Chronologic order of appearance of immune-mediated inflammatory diseases relative to diagnosis of psoriasis

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Background: Psoriasis is a common inflammatory skin disease associated with several immune-mediated inflammatory diseases (IMIDs); however, little is known of the chronology of disease development.

Objective: To investigate the chronology of IMIDs relative to psoriasis.

Methods: We utilized routinely collected data from Danish nationwide administrative registries to examine the occurrence of IMIDs in patients with psoriasis (n = 10,923) and general population controls (n = 109,230).

Results: Approximately 20% of patients with psoriasis developed ≥1 IMID, with a 5-fold increased risk compared with the general population. Most IMIDs were diagnosed before psoriasis, except for psoriatic arthritis. Psoriasis was significantly associated with having multiple IMIDs (odds ratio 15.2, 95% confidence interval 11.6-20.0). Human leukocyte antigen B27 positivity was significantly more frequent among psoriasis patients.

Limitations: Clinical measurements were unavailable.

Conclusion: IMIDs occur frequently in patients with psoriasis and most are diagnosed before psoriasis. The observed chronology might represent important mechanisms of disease development. (J Am Acad Dermatol 2019;81:1283-91.)

Key words: autoimmune; comorbidity; epidemiology; HLA-B27; inflammation; psoriasis; psoriatic arthritis.

Psoriasis is a common, chronic cutaneous immune-mediated inflammatory disease (IMID). Patients with psoriasis are more likely than those in the general population to have other IMIDs during their life course, the most frequent IMID being psoriatic arthritis (PsA) which occurs in ~1 in 5 psoriasis patients.[1] Presence of IMIDs might add considerably to the disease burden and confer

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excess morbidity and mortality in patients with psoriasis. Indeed, among patients with PsA, the presence of comorbidities is associated with impaired response to therapy with biologics.[2] Moreover, in a cohort of patients with inflammatory bowel disease (IBD), the presence of 1 IMID increased the susceptibility of developing other IMIDs, but whether the same holds true for psoriasis patients remains unclear.[3,4]

A number of IMIDs share genetic risk loci with psoriasis,[5] and previous epidemiologic studies have shown significant associations between psoriasis and certain IMIDs, including celiac disease, Crohn's disease, ulcerative colitis, rheumatoid arthritis, and systemic lupus erythematosus, but data on the frequency of IMIDs in large populations of patients with psoriasis remain scarce.[4,6] Importantly, a chronologic assessment of the appearance of IMIDs relative to diagnosis of psoriasis has not been done.

CAPSULE SUMMARY

- Psoriasis has been associated with a number of immune-mediated inflammatory diseases, but the chronology of these remains poorly understood.
- For most immune-mediated inflammatory diseases, onset occurred several years before diagnosis of psoriasis; however, psoriatic arthritis most often occurred after the diagnosis of psoriasis. These findings might lower the need for continuously screening for comorbidities in patients followed for psoriasis.

MATERIALS AND METHODS

Data sources and study population

Danish nationwide administrative registries served as data sources for this study. All citizens of Denmark are assigned a unique identification number at birth or migration. The number is used in all public records and enables linkage of information across several registries. The Civil Registration System contains demographic information on all citizens of Denmark, including date of birth, death, and migration.[7] Health care data were obtained through the Danish National Patient Registry (DNPR), which contains prospectively collected data on inpatient and outpatient contacts at all Danish hospitals, as well as a few private clinics.[8] Detailed records of contacts, including diagnostic codes according to the International Classification of Diseases, Tenth Revision (ICD-10), system were available. In addition, information regarding hospital procedures and hospital-dispensed medication are recorded in the DNPR by specific procedure code.[9] Routinely measured data, such as height, weight, and blood pressure, are also recorded by using specific procedure codes in the DNPR. On a national level, ~95% of data from routinely performed laboratory tests are recorded in the Register of Laboratory Results for Research. Data on all pharmacy-dispensed medication (including drug, drug strength, drug formulation, drug quantity, and indication for the prescription) are recorded in the Registry of Medicinal Products Statistics by anatomical therapeutic codes. Last, tax-reported income levels for each individual were obtained through Statistics Denmark.[10]

We identified all adult (persons ≥18 years of age) Danish patients with a first-time psoriasis diagnosis during January 1, 2007-December 31, 2016. To qualify, patients had to have received ≥1 diagnostic code for psoriasis (ICD-10 L40); the diagnosis date was defined as the date of the first of either of 2 events: the assignment of the first ICD code or receipt of the first prescription prescribed for the indication psoriasis (for cases in which patients received their first treatment by their general practitioner before they received a formal diagnosis of psoriasis in the DNPR). Patients who had ever been diagnosed with psoriasis before January 1, 2007, were excluded from the study population. For each patient, the date of their first-ever psoriasis diagnosis served as the index date. To enable comparison with the general population, each psoriasis patient was matched on sex and date of birth with 10 individuals from the general population by using incidence density sampling, ie, controls were persons who did not have psoriasis but were alive and resident in the source population at the time that the corresponding psoriasis patient received their diagnosed.

Outcomes

The following IMIDs were selected a priori: multiple sclerosis, PsA, pyoderma gangrenosum, rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, celiac disease, primary sclerosing cholangitis, primary biliary cholangitis, type 1 diabetes, asthma, sarcoidosis, Graves' disease, iridocyclitis, ulcerative colitis, and Crohn's disease. IMID diagnoses were identified by the first record of the ICD-10 code. Moreover, because a considerable proportion of patients with iridocyclitis or asthma probably received their diagnoses and had their conditions managed exclusively by their general

Abbreviations used:

CI:	confidence interval
DNPR:	Danish National Patient Registry
ICD-10:	International Classification of Diseases, Tenth Revision
IBD:	inflammatory bowel disease
IL:	interleukin
IMID:	immune-mediated inflammatory disease
IQR:	interquartile range
IRR:	incidence rate ratio
OR:	odds ratio
PsA:	psoriatic arthritis
SD:	standard deviation

practitioner, we also identified such patients using prescription data. Thus, patients with iridocyclitis were identified by either ICD-10 code or by their first receipt of topical corticosteroids or anticholinergics for ocular use prescribed for the treatment of iridocyclitis. Likewise, patients with asthma were identified by either ICD-10 code or by receipt of ≥2 inhalation medications prescribed for the treatment of asthma.

Statistical analysis

Descriptive statistics were made by using means and medians (with standard deviations [SDs] and interquartile ranges [IQRs]) for continuous variables and frequencies with percentages for categorical variables. Age at inclusion was handled as a continuous variable. Socioeconomic status was presented as percentiles of age-standardized means of tax-reported income during the 5 years before study inclusion. Medication use was presented as a binary variable of never-ever exposure during the study period. Odds ratios (ORs) were estimated by using conditional logistic regression. Incidence rates were calculated per 10,000 person-years, and incidence rate ratios (IRRs) were estimated by using Poisson regression models adjusted for age and sex. To test whether the risk was significantly different before and after psoriasis was diagnosed, we compared the incidence during the 10 years before the psoriasis diagnosis (serving as the reference group) with the incidence after psoriasis diagnosis because this would yield IRRs of comparable risk time within the same population. In these analyses, significantly increased IRRs would suggest the risk of IMIDs was greatest after psoriasis diagnosis, and decreased IRR estimates would suggest that the risk was highest before psoriasis diagnosis. All OR and IRR estimates were presented with 95% confidence intervals (CIs). Graphic depictions of study results were presented by box plots and bar charts. All analyses were performed by using SAS statistical software version 9.4 (SAS Institute Inc, Cary, NC) and STATA software version 13.0 (StataCorp, College Station, TX).

RESULTS

We identified a total of 10,923 patients with a first-ever diagnosis of psoriasis during the study period. These patients were matched with 109,230 individuals from the general population. The mean (SD) age at time of psoriasis diagnosis was 52.1 (15.5) years, and 52.9% were women. The prevalence of human leukocyte antigen B27 positivity was significantly higher among the psoriasis group (P = .03), whereas no significant differences were observed in the immunologic laboratory profile between psoriasis patients and the general population (Table I).

Before diagnosis of psoriasis (or the corresponding index date for the general population), 2181 (20.0%) psoriasis patients received a diagnosis of an IMID, compared with 8153 (7.4%) people in the general population (OR 3.10, 95% CI 2.94-3.26) (Table II). The highest number of coexisting IMIDs in a single individual before diagnosis of psoriasis was 5. After diagnosis of psoriasis, 14.7% (1607/10,923) of psoriasis patients developed ≥1 IMID, compared with 2.7% (2928/109,230) of people in the general population (OR 6.26, 95% CI 5.87-6.68). Likewise, after diagnosis of psoriasis, 1.2% (128/10,923) of psoriasis patients and 0.1% (85/109,230) of the general population received ≥2 IMID diagnoses (OR 15.2, 95% CI 11.6-20.0). The OR of ever (either before or after onset of psoriasis) having an IMID was 4.33 (95% CI 4.14-4.53) and ever having ≥2 IMIDs was 8.58 (95% CI 7.75-9.51). Excluding PsA from the models yielded no significant changes compared with our primary results (data not shown). To examine whether the observed associations could be explained by increased interaction with the health care system, we also examined the association with syphilis (serving as a negative control). In Denmark, syphilis is managed by dermatologists, and because the disease unlikely has a mechanistic link to psoriasis, increased health care contact with dermatologists observed in patients with syphilis would, therefore, suggest a positive association if the findings were affected by surveillance bias. Compared with the general population, there was no significant difference before psoriasis diagnosis (P = .171) or after psoriasis diagnosis (P = .264), and psoriasis was not significantly associated with syphilis (P = .271) when compared with the general population.

The most commonly occurring IMIDs before a psoriasis diagnosis were PsA (7.2%), followed by asthma (3.7%), rheumatoid arthritis (3.4%), and type

Table I. Characteristics of the study population

Characteristic	General population, n = 109,230	Psoriasis, n = 10,923
Age, years		
Mean (SD)	52.1 (15.5)	52.1 (15.5)
Median (IQR)	52.4 (40.4-63.2)	52.4 (40.4-63.2)
Sex, n (%)		
Women	57,770 (52.9)	5777 (52.9)
Men	51,460 (47.1)	5146 (47.1)
Socioeconomic status, n (%)		
Lowest	21,840 (20.0)	2190 (20.1)
Below average	21,627 (19.8)	2404 (22.0)
Average	21,778 (19.9)	2253 (20.6)
Above average	22,018 (20.2)	2013 (18.4)
Highest	21,967 (20.1)	2063 (18.9)
Body weight, kg, mean (SD)	76.9 (19.5)	81.8 (23.0)
Body mass index, mean (SD)	26.3 (6.5)	27.8 (7.4)
Blood pressure, mmHg, systolic/diastolic, mean (SD)	138/81 (22/13)	136/82 (21/13)
Medication, n (%)		
Acitretin	106 (0.1)	1244 (11.4)
Cyclosporine	139 (0.1)	231 (2.1)
Methotrexate	1601 (1.5)	2668 (33.6)
TNF inhibitors	325 (0.3)	783 (7.2)
HLA-B27, positive/total (%)	84/651 (12.9)	60/334 (18.0)
Immunologic laboratory profile,* positive/total (%)		
anti-dsDNA IgG	122/321 (38.0)	52/177 (29.4)
Anti-histidyl-tRNA-synthase IgG, Jo-1	5/98 (5.1)	<3/74 (NS)
ANA IgG	<3/82 (NS)	<3/66 (NS)
Anti-SSA IgG	10/128 (7.8)	5/98 (5.1)
Anti-SSB IgG	8/132 (6.1)	3/99 (3.0)
U1 snRNP IgG	6/108 (5.6)	3/79 (3.8)
Anti-topoisomerase antibody IgG, Scl-70	5/104 (4.8)	<3/76 (NS)
Anti-major centromere B IgG	5/98 (5.1)	<3/171 (NS)
Smiths antibody IgG	5/108 (4.6)	0/79 (0)
Rheumatoid factor IgM	222/645 (34.4)	114/344 (33.1)
Anti-CCP IgG	26/456 (5.7)	25/340 (7.4)

ANA, Antinuclear antibody; *CCP*, cyclic citrullinated peptide; *HLA*, human leukocyte antigen; *IQR*, interquartile range; *NS*, not shown for data security purposes; *SD*, standard deviation; *snRNP*, small nuclear ribonuclear protein; *TNF*, tumor necrosis factor; *tRNA*, transfer RNA.
*Only measurements within 1 year of psoriasis diagnosis are shown.

1 diabetes (2.5%). After psoriasis onset, the dominating comorbidity was PsA (10.5%).

Chronologic order of IMIDs relative to psoriasis diagnosis

Fig 1 shows the time of occurrence of IMIDs relative to the time of psoriasis diagnosis. Most IMIDs occurred before diagnosis of psoriasis, except for PsA, which predominantly occurred after psoriasis (Table II, Fig 1). Of the IMIDs occurring before psoriasis, a mean (SD) of 6.4 (5.9) years or a median (IQR) of 4.8 (1.2-10.4) years occurred before psoriasis diagnosis. The mean (SD) time from psoriasis diagnosis to occurrence of an IMID after psoriasis was 2.9 (2.5) years or a median (IQR) of 2.3 (0.8-4.7) years. The overall incidence of IMID after a psoriasis diagnosis was 297.97 (95% CI 283.75-321.90)/10,000 person-years compared with 49.43 (95% CI 47.68-51.26)/10,000 person-years in the general population (Table III). Patients with psoriasis had a considerably increased risk of ≥1 IMID after psoriasis diagnosis (IRR 5.49, 95% CI 5.16-5.83) compared with general population controls. Likewise, patients with psoriasis were at higher risk of having ≥2 IMIDs (IRR 15.06, 95% CI 11.45-19.82) (Fig 2). Psoriasis was associated with an increased risk of 11 out of the 16 studied IMIDs. These included rheumatic, gastrointestinal, respiratory, and endocrine IMIDs. No significant risk was found for systemic lupus erythematosus or neurologic and biliary IMIDs. For most individually examined IMIDs, the risk was significantly higher before diagnosis of psoriasis (Table II). When comparing the time at risk before and after diagnosis of psoriasis, there was an 81%

Table II. Proportion of patients with IMID onset before and after diagnosis of psoriasis

Comorbidity, disease onset, n (%)	General population	Psoriasis
Any IMID		
Before psoriasis	8153 (7.4)	2181 (20.0)
After psoriasis	2928 (2.7)	1607 (14.7)
Multiple sclerosis		
Before psoriasis	402 (0.4)	47 (0.4)
After psoriasis	82 (0.1)	10 (0.1)
Psoriatic arthritis		
Before psoriasis	88 (0.1)	783 (7.2)
After psoriasis	43 (0.1)	1063 (10.5)
Pyoderma gangrenosum		
Before psoriasis	9 (0)	9 (0.1)
After psoriasis	9 (0)	8 (0.1)
Rheumatoid arthritis		
Before psoriasis	831 (0.8)	373 (3.4)
After psoriasis	425 (0.4)	148 (1.4)
Ankylosing spondylitis		
Before psoriasis	146 (0.1)	111 (1.0)
After psoriasis	58 (0.1)	38 (0.4)
Systemic lupus erythematosus		
Before psoriasis	95 (0.1)	37 (0.3)
After psoriasis	28 (0)	5 (0.1)
Celiac disease		
Before psoriasis	109 (0.1)	34 (0.3)
After psoriasis	40 (0.1)	11 (0.1)
Primary sclerosing cholangitis		
Before psoriasis	78 (0.1)	10 (0.1)
After psoriasis	99 (0.1)	10 (0.1)
Primary biliary cholangitis		
Before psoriasis	22 (0)	10 (0.1)
After psoriasis	23 (0)	5 (0.1)
Type 1 diabetes		
Before psoriasis	1511 (1.4)	270 (2.5)
After psoriasis	587 (0.5)	136 (1.3)
Asthma		
Before psoriasis	2639 (2.4)	406 (3.7)
After psoriasis	1055 (1.0)	183 (1.7)
Sarcoidosis		
Before psoriasis	280 (0.3)	57 (0.5)
After psoriasis	85 (0.1)	22 (0.2)
Graves disease		
Before psoriasis	883 (0.8)	89 (0.8)
After psoriasis	206 (0.2)	45 (0.4)
Iridocyclitis		
Before psoriasis	977 (0.9)	173 (1.6)
After psoriasis	53 (0.1)	5 (0.1)
Crohn's disease		
Before psoriasis	203 (0.2)	109 (1.0)
After psoriasis	61 (0.1)	24 (0.2)
Ulcerative colitis		
Before psoriasis	484 (0.4)	84 (0.8)
After psoriasis	161 (0.2)	32 (0.3)

The psoriasis diagnosis date was used as the index date for the corresponding age- and sex-matched reference group from the general population.
IMID, Immune-mediated inflammatory disease.

higher risk of IMID diagnosis after onset of psoriasis (IRR 1.81, 95% CI 1.66-1.96); however, this finding was attributable to PsA. Thus, when excluding PsA, the risk of developing any IMID was significantly lower after a diagnosis of psoriasis than before (IRR 0.83, 95% CI 0.73-0.95).

DISCUSSION

Main findings

In a cohort of 10,923 patients with psoriasis, we found that ~20% and 14% of patients with psoriasis had an IMID develop before and after the onset of psoriasis, respectively. The predominant IMID developing after the onset of psoriasis was PsA. Patients with psoriasis had a 5-fold increased risk of subsequent IMID compared with the general population.

Interpretation

The increased prevalence of immune-mediated inflammatory comorbidities in patients with psoriasis is in line with previous studies on this association. A similar observational study including 25,341 participants from the United States showed a significant association between psoriasis and having ≥1 (OR 1.6, 95% CI 1.5-1.7) and ≥2 (OR 1.9, 95% CI 1.6-2.4) autoimmune diseases.[4] This study however did not investigate PsA as a study outcome, possibly resulting in lower estimates of the collective association. Likewise, in another large study involving data from US insurance claims, psoriasis and PsA were associated with multiple autoimmune diseases.[11] A systematic review from 2012 including 28 publications showed a convincing association between psoriasis and IBD; however, the available evidence for other autoimmune diseases was limited.[6]

In contrast with previous studies, we studied the temporality of psoriasis and the development of a wide range of associated IMIDs. We demonstrated that most IMIDs occurred before the diagnosis of psoriasis, apart from PsA. Some IMIDs, such as asthma and celiac disease, were expected to appear before psoriasis due to the tendency of these diseases for early onset. The term comorbidity is frequently used to describe an excess risk of IMIDs in patients with psoriasis; however, the term can be somewhat misleading. It might give the impression that the other co-occurring diseases are triggered by systemic changes caused by psoriasis, and that psoriasis is the main contributor for excess morbidity; however, the current study results suggest a different disease trajectory. Indeed, one may speculate whether psoriasis can, at least in a subset of patients, be considered a cutaneous manifestation of a complex composition of several coexisting

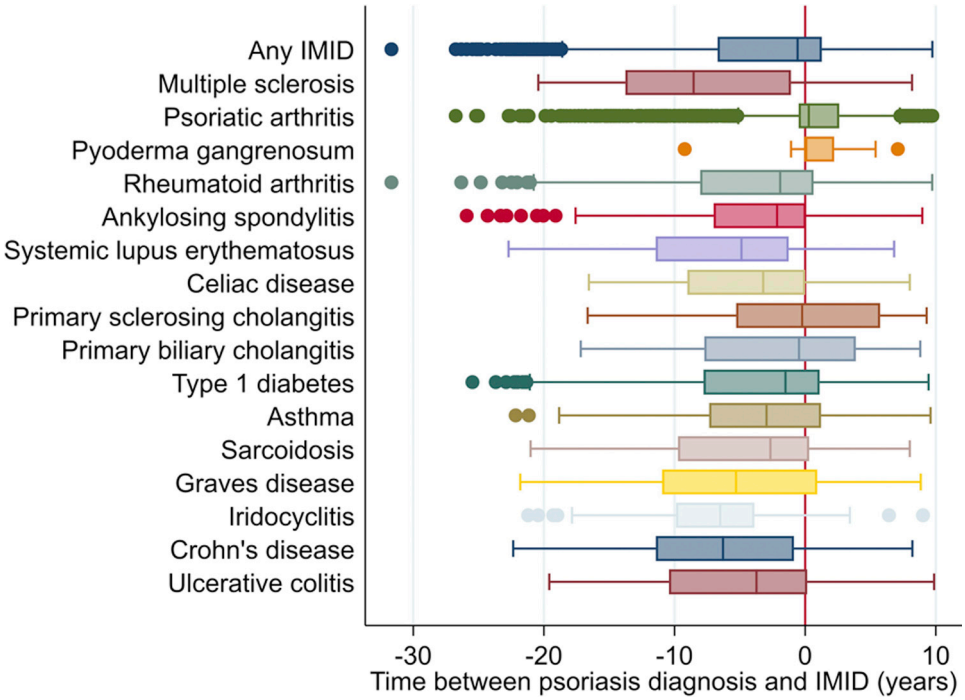

Fig 1. Appearance of different IMIDs relative to the time of psoriasis diagnosis. Data are presented as horizontal box plots where boxes represent the 25th through the 75th percentile. The vertical line inside the box is the median. Whiskers represent the 95% confidence intervals, and dots represent outliers. *IMID*, Immune-mediated inflammatory disease.

IMIDs. This observation provides new insight in possible pathophysiologic mechanisms of these associations.

Although the exact pathophysiologic mechanisms of the shown association are not yet known, collectively, the current evidence shows that psoriasis is associated with presence of other IMIDs. The associations are likely complex; however, common genetic susceptibility caused by overlapping risk genes and loci has been suggested as one of the major contributing factors in this association.[12-14] Such genetic links might further explain the tendency of disease clustering of IMIDs and supports the findings of the current study where we observed that patients with psoriasis had a 15-fold increased risk of developing ≥2 IMIDs compared with general population controls. Certain stressors, such as cigarette smoking and microbial agents, might also play a role as common trigger factors.[15-17] Higher prevalence of psoriasis and some IMIDs have also been observed in some geographic regions, especially areas with higher latitude; however, the exact environmental factors that can explain these links are unknown.[18-20] Furthermore, an upregulation of proinflammatory cells and cytokines might contribute to an environment triggering the co-occurrence of certain IMIDs. It is well-established that patients with psoriasis or PsA have increased levels of interleukin (IL) 17, IL-23, and tumor necrosis factor α and that patients with psoriasis and concurrent PsA tend to carry more inflammatory comorbidities compared with patients with skin manifestations alone.[21,22] This is in line with the findings of the current study, as we observed that PsA was highly represented in individuals with multiple IMIDs.

Beyond genetic, environmental, and common inflammatory pathways, other possible explanatory mechanisms include immune-modulating medications. Some drugs that are prescribed to treat psoriasis might contribute to the pathogenesis of certain IMIDs. Indeed, tumor necrosis factor α–inhibitors are contraindicated in patients with multiple sclerosis due to the risk of disease exacerbation.[23] Furthermore, worsening of IBD has been observed in treatment with IL-17 inhibitors.[24] In contrast, other biologics, such as adalimumab, infliximab, and ustekinumab, can be used to treat IBD.[25] Thus, certain immune-modulating drugs might interact and influence the risk of comorbidities by either preventing or triggering other IMIDs in patients with psoriasis or vice versa.

PsA was seen more frequently after the development of psoriasis. This finding is in line with the

Table III. Summary of time to IMIDs, incidence rates, and incidence rate ratios of IMIDs in patients with psoriasis compared with the general population

	Time from psoriasis to IMID, y		IMID in general population, IR (95% CI)	IMID in psoriasis population, IR (95% CI)	Psoriasis vs general population			After vs before (reference) psoriasis diagnosis*		
Category	Mean (SD)	Median (IQR)			IRR	95% CI	*P* value	IRR	95% CI	*P* value
Any IMID	2.9 (2.5)	2.3 (0.8-4.7)	49.43 (47.68-51.26)	297.97 (283.75-312.90)	5.49	5.16-5.83	<.0001	1.81[†]	1.66-1.96	<.0001
≥2 IMIDs	4.4 (2.5)	4.4 (2.1-6.5)	1.43 (1.16-1.77)	23.58 (19.89-28.04)	15.06	11.45-19.82	<.0001	2.45[‡]	1.95-3.07	<.0001
Multiple sclerosis	4.8 (3.1)	5.8 (2.5-7.4)	1.37 (1.10-1.70)	1.67 (0.90-3.11)	1.22	0.63-2.35	.5523	0.44	0.21-0.92	.0283
Psoriatic arthritis	2.8 (2.5)	2.1 (0.7-4.4)	0.72 (0.53-0.96)	206.66 (194.60-210.46)	266.08	196.16-360.93	<.0001	1.67	1.52-1.84	<.0001
Pyoderma gangrenosum	3.3 (2.6)	3.1 (1.0-5.4)	0.15 (0.08-0.29)	1.33 (0.67-2.67)	8.90	3.43-23.06	<.0001	0.89	0.34-2.31	.8098
Rheumatoid arthritis	3.7 (2.6)	3.3 (1.4-5.5)	7.12 (6.48-7.83)	25.67 (21.85-30.16)	3.58	2.97-4.31	<.0001	0.56	0.46-0.69	<.0001
Ankylosing spondylitis	2.3 (2.2)	1.3 (0.5-4.1)	0.97 (0.75-1.25)	6.41 (4.66-8.80)	6.61	4.39-9.95	<.0001	0.48	0.33-0.70	.0002
Systemic lupus erythematosus	1.9 (2.8)	0.8 (0.3-1.4)	0.47 (0.32-0.67)	0.84 (0.35-2.01)	1.79	0.69-4.63	.2304	0.20	0.08-0.52	.0010
Celiac disease	3.4 (2.7)	3.4 (0.3-5.9)	0.67 (0.49-0.91)	1.84 (1.02-3.32)	2.76	1.41-5.37	.0029	0.44	0.22-0.90	.0237
Primary sclerosing cholangitis	5.6 (2.3)	5.7 (4.9-6.6)	1.65 (1.35-2.00)	1.67 (0.90-3.10)	1.01	0.52-1.94	.9754	1.43	0.54-3.76	.4684
Primary biliary cholangitis	6.1 (3.4)	8.2 (3.9-8.4)	0.39 (0.25-0.58)	0.83 (0.35-2.00)	2.18	0.83-5.72	.1152	0.63	0.20-1.91	.4104
Type 1 diabetes	3.0 (2.4)	2.2 (1.1-4.6)	9.91 (9.14-10.74)	23.34 (19.74-27.62)	2.34	1.94-2.82	<.0001	0.73	0.58-0.91	.0048
Asthma	3.6 (2.4)	3.4 (1.6-5.4)	18.03 (16.97-19.15)	31.86 (27.56-36.83)	1.76	1.50-2.06	<.0001	0.60	0.50-0.72	<.0001
Sarcoidosis	2.5 (2.0)	1.9 (1.0-3.6)	1.42 (1.15-1.75)	3.69 (2.43-5.60)	2.60	1.62-4.15	.0001	0.58	0.34-0.98	.0427
Graves disease	3.2 (2.6)	2.5 (0.9-5.4)	3.45 (3.01-3.96)	7.57 (5.65-10.14)	2.18	1.58-3.02	<.0001	0.92	0.62-1.38	.6961
Iridocyclitis	4.5 (3.2)	3.4 (2.3-6.4)	0.89 (0.68-1.16)	0.85 (0.35-2.04)	0.95	0.28-2.38	.9127	0.04	0.02-0.10	<.0001
Crohn's disease	3.8 (2.5)	4.0 (1.6-5.4)	1.02 (0.79-1.31)	4.04 (2.71-6.02)	3.97	2.47-6.36	<.0001	0.40	0.25-0.65	.0002
Ulcerative colitis	2.7 (2.5)	2.0 (0.5-4.9)	2.69 (2.30-3.14)	5.37 (3.80-7.60)	1.99	1.36-2.91	.0004	0.60	0.38-0.92	.0202

CI, Confidence interval; *IMID*, immune-mediated inflammatory disease, *IQR*, interquartile range; *IR*, incidence rate per 10,000 person-years; *IRR*, incidence rate ratio; *SD*, standard deviation.

*In analyses of risk of IMIDs before versus after diagnosis of psoriasis, the incidence rate in the 10 years before psoriasis diagnoses serves as the reference group (ie, IRRs <1 suggests a higher risk before psoriasis diagnosis and IRRs >1 suggest a higher risk after psoriasis diagnosis).

[†]When excluding psoriatic arthritis, the IRR was 0.83 (95% CI 0.73-0.95), $P = .0046$.

[‡]When excluding psoriatic arthritis, the IRR was 0.90 (95% CI 0.61-1.32), $P = .5775$.

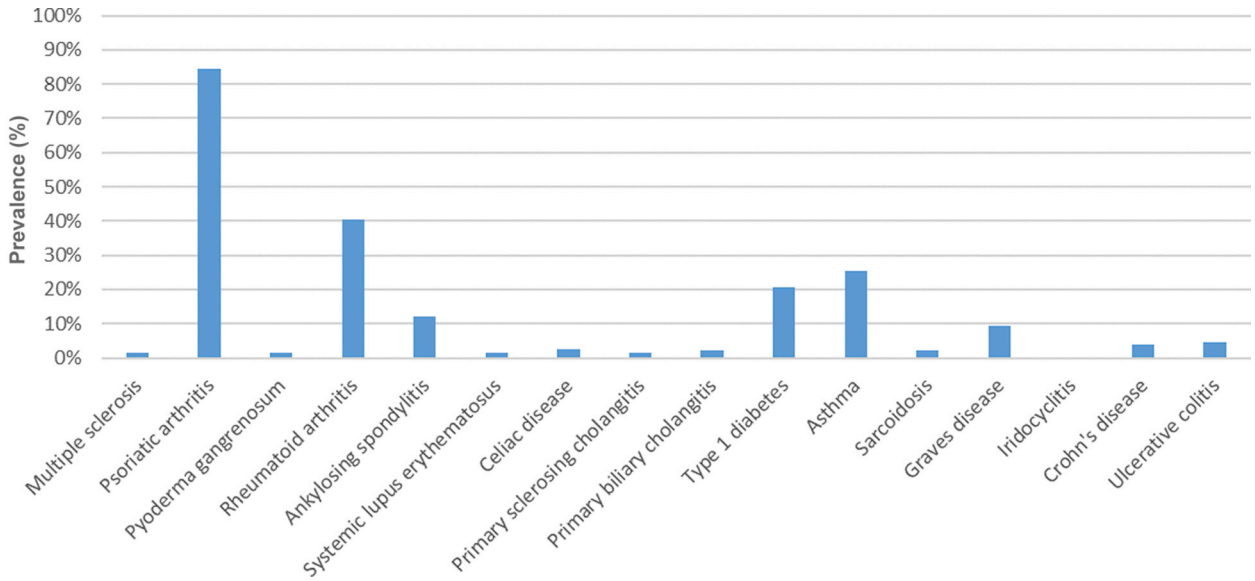

Fig 2. Prevalence of immune-mediated inflammatory diseases in patients with psoriasis that have ≥2 co-ocurring immune-mediated inflammatory diseases (in addition to psoriasis).

results of a UK observational study involving primary care and secondary care data sources that found that most participants (82.3% with primary care data and 61.3% with secondary care data) had psoriasis before PsA.[26] We further observed that PsA was associated with having multiple comorbid IMIDs. The clinical similarities between PsA and rheumatoid arthritis has been described previously, and because of overlapping symptoms, some diagnostic overlap might occur.[27] In some cases, rheumatologists depend on a psoriasis diagnosis before the PsA diagnosis is given. However, it is important to keep in mind that the date of psoriasis diagnosis does not necessarily represent the exact time of onset of skin manifestations of plaque psoriasis, as many patients might have plaques for several years before consulting a physician. This uncertainty in timing of disease onset might represent a study limitation. Furthermore, it is estimated the PsA often occurs ~10 years after a psoriasis diagnosis.[28] The association in the current study might therefore be underestimated due to the limited follow-up period. Patients with psoriasis might be seen by physicians more frequently than members of the general population, which might lead to a somewhat earlier diagnosis of IMIDs among these patients compared with the general population. However, since the total duration of this study was up to 4 decades, any such differences would arguably not lead to an overall bias of the absolute number of patients diagnosed with IMIDs during the study. Last, as with most observational studies involving routinely collected administrative data, we lacked objective measurement of psoriasis severity, such as the percentage of the affected body surface area or the Psoriasis Area and Severity Index, and we were therefore unable to assess whether more severe psoriasis was associated with a higher risk of IMID development.

Conclusion

Patients with psoriasis carried a 5-fold increased risk of developing any IMID compared with the general population. Most IMIDs were diagnosed before psoriasis, potentially providing important insight in the understanding of pathophysiologic mechanisms of concurrent IMIDs in patients with psoriasis. Presence of PsA among patients with psoriasis was strongly associated with having additional IMIDs, indicating that patients with psoriasis and concurrent PsA carry an increased burden of disease and might require increased diagnostic awareness among clinicians.

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