.69, 1.02) Current smoker: 0.94 (0.76, 1.1)

HR: hazard ratio; NHIS: The National Health Interview Survey; NR: not reported; OR: odds ratio; OXMIS: The Oxford Medical Information System; PsA: psoriatic arthritis; RR: risk ratio.

online. The majority of the studies revealed an increased risk of psoriasis among smokers, both for current smoking (15/26) and ever smoking (15/19). There were only two studies that found a reduced risk. In the meta-analysis, 16 articles were included, with 177 484 psoriasis cases and 827 997 controls, which suggested an increased prevalence of psoriasis among ever smokers (OR: 1.84; 95% CI: 1.4, 2.3) (Fig. 1).

Smoking and incident psoriasis

Four studies that looked at the effect of incidence of psoriasis among smokers suggested an increased risk of psoriasis (Table 3). Both current and former smoking was found to be a risk factor in the majority of those studies other than one study by Dai *et al.* in which former smoking was not a risk factor in a multivariate adjusted analysis [86].

The prevalence of psoriatic arthritis in the psoriasis population according to smoking status

The details of the 13 studies on the prevalence of PsA in the psoriasis population are given in Table 2 and Supplementary Table S2, available at *Rheumatology* online. Six of these studies found a reduced risk of PsA among smokers in the psoriasis patients.

To evaluate the effect of ever smoking on PsA in psoriasis, four articles were included in the meta-analysis with 1785 cases and 5912 controls. Prevalence of PsA was reduced in this group (OR: 0.70; 95% CI: 0.60, 0.81) (Fig. 2).

The prevalence of psoriatic arthritis in the general population according to smoking status

Twelve studies evaluated the effect of smoking on the risk of PsA within the general population and details are given in Table 2 and Supplementary Table S2 available at *Rheumatology* online. Half of the studies (6/12) detected an increased risk within the general population.

Three studies were included in the meta-analysis on 4118 and 521 391 controls, which suggested no association between ever smoking and prevalence of PsA compared with the general population (OR: 1.10; 95% CI: 0.92, 1.32) (Fig. 3).

Smoking and incident psoriatic arthritis

A total of three publications assessed the relation between smoking and the risk of incident PsA (Table 3). Nguyen *et al.* showed 1.2- to 1.3-fold increased risk of incident PsA with smoking in the general population [8]. However, current smoking was found to be protective from PsA in the psoriasis population. Li *et al.* identified increased risk of incident PsA among past or current smokers in the general population [9]. The risk of PsA in

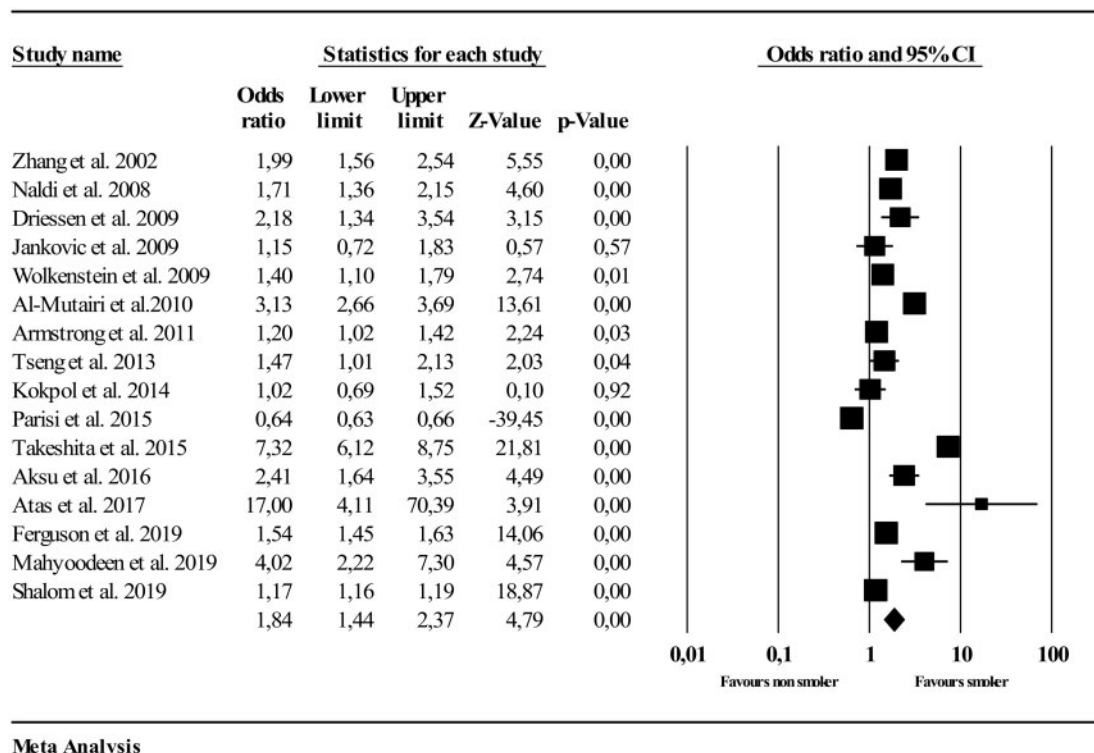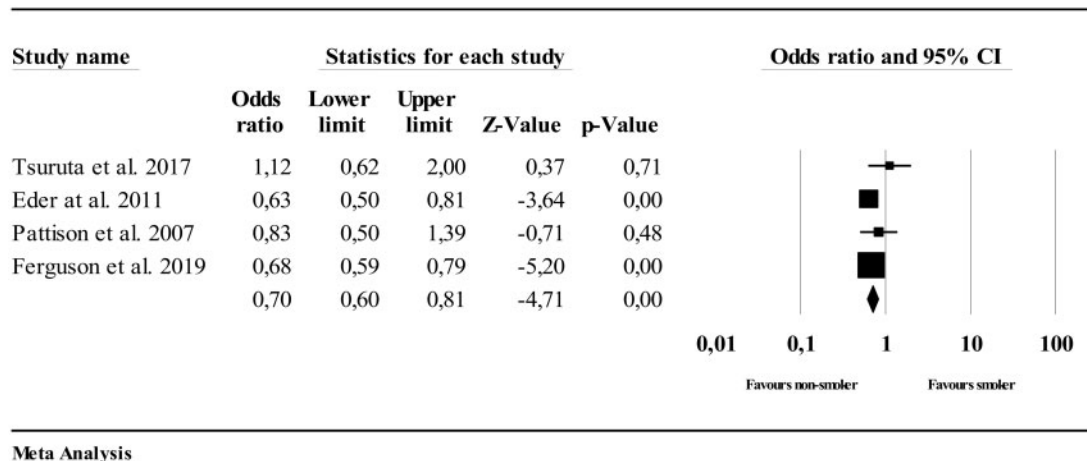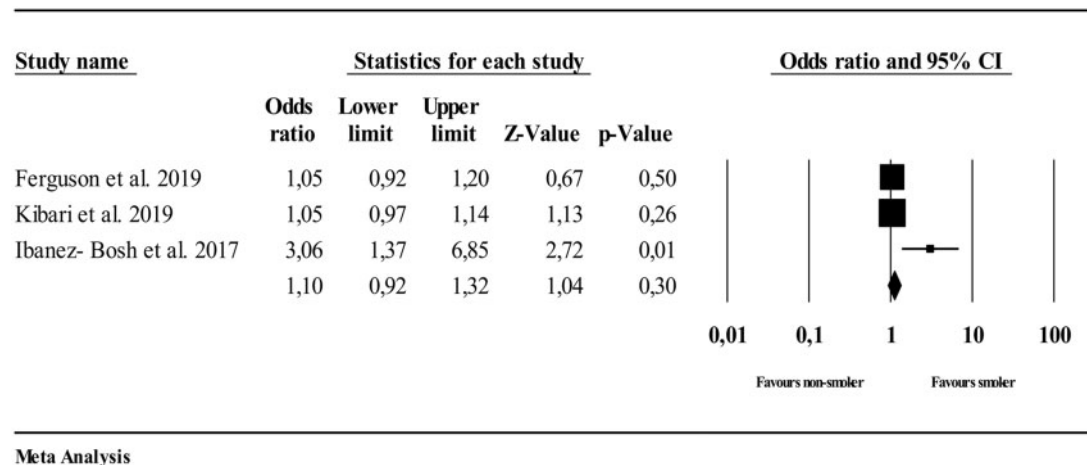**Fig. 1** Ever smoking in psoriasis (in comparison with general population)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Zhang et al. 2002	1,99	1,56	2,54	5,55	0,00
Naldi et al. 2008	1,71	1,36	2,15	4,60	0,00
Driessen et al. 2009	2,18	1,34	3,54	3,15	0,00
Jankovic et al. 2009	1,15	0,72	1,83	0,57	0,57
Wolkenstein et al. 2009	1,40	1,10	1,79	2,74	0,01
Al-Mutairi et al.2010	3,13	2,66	3,69	13,61	0,00
Armstrong et al. 2011	1,20	1,02	1,42	2,24	0,03
Tseng et al. 2013	1,47	1,01	2,13	2,03	0,04
Kokpol et al. 2014	1,02	0,69	1,52	0,10	0,92
Parisi et al. 2015	0,64	0,63	0,66	-39,45	0,00
Takeshita et al. 2015	7,32	6,12	8,75	21,81	0,00
Aksu et al. 2016	2,41	1,64	3,55	4,49	0,00
Atas et al. 2017	17,00	4,11	70,39	3,91	0,00
Ferguson et al. 2019	1,54	1,45	1,63	14,06	0,00
Mahyoodeen et al. 2019	4,02	2,22	7,30	4,57	0,00
Shalom et al. 2019	1,17	1,16	1,19	18,87	0,00
	1,84	1,44	2,37	4,79	0,00

Meta Analysis

Fɪɢ. 2 Ever smoking in psoriatic arthritis (in comparison with psoriasis)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Tsuruta et al. 2017	1,12	0,62	2,00	0,37	0,71
Eder at al. 2011	0,63	0,50	0,81	-3,64	0,00
Pattison et al. 2007	0,83	0,50	1,39	-0,71	0,48
Ferguson et al. 2019	0,68	0,59	0,79	-5,20	0,00
	0,70	0,60	0,81	-4,71	0,00

Meta Analysis

Fɪɢ. 3 Ever smoking in psoriatic arthritis (in comparison with general population)

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Ferguson et al. 2019	1,05	0,92	1,20	0,67	0,50
Kibari et al. 2019	1,05	0,97	1,14	1,13	0,26
Ibanez- Bosh et al. 2017	3,06	1,37	6,85	2,72	0,01
	1,10	0,92	1,32	1,04	0,30

Meta Analysis

psoriasis cases was also linked to smoking intensity and duration, which could only be shown in the heavy smoking group (in current smokers with 15 or more cigarettes per day, with duration of 25 years or more, or 20 or more pack-years). In the third study, Green *et al.* did not find any significant association in either past or current smoker groups compared with the non-smoking psoriasis population [90].

Quality assessment

In 52 studies in psoriasis, 10 articles were rated as 'poor', 27 articles as 'fair' and 15 articles as 'good'. In the 24 studies evaluating in PsA, seven studies were rated as 'poor', nine as 'fair' and eight as 'good' (Supplementary Tables S3–S5, available at *Rheumatology* online).

Discussion

In this systematic review and meta-analysis, we evaluated the relationship between smoking and psoriasis and PsA. Our results suggest that the prevalence of ever smoking is higher in psoriasis patients compared with the general population. There are biochemical changes associated with smoking such as increase in free radicals activating mitogen-activated protein kinase, nuclear factor κB, and the Janus kinase–signal transducer and activator of transcription pathways [2]. Nicotine also activates the release of various cytokines such as IL-2, IL-12, TNF and granulocyte-macrophage colony-stimulating factor, as well as the stimulation of pathological angiogenesis through overexpression of vascular endothelial growth factor, which may all contribute to the risk of psoriasis [2, 91].

On the other hand, the data on the risk of PsA in psoriasis patients is contradictory. An inverse association between PsA development and smoking in psoriasis is found in a few studies. In Pattison *et al.*'s study, smokers had ∼50% reduced risk for PsA in psoriasis [6]. Eder *et al.* also found a reduced risk with smoking and PsA in the psoriasis patients who were HLA-C*06-negative [7]. In a large cohort representative of the UK general population, smoking was negatively associated with PsA among patients with psoriasis [8]. However Tey *et al.* found no association and Li *et al.* found that smoking had an increased risk of PsA among patients with psoriasis [9, 10]. Our meta-analysis found that ever smoking is associated with a lower prevalence of PsA among psoriasis. Although the reason for this paradox is not fully understood, there are some potential biological mechanisms. Smoking increases lipid peroxidation and modifies the immune response. It has been proposed that low levels of carbon monoxide in smokers inhibit the expression of pro-inflammatory cytokines (TNF-α, IL-1β, IL-8) and increase IL-10, which was hypothesized to be the reason for a better disease activity among smokers with ulcerative colitis [92]. A similar mechanism may play a role in the development of PsA. Another explanation is that nicotine may be inhibiting intracellular pro-inflammatory pathways through activating α7 nicotinic acetylcholine receptors, which are present in synoviocytes, macrophages and fibroblasts [93, 94].

In addition to these biological pathways to explain this paradox, there are also methodological concerns. The effect of smoking on the development of PsA in the psoriasis group involves a selection bias by definition for including patients who already have been exposed to the increased risk by smoking. To be able to understand the true effect of smoking on the risk of PsA in psoriasis, an inception cohort of psoriasis patients who never smoked needs to be followed prospectively and groups should be compared according to their smoking habits after the onset of psoriasis. Any other connections between psoriasis and PsA are affected by the collider effect, and the risk related to smoking can be misleading.

Alternatively, it is assumed that smokers have a more sedentary life, which may lead to less mechanical stress on the entheses. This may, in theory, lead to a reduced risk of PsA since mechanical loading on the entheses has been demonstrated to be important for the development of SpA [95]. Another potential mechanism can be the effect of smoking on the microbiota by changing the oral flora [96, 97].

It is challenging to evaluate the relationship between the disease and duration and/or intensity of smoking as these are hard to measure. The cessation of smoking may also be relevant as the effect of smoking may be reduced over time. Information on ex-smoking as well as intensity is not clearly reported in the majority of the publications. For that reason, we have summarized all the literature in our tables, but only performed the meta-analysis when 'ever'-smoking data were clearly provided.

Our study has some limitations. Although the number of articles identified was high for a systemic literature review, only a small group of studies have clearly given numbers on current *vs* ex-smoking data, which reduced our sample size in the meta-analyses. In addition we evaluated some studies as poor or fair according to quality assessment, but we could not perform a subgroup analysis due to low number of articles and sample size.

In summary our systemic literature review and meta-analysis suggest an increased prevalence of smoking in psoriasis, whereas the prevalence decreases among PsA patients compared with the psoriasis population. Whether smoking cessation neutralizes the risk of developing psoriasis requires a well-defined smoking data collection for past history and this is currently unavailable in the literature.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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