



## **Prevalence of psoriatic arthritis in patients with psoriasis**

### **A systematic review and meta-analysis of observational and clinical studies**

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# **TITLE PAGE**

## **Title**

Prevalence of psoriatic arthritis in patients with psoriasis: A systematic review and meta-analysis of observational and clinical studies

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Drs. Alinaghi and Calov had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Egeberg and Thyssen.

*Acquisition, analysis, and interpretation of data:* All authors. *Drafting of the manuscript:* Alinaghi and Egeberg. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Egeberg. *Obtained funding:* Not applicable. *Administrative, technical, or material support:* Egeberg and Thyssen. *Study supervision:* Egeberg and Thyssen.

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Reddy Labs, Valeant, Dermira, Allergan, and Sun Pharmaceutical Industries, and received research funding from Janssen, Incyte, Lilly, Novartis, Allergan, and Leo Pharma. **Dr. Gisondi** has received honoraria as consultant and/or speaker from AbbVie, Celgene, Eli Lilly, Janssen, Leo Pharma, MSD, Novartis, Pfizer, and UCB. **Dr. Wu** is an investigator for AbbVie, Amgen, Eli Lilly, Janssen, Novartis, and Regeneron. **Dr. Thyssen** is supported by an unrestricted grant from the Lundbeck Foundation and has received speaker honoraria from Galderma, Sanofi-Genzyme and MEDA and attended advisory board meetings for Roche and Sanofi-Genzyme. He is an investigator for LEO Pharma. **Dr. Egeberg** has received research funding from Pfizer, Eli Lilly, the Danish National Psoriasis Foundation, and the Kgl Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from Almirall, Leo Pharma, Samsung Bioepis Co., Ltd., Pfizer, Eli Lilly, Novartis, Galderma, and Janssen Pharmaceuticals.

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## **Abstract**

### **Background**

Wide-ranging prevalence estimates of psoriatic arthritis (PsA) in patients with psoriasis have been reported.

### **Objectives**

To assess the prevalence and incidence of PsA in patients with psoriasis.

### **Methods**

Two authors independently searched three databases for studies reporting on the prevalence or incidence of PsA in patients with psoriasis. A proportion meta-analysis was performed to calculate the pooled proportion estimates of PsA in patients with psoriasis.

### **Results**

A total of 266 studies were included, examining 976,408 patients with psoriasis. Overall, the pooled proportion (95% confidence interval) of PsA among patients with psoriasis was 19.7% (18.5%-20.9%). In children and adolescents (<18 years), the pooled prevalence was 3.3% (2.1%-4.9%). The PsA prevalence was 22.7% (20.6%-25.0%) in European, 21.5% (15.4%-28.2%) South American, 19.5% (17.1%-22.1%) North American, 15.5% (0.009%-51.5%) African, and 14.0% (11.7%-16.3%) in Asian psoriasis patients. The prevalence of PsA was 23.8% (20.1%-27.6%) in studies where the CLASSification criteria for Psoriatic ARthritis (CASPAR) was applied. The incidence of PsA among psoriasis patients ranged from 0.27 to 2.7 per 100 person-years.

### **Limitations**

Between-study heterogeneity may have affected the estimates.

### **Conclusions**

We found that one in five patients with psoriasis have PsA. With the growing recognition of CASPAR, more homogenous and comparable prevalence estimates are expected to be reported.

## **Capsule summary**

- Wide-ranging estimates have been reported for the occurrence of psoriatic arthritis in patients with psoriasis.
- We found an overall pooled prevalence of 19.7% for psoriatic arthritis in patients with psoriasis and 24.6% in patients with moderate-to-severe disease.
- Screening psoriasis patients for psoriatic arthritis may be warranted, especially for those with moderate-to-severe disease..

Key words: Psoriasis, psoriatic, arthritis, arthropathy, incidence, prevalence.

## **Introduction**

Psoriatic arthritis (PsA), classified as a seronegative spondyloarthropathy, is strongly associated with cutaneous psoriasis; dactylitis and enthesitis represent the hallmarks of the disease<sup>[1]</sup>. Since its formal acceptance as a distinct entity, several attempts have been made to devise the most sensitive and specific set of diagnostic criteria<sup>[2-10]</sup>. In 1973, Moll and Wright defined PsA as the presence of inflammatory arthritis with the concurrent existence of psoriasis and seronegativity for rheumatoid factor<sup>[2]</sup>, and in 2006 the CIASsification for Psoriatic ARthritis (CASPAR) criteria were introduced<sup>[10]</sup>.

Despite the increasing recognition of PsA as a distinct disease, the lack of a widely accepted and validated case definition has yielded considerable variability in PsA prevalence estimates<sup>[11-15]</sup>. Several observational studies have investigated the latter issue<sup>[16, 17]</sup>, but no meta-analysis has yet been performed to estimate the exact prevalence in patients with psoriasis. Applying a broad and inclusive search strategy, we examined the occurrence of PsA in patients with psoriasis in a systematic review and meta-analysis.

## **Methods**

### **Literature search**

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and a study protocol was developed *a priori* (supplementary materials).

All articles from database inception through November 2017 were potentially eligible for inclusion. Two authors independently screened the three databases (Pubmed, Web of Science and EMBASE) using the following search terms: “(psoriasis) AND (psoriatic OR arthritis OR arthropathy OR incidence OR prevalence)”.

### **Inclusion and exclusion criteria**

To qualify for inclusion, studies had to a) be original, b) be written in English and available in full-text, c) have a source population of patients with psoriasis, d) include absolute numbers or percentage of PsA cases to calculate a prevalence of PsA among patients with psoriasis. Studies were excluded if they reported the occurrence of “arthritis” without distinctly specifying the type of arthritis. Studies of juvenile idiopathic arthritis (JIA) were not included since this may comprise several different types of arthritis. Furthermore, we discerned PsA from psoriatic arthropathy as the latter is a vague term referring to musculoskeletal pain and complaints in general that may be unrelated to PsA.

### **Data-extraction and quality assessment**

Records were screened according to the title and abstract. The relevant abstracts, or articles without abstract, were selected for full-text review. References from the included studies were also screened for additional studies not identified through the initial search strategy. The extracted data from each study are presented as a supplementary dataset on Mendelay and can be accessed here: [\[INSERT LINK\]](#). Quality assessment was performed using the Newcastle-Ottawa Scale (NOS)<sup>[18]</sup>. An adapted version was used for cross-sectional studies where a maximum score of either 8 or 10 could be achieved. Thus, studies receiving 6 or above and 7 or above, respectively, were considered of high quality. For case-control studies and cohort studies, those receiving a score of 7 or above were considered of high quality.

### **Data analysis**

All statistical analyses were performed using StatsDirect version 3.1.4 (StatsDirect Ltd., Cheshire, UK). The Freeman-Tukey double arcsine method was applied to transform proportions<sup>[19]</sup>, and an inverse-variance weighted random effects meta-analysis was performed using the DerSimonian and Laird method<sup>[20]</sup>. *A priori*, we opted for the DerSimonian-Laird random effects methods since we expected to find significant between-study heterogeneity. A proportion meta-analysis was completed to obtain pooled proportions with 95% confidence intervals (CIs) of PsA in patients with psoriasis. Heterogeneity of included studies was



assessed using the Cochran Q test and I<sup>2</sup> statistics, and forest plots were constructed. Furthermore, we calculated the prevalence of PsA in psoriasis patients for the following stratifications: all studies, by gender, by decade published (pre-2000, 2000-2009, and 2010-2017), children and adolescent populations only, i.e. those <18 years), studies of adults only (≥18 years), diagnosis according to CASPAR, diagnosis according to the Moll and Wright criteria, by population size (n<500, 500-1000, and ≥1000), by study type (clinical, register-based, population-based, and observational studies), by geographic area and country, and by Newcastle Ottawa Scale (NOS) score (good quality or fair/poor quality), and by severity of psoriasis disease defined as moderate-to-severe disease (psoriasis area severity index (PASI) ≥10 or body surface area (BSA) ≥10) and mild disease (PASI <10 or BSA <10).

## **Results**

We identified 6331 records through database searching (PubMed=2139; Web of Science=1217; EMBASE=2975); 4323 non-duplicate records were screened by title and abstract, yielding 1302 articles for full-text assessment. Combined with the additional 41 studies identified by screening references, 287 studies were included for data-extraction and 266 studies were selected for quantitative analysis (figure 1), including 976,408 psoriasis patients (12,884 children/adolescents). The results of all analyses performed are summarized in table 1.

### **Prevalence of PsA in patients with psoriasis**

Overall, quantitative analysis of 266 studies yielded a pooled PsA prevalence (95% CI) of 19.7% (18.5%-20.9%) in patients with psoriasis (supplementary figure 1). Twenty-one studies<sup>[21-41]</sup> reported data on children/adolescents yielding a pooled prevalence of 3.3% (2.1%-4.9%) (supplementary figure 2), and a total of 245 studies<sup>[11-17, 42-279]</sup> reported data for PsA in adults with psoriasis with a pooled prevalence of 21.6%

(20.3%-22.9%) (supplementary figure 3). Thirty-six studies<sup>[11, 14, 22, 42, 44, 48, 49, 52, 57, 63, 64, 69, 70, 80, 91, 100, 112, 117, 140, 156, 159, 169, 177, 179, 188, 189, 200, 208, 214, 217, 223, 239, 241, 245, 275, 280]</sup> reported data on PsA stratified by sex (supplementary figures 4 and 5), with the prevalence for men and women being 23.3% (19.4%-27.5%) and 24.0% (20.1%-28.1%), respectively. Forty-five studies<sup>[11, 14, 90, 119, 129, 130, 135, 137, 141, 142, 146-148, 155, 156, 159, 163, 164, 174, 177, 180, 186, 197, 198, 200, 208-210, 217, 218, 229, 231, 233, 235, 241, 245, 247, 249, 257-259, 271, 273, 275, 280]</sup> used CASPAR as the underlying diagnostic approach for PsA assessment, with a pooled prevalence of 23.8% (20.1%-27.6%) (supplementary figure 6). Similarly, twenty studies<sup>[43, 44, 47, 49, 57, 63, 75, 80, 87, 88, 92, 93, 102, 157, 199, 219, 239, 240, 276, 281]</sup> used the Moll and Wright criteria, yielding a prevalence of 24.1% (15.0%-34.5%) (supplementary figure 7).

### **Variations in PsA prevalence by geographic region and country**

There were 119 studies<sup>[11, 16, 17, 21, 31-36, 41, 42, 44, 45, 48, 49, 51, 52, 55, 57, 58, 62, 65, 66, 68-71, 74, 90, 93, 100, 104, 106, 107, 111-113, 115, 116, 123, 127, 129, 131, 133, 135, 136, 139-142, 149-152, 156-159, 162-164, 167, 168, 170, 171, 173-176, 178-180, 188, 191, 192, 194, 197, 199, 200, 202-205, 211, 215, 220, 223, 224, 226, 227, 229-231, 234, 235, 237-239, 242, 249-251, 253, 254, 260, 261, 264, 265, 268-270, 272, 276, 277, 279, 282-284]</sup> from Europe with a resulting pooled prevalence of 22.7% (20.6%-25.0%). From Asia, there were fifty-nine studies<sup>[12-15, 22-24, 27, 37, 39, 54, 59, 60, 63, 72, 73, 80, 88, 94, 102, 103, 105, 108, 110, 117, 128, 130, 132, 138, 146, 147, 155, 160, 184, 186, 198, 206, 216, 217, 221, 222, 233, 240, 241, 244-248, 255, 257, 258, 263, 266, 267, 271, 273-275]</sup> included for analysis, yielding a pooled prevalence of 14.0 (11.7%-16.3%). Furthermore, forty-seven studies<sup>[25, 28, 29, 46, 47, 50, 53, 56, 61, 64, 75, 76, 79, 81, 86, 87, 91, 95-98, 109, 118, 120, 121, 125, 143, 144, 148, 154, 161, 169, 183, 193, 196, 201, 212, 214, 218, 232, 236, 243, 252, 259, 262, 280, 285]</sup> were included from North America with a pooled prevalence of 19.5% (17.1% - 22.1%). There were ten studies<sup>[126, 137, 145, 172, 177, 190, 208, 209, 219, 228]</sup> from South America resulting in a pooled estimate of 21.5% (15.4%-28.2%). We included three studies<sup>[40, 43, 119]</sup> from Africa; the pooled prevalence was 15.5% (0.009%-51.5%).

By country, the following estimates were calculated: 30.5% (24.8%-36.4%) from Italy<sup>[11, 21, 35, 44, 49, 52, 65, 69, 71, 74, 112, 115, 116, 135, 136, 139, 141, 142, 150, 158, 163, 164, 173, 174, 178, 179, 191, 197, 199, 211, 220, 225, 229, 230, 238, 253]</sup>, 18.7% (15.0%-22.7%) from Spain<sup>[58, 113, 123, 133, 149, 170, 175, 176, 192, 194, 200, 205, 215, 224, 250, 253, 254]</sup>, 20.5% (17.6%-23.5%) from Germany<sup>[17, 36, 70, 93, 107, 129, 171, 180, 189, 231, 237, 253]</sup>, 19.2% (9.2%-31.8%) from The Netherlands<sup>[26, 32, 104, 127, 152, 162, 167, 168, 235, 261, 279]</sup>, 22.4% (16.4%-29.0%) from Sweden<sup>[16, 33, 55, 57, 66, 140, 188, 265]</sup>, 24.1% (9.2%-43.2%) from Denmark<sup>[16, 42, 189, 203, 260]</sup>, 18.2% (3.6%-40.6%) from Greece<sup>[31, 45, 131, 239, 276]</sup>, 17.0% (6.2%-31.7%) from Poland<sup>[62, 151, 268, 272]</sup>, 30.0% (25.3%-35.0%) from Finland<sup>[16, 48]</sup>, 27.1% (13.3%-43.7%) from Norway<sup>[16, 51]</sup>, 16.3% (7.9%-26.9%) from France<sup>[34, 41, 189, 202, 226, 253, 282]</sup>, 19.4% (12.5%-27.6%) from UK<sup>[90, 156, 204, 223, 227, 242, 253, 270, 277, 283]</sup>, 22.0% (10.7%-35.9%) from Iceland<sup>[16, 68]</sup>, 14.2% (8.6%-21.0%) from Turkey<sup>[12, 23, 27, 39, 59, 63, 72, 102, 103, 138, 160, 198, 241, 248, 258]</sup>, 13.5% (7.8%-20.6%) from India<sup>[22, 105, 108, 110, 128, 147, 186, 216, 233, 244, 247, 257, 263, 266, 271]</sup>, 8.3% (1.6%-19.6%) from Japan<sup>[13, 60, 94, 273, 275]</sup>, 4.9% (1.9%-9.3%) from China<sup>[15, 73, 130, 132, 146]</sup>, 35.5% (11.8%-64.0%) from Thailand<sup>[14, 184, 222, 240]</sup>, 18.5% (5.8%-36.3%) from Taiwan<sup>[206, 255, 267]</sup>, 10.4% (8.3%-12.8%) from South Korea<sup>[54, 217, 245]</sup>, 13.0% (5.5%-23.0%) from Iran<sup>[80, 117]</sup>, 41.8% (35.8%-48.0%) from Pakistan<sup>[88, 246]</sup>, 19.0% (16.3%-21.8%) from the United States<sup>[28, 29, 46, 47, 50, 53, 56, 61, 64, 75, 79, 86, 87, 96-98, 109, 118, 120, 121, 125, 134, 144, 148, 154, 169, 189, 193, 201, 212, 214, 232, 243, 252, 262, 286]</sup>, 24.6% (17.3%-32.7%) from Canada<sup>[91, 95, 189, 196, 218, 236, 280]</sup>, 25.2% (18.6%-32.3%) from Brazil<sup>[137, 172, 190, 208, 209, 219, 228]</sup>, and 17.8% (12.4%-24.0%) from Argentina<sup>[145, 177]</sup> (Figure 2 and supplementary table 1).

### **Prevalence estimates by population size**

The population size per study ranged from 25 to 198,366 patients with psoriasis.

There were 173 studies<sup>[11, 12, 21-26, 29, 30, 32-34, 36-45, 47, 50-55, 57, 59, 62, 63, 66, 67, 69, 72, 74-76, 79-81, 85-88, 90, 92, 98, 102-105, 107, 108, 110, 113, 115-119, 123-129, 131, 136-142, 144-147, 149-152, 155-160, 163-170, 172-181, 184, 185, 190, 191, 194, 196-200, 205, 229, 230, 233, 234, 236, 238-248, 250, 257-259, 263, 266-268, 271-273, 275-277, 279, 280, 282, 283, 287]</sup> with a population of <500

psoriasis patients, with a pooled prevalence of 22.2% (20.0%-24.4%). Thirty-five studies<sup>[27, 31, 49, 61, 64, 65, 70, 73, 77, 82, 91, 94, 95, 101, 106, 109, 111, 114, 121, 133, 189, 193, 195, 208, 211, 213-215, 218, 249, 251, 253, 264, 270, 274]</sup> had study size between 500 and 1000 patients, with a pooled prevalence of 18.5% (15.0%-22.3%), and fifty-seven studies<sup>[13, 15, 17, 28, 46, 48, 56, 58, 60, 68, 71, 83, 84, 89, 93, 96, 97, 100, 112, 120, 130, 132, 135, 143, 148, 154, 161, 162, 171, 182, 186-188, 192, 201, 203, 204, 207, 212, 221, 227, 231, 232, 235, 237, 252, 254-256, 260-262, 265, 269, 278, 285, 286]</sup> had a study population of 1000 or greater resulting in a prevalence of 14.4% (12.5%-16.3%).

### **Prevalence of PsA by publication year and study design**

Stratified by year of publication, there were 13 studies<sup>[21, 42-53]</sup> from pre-2000, resulting in a pooled prevalence estimate of 22.0% (16.1%-28.5%).

There were 51 studies<sup>[12, 16, 17, 22-25, 54-77, 79-97, 282]</sup> and 202 studies<sup>[11, 13-15, 26-41, 98, 100-121, 123-133, 135-182, 184-212, 214-280, 285-288]</sup> published between 2000-2009 and 2010-2017, respectively. The corresponding pooled prevalence estimates were 16.5% (13.1%-20.3%) and 20.4% (19.1%-21.8%), respectively.

There were 34 clinical studies<sup>[25, 42, 61, 67, 76, 77, 81-85, 101, 111, 114, 118, 121, 125, 143, 161, 165, 166, 181, 185, 187, 195, 207, 213, 256, 264, 273, 278, 282, 287, 289]</sup>, resulting in a pooled prevalence of 22.9% (20.7%-25.2%).

Moreover, there were 160 observational studies<sup>[11-15, 21, 23, 24, 26, 27, 29-31, 33-41, 43-47, 49, 50, 52, 54, 55, 62, 63, 65, 66, 69, 70, 72-75, 79, 80, 87, 88, 92, 98, 100, 102-108, 110, 113, 116, 117, 119, 123, 126-133, 135-142, 145, 147, 149-151, 155, 157-160, 163, 164, 167, 169, 170, 172-180, 184, 186, 189-191, 194, 195, 197-200, 205, 206, 208-211, 214-220, 222, 224, 225, 228-230, 233, 238-241, 243-248, 253, 257-259, 263, 266-268, 270-273, 275-277, 280, 283]</sup>, yielding a pooled prevalence of 20.7% (18.3%-23.2%). Pertaining to the register-based studies, 48 such studies<sup>[22, 28, 32, 35, 53, 56, 57, 59, 86, 90, 94-97, 112, 115, 120, 144, 148, 152, 154, 168, 171, 182, 188, 201, 203, 204, 212, 221, 223, 226, 227, 232, 234-236, 250, 252, 254, 255, 260-262, 265, 269, 274, 279]</sup> were included in the analysis, with a pooled prevalence of 15.1% (13.3%-17.1%). Finally, 46 population-based studies<sup>[16, 17, 48, 51, 56-58, 60,</sup>

64, 68, 71, 86, 89-91, 93, 95-97, 109, 112, 120, 146, 148, 154, 156, 162, 188, 192, 193, 201, 202, 212, 221, 223, 227, 231, 235, 237, 242, 249, 251, 260, 262, 285, 286] were included with a pooled prevalence estimate of 15.6% (13.7%-17.7%).

### **Prevalence of PsA by severity of disease**

There were 122 studies<sup>[17, 25, 32, 35, 36, 38, 42, 46, 47, 61, 67, 69, 70, 74, 76, 77, 80-85, 87, 88, 91-93, 95, 100, 101, 104, 106, 107, 109, 111-119, 121-123, 125, 127, 129, 136, 138, 141, 143, 152, 157, 161-163, 165, 166, 168, 171, 173-175, 178, 179, 181, 182, 184, 185, 187, 191, 192, 194-197, 201, 203-207, 210, 211, 213, 214, 216, 217, 220, 222, 224, 226, 229, 230, 233, 234, 236, 241, 243, 250, 252-254, 256-258, 264-269, 273, 274, 277-279, 282, 283, 289]</sup> including psoriasis patients with moderate-to-severe disease resulting in a pooled prevalence of 24.6% (22.9% - 26.4). Furthermore, there were 58 studies<sup>[11, 12, 16, 28, 31, 33, 52, 53, 59, 64, 65, 79, 90, 102, 103, 105, 120, 130, 135, 139, 140, 142, 144, 145, 147, 149, 155, 156, 160, 164, 167, 170, 172, 183, 186, 198, 200, 212, 215, 223, 225, 227, 228, 235, 237, 238, 240, 242, 245, 247, 248, 251, 259, 260, 263, 270, 272, 280]</sup> with mild disease resulting in a pooled estimate of 15.8% (14.3% - 17.2%).

### **Study quality and bias assessment**

A total of 134 studies<sup>[15-17, 21, 22, 27-34, 36, 38, 39, 41, 54, 56, 57, 62, 63, 65, 68-71, 74, 79, 80, 92-95, 97, 98, 100, 103, 104, 106, 107, 112, 115, 117, 119, 120, 127-132, 136, 137, 141, 142, 144, 147-149, 154, 156-160, 162-164, 167, 170-173, 175-178, 180, 182-184, 186, 188-192, 194, 197, 199, 201-204, 206, 209, 211, 212, 215, 218-221, 226, 227, 229, 231, 232, 235, 237, 240, 242, 243, 246-248, 250-252, 254, 255, 260, 262, 263, 265, 268-270, 274-276, 279, 285]</sup> had good quality according to the NOS, with a pooled prevalence of 18.1% (16.6%-19.6%). Furthermore, there were 84 studies<sup>[11-14, 23, 24, 40, 43-53, 55, 58-60, 64, 66, 72, 73, 75, 86-91, 102, 105, 108, 110, 113, 116, 125, 126, 133, 135, 138-140, 145, 146, 151, 155, 169, 174, 193, 198, 200, 205, 208, 210, 214, 216, 217, 223, 225, 228, 230, 233, 234, 236, 238, 239, 241, 244, 245, 249, 253, 257, 258, 261, 266, 267, 271, 272, 280, 283]</sup> categorized as fair or poor quality, entailing an estimate of 21.5% (17.7%-25.6%). Studies categorized as fair or poor quality scored a maximum of 2 regarding the representativeness of the study population. Correspondingly, for studies with good quality 66 of 134 scored at least 4 with a minimum score of 3 for all studies (supplementary table 2).

Furthermore, the Egger test indicated a significant risk of bias for all studies included ( $p < 0.0001$ ).

There was a very high level of heterogeneity between all studies included given by the  $I^2$  of 99.5% (99.5% to 99.5%). The high level of heterogeneity persisted in all subgroups except from Pakistan, South Korea and Argentina from the subgrouping by country where the Cochran Q test was not significant (supplementary table 3).

### **Incidence of PsA among patients with psoriasis**

Ten studies reported incidence estimates of PsA among psoriasis patients. Wilson et al.<sup>[96]</sup> conducted a population-based retrospective cohort study based on medical chart reviews in 1593 psoriasis patients from the United States. Patients were followed for up to 30 years (1970-1999) and the incidence rate was 2.7 per 1000 person-years. Furthermore, a cumulative incidence of 1.7%, 3.1%, and 5.1% was reported at 5-, 10-, and 20-years follow-up, respectively. Li et al.<sup>[290]</sup> reported an annual incidence of 2.1% during 15-years follow-up (1991-2005) in a US population-based setting of women from the Nurses' Health Study.

Furthermore, in a population-based cohort study from UK<sup>[291]</sup> an incidence rate of 26.5 per 10,000 person-years was reported during 15-years follow-up (1995-2010). In a European study enrolling patients from UK, Italy, France, Spain and Germany, Christophers et al.<sup>[100]</sup> followed 1560 patients with plaque psoriasis from secondary care units for a total of 30 years. The cumulative PsA incidence was 13% at 20-years follow-up. Eder et al.<sup>[292]</sup> followed 313 Canadian psoriasis patients for 4 years (2006-2010), mainly enrolled from secondary care clinics, and reported an incidence rate of 1.9 per 100 person-years.

In a study from Italy<sup>[139]</sup> an annual mean incidence of 1.7% was reported at 3-years follow-up (2008-2011) for psoriasis patients attending an outpatient dermatology clinic. Tinazzi et al.<sup>[11]</sup> from Italy, enrolling patients with severe psoriasis, reported a cumulative incidence of 8.4% at 12-months follow-up. Brunasso et al.<sup>[115]</sup> from Italy reported an incidence rate of 22.7 per 1000 person-years during a mean follow-up of 39 months for 55 psoriasis patients treated with Efalizumab. In a study from Canada<sup>[218]</sup> a cumulative incidence

of 8.4% was reported during 8-years follow up (2006-2014). In another prospective cohort study from Canada<sup>[293]</sup> the incidence rate was reported to be 2.7 per 100 person-years at 8-years follow-up (2006-2014).

## Discussion

Quantitative analysis of 266 studies yielded a PsA prevalence of 19.7% among 976,408 patients with psoriasis. The prevalence of PsA was markedly lower in children and adolescents when compared to adults, but equally frequent in both sexes. Notably, higher estimates were found in psoriasis patients with moderate-to-severe psoriasis compared to patients with mild psoriasis suggesting that increased attention is warranted among this group of patients.

The prevalence of PsA among psoriasis patients was lowest in Asia. Previously, Tam et al.<sup>[294]</sup> reported a prevalence range of 1-9% in psoriasis patients from Asia. Moreover, our data show congruence in the estimates from Europe and North America, which is supported by previous findings. Furthermore, the pooled estimate for South America was unexpectedly high in light of a previous review which reported complete absence of psoriasis in the Andean region<sup>[295]</sup>. Studies have shown that both psoriasis and PsA have strong genetic components<sup>[99, 296]</sup>. Accordingly, HLA-C\*06 positivity in psoriasis patients is generally higher in Caucasians compared to Asians<sup>[297]</sup>. Moreover, strong genetic associations have linked HLA-B7, HLA-B27 and HLA-B39 with PsA in particular<sup>[298]</sup> and data has shown higher occurrence of HLA-B27 in non-Hispanics whites.

It is generally accepted that PsA is uncommon in children, which is supported by the pooled prevalence of 3.3%. The low estimate might, at least in part, be explained by lack of clear segregation of PsA from JIA. However, juvenile PsA represents approximately 5% of patients with JIA, emphasizing the importance of

discerning it from JIA as a distinct entity<sup>[299]</sup>. Moreover, PsA in children often presents before psoriasis<sup>[300]</sup>. We only examined studies of those children with psoriasis, and thus children with PsA that developed cutaneous manifestations later on could have been missed in our study. Furthermore, we observed decreasing proportion estimates as the population size increased. This might partly be explained by more thorough examination of psoriasis patients in smaller studies and underdiagnosis of PsA in larger ones, e.g. in register-based studies where PsA assessment is based on diagnostic codes, as such studies may tend to predominantly capture those patients with more severe joint symptoms.

The reported incidence rates ranged from 0.27 per 100 person-years, reported by Wilson et al.<sup>[96]</sup> and Love et al.<sup>[291]</sup> to 2.7 per 100 person-years, reported in a prospective setting by Eder et al.<sup>[293]</sup>. Interestingly, both studies reporting the lowest estimates were conducted in a non-selected population-based setting. However, the higher incidence rates could also be explained by improving diagnostic abilities as there seems to be a link between more recent studies and higher incidence rates.

High levels of heterogeneity were observed between studies both overall and across subgroups. Such heterogeneity may be attributed to the lack of widely accepted diagnostic criteria in the past, different study designs, geographical variations, ethnicity, the remitting and relapsing nature of the disease, and study inclusion criteria, e.g. whether patients with psoriasis were selected from primary, secondary, or tertiary care settings.

In 2015, Villani et al. reported a 15.5% prevalence of undiagnosed PsA among psoriasis patients in a systematic review and meta-analysis<sup>[301]</sup>. However, the focus was only directed to the occurrence of newly diagnosed PsA among patients with cutaneous psoriasis. While few review articles have examined the prevalence of PsA among patients with plaque psoriasis<sup>[301-303]</sup>, these studies have generally applied a narrow search strategy, thus excluding a vast number of relevant studies.



Strengths of this study include the sheer number of studies, the focused inclusion of PsA patients rather than any type of arthritis, the liberal inclusion of various types of study populations and designs and lastly the inclusion of all types of diagnostic methods for PsA. On the other hand, our study was limited by the few studies from Africa and Australia complicating an accurate assessment of the prevalence of PsA among psoriasis patients in these regions. The exclusion of studies written in languages other than English, and a significant risk of publication-bias may also have affected our estimates. Furthermore, due to lack of available data we were not able to assess whether severity of psoriasis could explain the lower prevalence of PsA observed in children and in patients from Asia and Africa.

In conclusion, this meta-analysis showed that one in five patients with psoriasis have PsA, with very consistent results across numerous strata. However, high levels of heterogeneity were observed between the included studies, which may affect interpretation.

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