Clinical, laboratory, and genetic markers for the development or presence of psoriatic arthritis in psoriasis patients: a systematic review

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Abstract
Twenty to thirty percent of psoriasis (Pso) patients will develop psoriatic arthritis (PsA). Detection of Pso patients that are (at risk for) developing PsA is essential to prevent structural damage. We conducted a systematic search of five bibliographic databases, up to May 2020. We searched for studies assessing markers (clinical, laboratory, genetic) associated with the development or presence of PsA in Pso patients. Study selection and quality assessment of the included studies was performed, followed by a qualitative best evidence synthesis to determine the level of evidence for a marker and its association with concomitant/developing PsA in Pso. Overall, 259 possible markers were identified in 119 studies that met the inclusion criteria. Laboratory markers related to inflammation and bone metabolism reached a strong level of evidence for the association (not prediction) of PsA in Pso. Only CXCL10 showed strong evidence for a positive predictive value for PsA in Pso. The importance of timely detecting PsA in a Pso population, and finding more (bio)markers contributing to early detection, remains high.

Keywords: Psoriasis, Psoriatic arthritis, Systematic review, (Bio)marker, Screening, Clinical, Laboratory, Genetic

Introduction
Psoriatic arthritis (PsA) is an immune-mediated inflammatory disease affecting joints and entheses and is strongly associated with psoriasis (Pso). Twenty to thirty percent of Pso patients will develop PsA, with an average lag time between Pso and PsA of 10 years [1, 2]. This lag time creates a unique opportunity to identify patients with an increased risk for (developing) PsA. The (timely) recognition of concomitant PsA, or ideally early prediction, is important, because untreated PsA can lead to irreversible joint damage [3, 4]. Treatment of arthritis leads to an improvement of both function and quality of life [5]. However, patients with Pso are mostly seen by physicians (e.g., dermatologists) who are not trained in recognizing early signs of arthritis. Identifying markers for PsA in patients with Pso can optimize screening to detect the onset of PsA as early as possible.

Current screening strategies mostly use questionnaires based on clinical characteristics to detect PsA [6, 7]. Both characteristics of Pso as well as environmental factors may be relevant variables for PsA screening [8–10]. Next to clinical characteristics, extensive research has been done on genetic markers, in both HLA (human leukocyte antigen) and non-HLA regions [10–12]. Likewise, there are laboratory markers involved in...
inflammation pathways who might be able to help detect PsA in Pso patients [13, 14]. However, most research focuses on the differentiation between Pso and/or PsA on one side and healthy controls on the other side. To our knowledge, no comprehensive overview has been made to summarize the evidence for these clinical, genetic and laboratory markers.

Therefore, we conducted a systematic review to identify possible markers for the onset of PsA in a Pso population, with the purpose of providing a comprehensive summary of the available markers for PsA in Pso.

Material and methods

Protocol
The protocol was designed according to the Preferred Reporting Items for Systematic review and Meta-Analysis [15] and registered in Prospero (CRD42018093982).

Search strategy
Five bibliographic databases (PubMed, EMBASE, Web of Science, Medline and Cochrane) were searched for studies from January 1, 1990, up to April 29, 2020. Search terms compromised keywords involving study population, study design, and etiology (supplementary table 1). In addition, reference lists of included articles were used for cross-reference checking.

Study selection
Studies were screened for eligibility based on title and abstract by two independent reviewers (MM, JV for laboratory and genetic studies; MM and TH for clinical studies). Potentially relevant papers were assessed in full text (MM, TH). Any disagreement was resolved by consensus or by discussion with a third reviewer (JR, MW, JV). Studies were excluded based on the following criteria: (1) < 10 patients per group (Pso and PsA, respectively), (2) age of patients < 18 years, (3) no statistical comparison between Pso and PsA, and (4) languages other than English, German, or Dutch. We primarily focused on studies with a longitudinal design, meaning that the marker was present before the presentation of PsA. A very low number of longitudinal studies was available for laboratory studies (n = 2), and none for genetic studies. To not miss potential relevant markers in these two categories, we also included genetic and laboratory studies with a cross-sectional design (i.e., marker was present at the same time as PsA) as a “second best” option. While these might not be useful to identify predictors for development of PsA, they could provide information about possible markers for comitant PsA.

Data extraction
Data extracted included study design, patient characteristics, markers, and outcome. Extraction was performed by two reviewers, with 10% overlap to check extraction quality (MM, TH).

Assessment of risk bias
Risk bias was assessed using the Newcastle Ottawa Scale for case-control and cohort studies [16]. This tool comprises three domains: selection, comparability, and outcome/exposure. A study was considered of “good” quality when it had a minimum of 3 stars in the selection domain, 1 star in the comparability domain, and 2 stars in the outcome/exposure domain. “Fair” quality was given when a study had a minimum of 2 stars in the selection, 1 star in the comparability, and 2 stars in the outcome/exposure domain [17]. If a study failed to meet these standards, it was considered to be of “poor” quality. Risk of bias assessment was performed by two reviewers (MM, TH) independently. Any disagreement was resolved by consensus or by discussion with a third reviewer (JR, MW, JV).

Best evidence synthesis
For the best evidence synthesis (BES), we included markers that either showed a significant difference between Pso and PsA in at least one study or markers that showed no significant results in at least two studies (i.e., we excluded markers who were only investigated once and showed no association). Markers were grouped into overarching categories (see Tables 1, 2 and 3). In addition, for markers presented as a categorical variable, we used the data of the most extreme level. For example, in the study from Love et al., body mass index (BMI) was categorized into four levels: < 25 (normal), 25–30, 30–35, > 35 kg/m² [33]. For the best evidence synthesis, we looked at the highest level (i.e., BMI > 35 kg/m²) compared to reference level (i.e., BMI < 25 kg/m²). We then assessed the consistency of the results within and across studies. If within a study, a marker was represented in multiple non-hierarchal conceptually similar constructs, we considered the result consistent if ≥ 75% of the constructs pointed in the same direction. Otherwise, we considered the result for that marker “mixed.” For example, one study looked at fracture, any trauma, and trauma leading to medical care [21]. Because two of these were not predictive of PsA, and one was, we considered this study to have “mixed results” with respect to the marker “trauma.”

If across multiple studies, < 75% of studies were in agreement with each other, we considered this “conflicting evidence.” If ≥ 75% of studies were in agreement, we applied the evidence grading according to Sackett [17]. Because only a small minority of the included studies were of “good” quality, we adapted the Sackett best evidence synthesis as follows: strong evidence in case of two or
Table 1 Best evidence synthesis of clinical markers

| Category                  | Marker                        | Good/fair quality studies                                      | Poor quality studies | Evidence                      |
|---------------------------|-------------------------------|-----------------------------------------------------------------|----------------------|-------------------------------|
| Comorbidities             | Diabetes mellitus             | 2x no association [18, 19]                                       |                      | Strong evidence of no association |
|                           | Diarrhea                      | 2x no association [18, 20]                                       | 1x no association [21]| Strong evidence of no association |
|                           | Infection requiring antibiotics| 1x positive association [20]                                    | 1x no association [18]| Conflicting evidence          |
|                           | Uveitis                       | 1x positive association [18]                                    |                      | Moderate evidence of positive association |
| Disease characteristics   | (worsening) Fatigue           | 1x positive association [22]                                    |                      | Moderate evidence of positive association |
| (general)                 | Worsening function            | 1x positive association [22]                                    |                      | Moderate evidence of positive association |
|                           | Younger age at Pso onset      | 2x positive association [23, 24]                                | 1x no association [25]| Conflicting evidence          |
| Disease characteristics   | Arthralgia in women (not men) | 1x positive association [22]                                    |                      | Moderate evidence of positive association |
| (joints)                  | Cortical vBMD entheseal       | 1x negative association [26]                                    |                      | Moderate evidence of negative association |
|                           | Heel pain                     | 1x positive association [22]                                    |                      | Moderate evidence of positive association |
|                           | (worsening) Stiffness         | 1x positive association [22]                                    |                      | Moderate evidence of positive association |
|                           | Structural entheseal lesion   | 1x positive association [26]                                    |                      | Moderate evidence of positive association |
|                           | Worsening pain                | 1x positive association [22]                                    |                      | Moderate evidence of positive association |
| Disease characteristics   | Duration of Pso               | 1x no association [27]                                           | 1x positive association [28]| Conflicting evidence |
| (skin/nails)              | Intergluteal lesions          | 1x positive association [25]                                    |                      | Moderate evidence of positive association |
|                           | Nail pitting                  | 1x positive association [18]                                    |                      | Moderate evidence of positive association |
|                           | Psoriatic nail lesion         | 3x no association [18, 19, 27]                                  | 1x positive association [25]| Strong evidence of no association |
|                           | Scalp lesions                 | 1x no association [27]                                           | 1x positive association [25]| Conflicting evidence |
|                           | Severity of Pso               | 2x no association [20, 27]                                       | 3x positive association [18, 22, 25]| Conflicting evidence |
| Fertility                 | Fertility treatment           | 1x no association [20]                                           | 1x no association [21]| Moderate evidence of no association |
|                           | Hormone replacement therapy   | 1x no association [20]                                           | 1x no association [21]| Moderate evidence of no association |
|                           | Menopause                     | 3x no association [18–20]                                       |                      | Strong evidence of no association |
|                           | Oral contraceptives           | 2x no association [19, 20]                                       | 1x no association [21]| Strong evidence of no association |
|                           | Pregnancy                     | 1x no association [20]                                           | 1x negative association [19]| Conflicting evidence |
|                           | Alcohol consumption           | 3x no association [18–20]                                       | 1x mixed results [29]| Strong evidence of no association |
|                           | Current smoking               | 2x negative association [20, 31]                                | 1x negative association [28]| Conflicting evidence |
|                           | Past smoking                  | 3x no association [18, 29, 31]                                  | 2x no association [28, 32]| Strong evidence of no association |
|                           | Smoking intensity             | 1x negative association [20]                                    | 1x positive association [32]| Limited evidence of positive association |
| Medication                | Corticosteroids use           | 1x positive association [19]                                    |                      | Moderate evidence of positive association |
|                           | Influenza vaccination         | 1x no association [20]                                           | 1x no association [21]| Moderate evidence of
more studies with good or fair quality, moderate evidence in case of two or more studies with low quality or one study of good or fair quality, and limited evidence in case of one study with low quality. In case of two or more good/fair quality studies, the results of the poor quality studies were not taken into account for the BES. The heterogeneity of the markers and statistics precluded a quantitative meta-analysis.

Results
Study selection
The search yielded 5517 non-duplicate articles and, in addition, 14 studies were included via cross-reference checking. After screening on title and abstract, 221 articles were assessed in full text. A total of 119 studies met the selection criteria and were included. Of these, 19 studied clinical markers [18–36], 69 studied laboratory markers [27, 37, 38, 40–55, 57–73, 75–96, 124–133], and 32 studied genetic markers [97–113, 115–123, 134–139]. One study described both clinical and laboratory markers [27]. A flow chart of the selection process is shown in Fig. 1.

Study characteristics
The characteristics of the included studies are listed in supplementary table 2. All clinical studies had a

Table 1 Best evidence synthesis of clinical markers (Continued)

| Category                        | Marker                              | Good/fair quality studies | Poor quality studies | Evidence                  |
|---------------------------------|-------------------------------------|---------------------------|----------------------|---------------------------|
|                                 |                                     |                           |                      |                           |
| Methotrexate use                | 2x no association [18, 19]           |                           |                      | no association            |
| Retinoid use                    | 1x positive association [18]        |                           |                      | Strong evidence of no association |
| Rubella vaccination             | 1x no association [20]              | 1x positive association [21]|                      | Moderate evidence of positive association |
| Tetanus vaccination             | 1x no association [20]              | 1x no association [21]    |                      | Conflicting evidence      |
| Patient characteristics         |                                     |                           |                      |                           |
| Age                             | 4x no association [20, 22, 25, 27]   |                           |                      | Strong evidence of no association |
| BMI                             | 3x no association [18, 22, 27]       | 1x positive association [34]|                      | Conflicting evidence      |
| BMI at 18 years                 | 1x positive association [24]        | 1x no association [34]    |                      | Conflicting evidence      |
| Patient reported family history of PsA | 3x no association [18, 20, 27]   |                           |                      | Strong evidence of no association |
| Female sex                      | 3x no association [20, 22, 27]       | 1x no association [28]    |                      | Strong evidence of no association |
| Hip circumference               |                                     | 1x positive association [34]|                      | Limited evidence of positive association |
| University or high school level of education | 1x no association [20]               |                           |                      | Conflicting evidence      |
| Waist circumference             | 1x no association [20]               | 1x negative association [18]|                      | Strong evidence of no association |
| Waist-hip ratio                 |                                     | 1x positive association [34]|                      | Limited evidence of positive association |
| Weight increase from 18 years   |                                     | 1x positive association [34]|                      | Limited evidence of positive association |
| Physical stress                 |                                     |                           |                      |                           |
| Lifting heavy loads             | 1x positive association [20]         |                           |                      | Moderate evidence of positive association |
| Trauma                          | 2x no association [19, 20]           | 1x mixed results [21]     | 1x positive association [35]| Strong evidence of no association |
| Psychological distress          |                                     |                           |                      |                           |
| Anxiety/depression              | 2x no association [18, 20]           | 1x no association [21]    |                      | Conflicting evidence      |
| Change in work status           | 1x no association [20]               | 1x no association [21]    |                      | Moderate evidence of no association |
| Death of a family member        | 1x no association [20]               | 1x no association [21]    |                      | Moderate evidence of no association |
| Move to a new house             | 1x no association [20]               | 1x positive association [21]|                      | Conflicting evidence      |
| Psychological distress          | 1x no association [32]               | 1x no association [19]    |                      | Strong evidence of no association |

A positive association is defined as a higher risk of PsA when the marker is present/increased/higher. A negative association is defined as a lower risk of PsA when the marker is present/increased/higher.

BMI body mass index, PsA psoriatic arthritis, PsO psoriasis, vBMD volumetric bone mineral density
Table 2 Best evidence synthesis of laboratory markers

| Category | Marker | Good/fair quality studies | Poor quality studies | Evidence |
|----------|--------|---------------------------|----------------------|----------|
| ACPA     | Anti-CCP | 3x positive association [37–39] | 1x not associated [40] | Moderate evidence of positive association |
|          | Anti-MCV | 1x positive association [41] |                      | Limited evidence of positive association |
| Bone metabolism | 25(OH) vitamin D | 2x no association [42, 43] | 3x no association [44–46] | Strong evidence of no association |
|          | Alkaline phosphatase | 1x no association [43] | 2x no association [47, 48] | Moderate evidence of no association |
|          | Calcium | 2x no association [47, 48] |                      | Moderate evidence of no association |
|          | COMP | 1x no association [49] | 1x no association [50] | Moderate evidence of no association |
|          | CPITC2C | 1x positive association [49] |                      | Moderate evidence of positive association |
|          | Osteocalcin | 2x no association [47, 51] |                      | Moderate evidence of no association |
|          | DKK-1 | 1x no association [52] | 1x positive association [53] | Conflicting evidence |
|          | MMP3 | 3x positive association [49, 52, 54] | 1x no association [51] | Strong evidence of positive association |
|          | OPG | 2x positive association [49, 52] | 4x no association [50, 51, 53, 55] | Strong evidence of positive association |
|          | OPG/RANKL ratio | 2x negative association [50, 56] |                      | Moderate evidence of negative association |
|          | Osteoclast precursors | 1x positive association [56] |                      | Limited evidence of positive association |
|          | Phosphate | 1x no association [43] | 1x no association [47] | Moderate evidence of no association |
|          | RANKL | 1x no association [49] | 2x positive association [56, 57] | Conflicting evidence |
|          | Urine Hp | 1x negative association [48] |                      | Limited evidence of negative association |
| Cell culture | IL-2 secretion | 1x positive association [58] |                      | Limited evidence of positive association |
|          | IL-17 secretion | 1x positive association [59] | 1x no association [58] | Conflicting evidence |
|          | (Change in) CXCL10 | 1x positive association [27] | 1x positive association [60] | Strong evidence of positive association |
|          | IL-6 | 1x positive association [61] | 1x positive association [63] | Strong evidence of positive association |
|          | IL-12/23 p40 | 1x no association [49] | 1x positive association [56] | Conflicting evidence |
|          | IL-23 | 1x positive association [65] |                      | Limited evidence of positive association |
|          | IL-33 | 1x positive association [56] |                      | Limited evidence of positive association |
|          | IL-34 | 1x positive association [66] | 1x positive association [56] | Moderate evidence of positive association |
|          | IL-35 | 1x positive association [56] |                      | Limited evidence of positive association |
|          | IL-36a | 1x negative association [56] |                      | Limited evidence of negative association |
|          | IL-38 | 1x positive association [56] |                      | Limited evidence of positive association |
|          | M-CSF | 1x negative association [52] | 1x positive association [53] | Conflicting evidence |
| Category               | Marker                           | Good/fair quality studies | Poor quality studies | Evidence               |
|------------------------|----------------------------------|---------------------------|----------------------|------------------------|
|                        |                                  |                           |                      |                        |
|                        | **TNFα**                         |                           | 2x positive association [56, 64] | Moderate evidence of positive association |
| **Cytologic phenotype**| **CD3+ CD71+ count**             |                           | 1x positive association [58] | Limited evidence of positive association |
|                        | **CD4 + CD45RA-CXCR3 + CCR4-**   |                           | 1x negative association [67] | Limited evidence of negative association |
|                        | **CD4 + CD45RA-CXCR3 + CCR6-**   |                           | 1x negative association [67] | Limited evidence of negative association |
|                        | **CD4 + CD45RA-IFNγ+**           |                           | 1x negative association [67] | Limited evidence of negative association |
|                        | **CD4 + CD45RA-IL17+**           |                           | 1x positive association [67] | Limited evidence of positive association |
|                        | **CD4 + T EMV CXCR3 + CCR4-**    |                           | 1x negative association [67] | Limited evidence of negative association |
|                        | **CD4 + T EMV IL17A+**           |                           | 1x negative association [67] | Limited evidence of negative association |
|                        | **CD8 + CD45RA-CCR6 + CXCR3-CD69+** |                       | 1x positive association [67] | Limited evidence of positive association |
|                        | **CD8 + CD45RA-IL17+**           |                           | 1x positive association [67] | Limited evidence of positive association |
|                        | **CD8 + T EMV CD69+**            |                           | 1x positive association [67] | Limited evidence of positive association |
|                        | **CD8 + T EMV IL17A+**           |                           | 1x positive association [67] | Limited evidence of positive association |
|                        | **CD8 + T EMV CCR6 + CXCR3-CD69+** |                       | 1x positive association [67] | Limited evidence of positive association |
|                        | **CD8 + T EMV CXCR3 + CCR6-CD69+** |                       | 1x positive association [67] | Limited evidence of positive association |
|                        | Mean platelet volume              |                           | 2x positive association [68, 69] | Moderate evidence of positive association |
|                        | Monocyte count                    |                           | 1x positive association [70] | Limited evidence of positive association |
|                        | Neutrophil count                  |                           | 1x positive association [70] | Limited evidence of positive association |
|                        | Neutrophil to lymphocyte ratio    |                           | 1x positive association [70] | Limited evidence of positive association |
|                        | Platelet count                    |                           | 1x positive association [70] | Conflicting evidence |
|                        | Platelet to lymphocyte ratio      |                           | 1x positive association [70] | Limited evidence of positive association |
|                        | White blood count                 |                           | 1x positive association [70] | Conflicting evidence |
| **Inflammation marker**| CRP                              |                           | 5x positive association [43, 49, 54, 66, 71] | Strong evidence of positive association |
|                        |                                  |                           | 1x no association [27] |                        |
|                        |                                  |                           | 8x positive association [44, 47, 53, 56, 70, 72–74] |                        |
|                        |                                  |                           | 4x no association [46, 58, 64, 75] |                        |
|                        | ESR                              |                           | 1x positive association [66] | Conflicting evidence |
|                        |                                  |                           | 1x no association [43] |                        |
|                        |                                  |                           | 5x positive association [44, 47, 56, 70, 74] |                        |
|                        |                                  |                           | 2x no association [62, 75] |                        |
| **Lipid metabolism**   | Adiponectin                       |                           | 1x positive association [71] | Conflicting evidence |
|                        | ApoA to ApoB ratio                |                           | 1x negative association [64] | Limited evidence of positive association |
|                        |                                  |                           | 1x positive association [76] |                        |
Table 2  Best evidence synthesis of laboratory markers (Continued)

| Category     | Marker      | Good/fair quality studies | Poor quality studies             | Evidence                                      |
|--------------|-------------|---------------------------|----------------------------------|-----------------------------------------------|
|              |             |                           |                                  |                                               |
| ApoB         |             | 1x positive association [76]| Limited evidence of positive    |                                               |
|              |             |                           | association                      |                                               |
| CER          |             | 1x positive association [46]| Limited evidence of positive    |                                               |
|              |             |                           | association                      |                                               |
| Glucose      |             | 2x no association [42, 71]| 4x no association [46, 62, 76, 77]| Strong evidence of no association             |
| HDL          |             | 2x no association [42, 71]| 3x no association [62, 72, 77]   | Strong evidence of no association             |
| Insulin      |             |                           | 1x negative association [77]    | Limited evidence of negative association      |
| LDL          |             | 2x no association [42, 71]| 3x no associated [46, 72, 76]   | Strong evidence of no association             |
|              |             |                           | 1x positive association [62]    |                                               |
| LDL:HDL ratio|             | 2x positive association [62, 76]|                          | Moderate evidence of positive association     |
| Leptin       |             | 1x positive association [71]| 1x no association [64]          | Conflicting evidence                          |
| Total cholesterol |   | 1x negative association [42]| 2x no association [76, 77]   | Conflicting evidence                          |
|              |             |                           | 1x positive association [62]    |                                               |
| Total cholesterol/HDL |  | 1x no association [42]| 1x positive association [76]   | Conflicting evidence                          |
| Triglycerides|             | 2x no association [42, 71]| 4x no association [42, 46, 76, 77]| Strong evidence of no association             |
|              |             |                           | 2x positive association [62, 72]|                                               |
| miRNA expression |   |                           |                                  |                                               |
|              |             |                           |                                  |                                               |
| let-7b-3p    |             | 1x negative association [78]|                          | Moderate evidence of negative association     |
| let-7b-5p    |             | 1x negative association [78]|                          | Moderate evidence of negative association     |
| let-7e-5p    |             | 1x positive association [78]|                          | Moderate evidence of positive association     |
| miR-26a-5p   |             | 1x positive association [78]|                          | Moderate evidence of positive association     |
| miR-27a-3p   |             | 1x positive association [78]|                          | Moderate evidence of positive association     |
| miR-27b-3p   |             | 1x positive association [78]|                          | Moderate evidence of positive association     |
| miR-29a-3p   |             | 1x positive association [78]|                          | Moderate evidence of positive association     |
| miR-30e-5p   |             | 1x positive association [78]|                          | Moderate evidence of positive association     |
| miR-92a-3p   |             | 1x negative association [78]|                          | Moderate evidence of negative association     |
| miR-92b-3p   |             | 1x negative association [78]|                          | Moderate evidence of negative association     |
| miR-98-5p    |             | 1x positive association [78]|                          | Moderate evidence of positive association     |
| miR-139-3p   |             | 1x negative association [78]|                          | Moderate evidence of negative association     |
| miR-146a-5p  |             | 1x positive association [78]| 1x positive association [79]   | Moderate evidence of positive association     |
| miR-203a     |             | 1x negative association [78]|                          | Moderate evidence of negative association     |
| miR-486-5p   |             | 1x negative association [78]|                          | Moderate evidence of negative association     |
Table 2 Best evidence synthesis of laboratory markers (Continued)

| Category       | Marker   | Good/fair quality studies | Poor quality studies | Evidence                      |
|----------------|----------|---------------------------|----------------------|-------------------------------|
| mRNA expression whole blood | miR-1180-3p | 1x negative association [78] |                       | Moderate evidence of negative association |
|                | miR-2379-5p | 1x positive association [78] |                       | Moderate evidence of positive association |
|                | miR-3158-3p | 1x negative association [78] |                       | Moderate evidence of negative association |
|                | miR-4732-3p | 1x negative association [78] |                       | Moderate evidence of negative association |
| mRNA expression whole blood | CCL1 | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | CCL7 | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | CCL20 | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | CX3CL1 | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | CXCL2 | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | CXCL5 | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | HAT1 | 1x positive association [81] |                       | Limited evidence of positive association |
|                | IL-3 | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | IL-6 | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | IL-8 | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | IL-17C | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | IL-17F | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | ISG20 | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | MMP-3 | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | NOTCH2NL | 1x negative association [81] |                       | Limited evidence of negative association |
|                | SET2D | 1x negative association [81] |                       | Limited evidence of negative association |
|                | STAT3 | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | STAT6 | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | SYK | 1x negative association [80] |                       | Moderate evidence of negative association |
|                | TBX21 | 1x negative association [80] |                       | Moderate evidence of negative association |
| Serum          | CDSL | 1x positive association [54] |                       | Moderate evidence of positive association |
|                | Creatinine | 1x no association [43] | 1x no association [53] | Moderate evidence of no association |
|                | Complement C9 | 1x negative association [82] |                       | Limited evidence of negative association |
| Category | Marker | Good/fair quality studies | Poor quality studies | Evidence |
|----------|--------|--------------------------|----------------------|----------|
| IFI16    | 1x negative association [83] | | Moderate evidence of negative association |
| sIL2R    | 1x positive association [61] | | Moderate evidence of positive association |
| ITGB5    | 1x positive association [54] | | Moderate evidence of positive association |
| Gelsolin | 1x negative association [44] | 1x positive association [84] | Limited association of negative association |
| K17      | 1x positive association [84]| | Limited evidence of positive association |
| M28P     | 1x positive association [54]| | Limited evidence of positive association |
| MPO      | 1x positive association [54]| | Moderate evidence of positive association |
| PRL      | 1x positive association [85]| | Limited evidence of positive association |
| STIP1    | 1x positive association [84]| | Limited evidence of positive association |
| Uric acid | 1x positive association [86]| 1x no association [88]| Conflicting evidence |
| VCP      | 1x positive association [89]| | Limited evidence of positive association |
| VEGFR-3  | 1x positive association [90]| | Limited evidence of positive association |
| YKL-40   | 1x positive association [91]| | Limited evidence of positive association |
| Skin     | C16ORF61 | 1x positive association [92]| | Limited evidence of positive association |
| CPN2     | 1x positive association [92]| | Limited evidence of positive association |
| CXCL12   | 1x positive association [93]| | Limited evidence of positive association |
| FHL1     | 1x positive association [92]| | Limited evidence of positive association |
| GPS1     | 1x positive association [92]| | Limited evidence of positive association |
| IL23R    | 1x positive association [94]| | Limited evidence of positive association |
| ITGB5    | 1x positive association [92]| | Limited evidence of positive association |
| POSTN    | 1x positive association [92]| | Limited evidence of positive association |
| PP2R4    | 1x positive association [92]| | Limited evidence of positive association |
| SNCA     | 1x positive association [92]| | Limited evidence of positive association |
| SRP14    | 1x positive association [92]| | Limited evidence of positive association |
| SRPX     | 1x positive association [92]| | Limited evidence of positive association |
| Miscellaneous | Anti-ADAMTS-L5 IgG antibodies | 1x positive association [95]| | Limited evidence of positive association |
|         | Anti-LL37 antibodies | 1x positive association [95]| 1x mixed results [82]| Conflicting evidence |
longitudinal design. Two laboratory studies had a longitudinal design and 67 had a cross-sectional design. All of the genetic studies had a cross-sectional design. Based on the criteria described in the best evidence synthesis, 259 markers were selected for further description (clinical 51, laboratory 137, genetic 71), of which 104 were described in multiple studies (clinical 32, laboratory 36, genetic 36). All markers are shown in supplementary tables 3, 4, 5.

Quality assessment
Of the included studies, 19 studies were qualified as good quality, 11 studies were qualified as fair quality, and 89 studies were qualified as poor quality. Quality assessment of the included studies is shown in supplementary tables 6 and 7.

Best evidence synthesis
Qualitative best evidence synthesis is depicted separately for clinical, laboratory, and genetic studies in Tables 1, 2 and 3. With respect to predictive markers for PsA in Pso, we report the markers for which there was at least a moderate level of evidence, or which were investigated in more than one study. With respect to markers associated with the presence of PsA in Pso, we report only the markers which were investigated in more than one study. An overview of the most promising findings is also shown in Fig. 2.

Clinical markers
Strong level of evidence
Strong evidence was available for 13 of the 51 investigated clinical markers. All these markers showed no association with the development of PsA in Pso patients.

These markers included the following: diabetes [18, 19], diarrhea [18, 20], psoriatic nail lesion [18, 19, 25, 27], menopause [18–20], oral contraceptives [19, 20], alcohol consumption [18–21, 28–30], past smoking [18, 20, 28, 29, 31, 32], methotrexate use [18, 19], age [20, 22, 27, 29], a patient reported family history of PsA [18, 20, 27], female sex [20, 22, 27, 28], trauma [19–21, 35], and psychological distress [22, 23]. There was no strong evidence available for clinical markers that had a positive or negative (i.e., protective) association with the development of PsA.

Moderate level of evidence
Moderate evidence was available for 20 of 51 clinical markers. Only six of them were investigated in more than one study. All of these markers showed no association with the development of PsA in Pso. These markers included the following: fertility treatment [20, 21], hormone replacement therapy [20, 21], influenza vaccination [20, 21], tetanus vaccination [20, 21], change in work status [20, 21], and death of a family member [20, 21].

Moderate evidence of a positive association was available for 13 clinical markers. These included the following: uveitis [18], (worsening) fatigue [22], (worsening) function [22], (worsening) pain [22], (worsening) stiffness [22], arthralgia in women [22], heel pain [22], structural enthesal lesions [26], intergluteal skin lesion [25], nail pitting [18], corticosteroid use [19], retinoid use [18], and lifting heavy loads [20].

Moderate evidence of a negative association was available for 1 marker: entheseal cortical volumetric bone mineral density (vBMD) [26].

### Table 2 Best evidence synthesis of laboratory markers (Continued)

| Category        | Marker                                         | Good/fair quality studies | Poor quality studies | Evidence                          |
|-----------------|------------------------------------------------|---------------------------|----------------------|-----------------------------------|
| Arylesterase activity |                                              | 1x positive association [72] |                      | Limited evidence of positive association |
| Hemoglobin                                         |                                              | 1x negative association [70] |                      | Limited evidence of negative association |
| IgG response to C region of m12 protein |                                              | 1x positive association [96] |                      | Limited evidence of positive association |
| Category | Marker | Good/fair quality studies | Poor quality studies | Evidence |
|----------|--------|---------------------------|----------------------|----------|
|          |        | 1x positive association [97] | Limited evidence of positive association |          |
| HLA      | Haplotype B*08:C*07-MICA*00801 | 1x positive association [98] | Moderate evidence of positive association |          |
|          | Haplotype B*18:C*07 | 1x positive association [99] | Limited evidence of positive association |          |
|          | Haplotype B*27:C*01 | 2x positive association [97, 99] | Moderate evidence of positive association |          |
|          | Haplotype B*27:C*02 | 3x positive association [97, 99, 100] | Moderate evidence of positive association |          |
|          | Haplotype B*27:C*02-MICA*00701/026 | 1x positive association [98] | Moderate evidence of positive association |          |
|          | Haplotype B*37:C*06 | 1x negative association [97] | Limited evidence of negative association |          |
|          | Haplotype B*38:C*12 | 3x positive association [97, 99, 100] | Moderate evidence of positive association |          |
|          | Haplotype B*39:01-C*12 | 2x positive association [97, 100] | Moderate evidence of positive association |          |
|          | Haplotype B*57:C*06 | 2x negative association [97, 99] | Moderate evidence of negative association |          |
|          | Haplotype B*57:C*06-MICA*017 | 1x negative association [99] | Limited evidence of negative association |          |
|          | HLA-A*03 | 1x mixed results [101] | Conflicting evidence |          |
|          | HLA-B*08 | 2x positive association [97, 99] | Conflicting evidence |          |
|          | HLA-B*08 | 3x no association [100, 102, 103] | Conflicting evidence |          |
|          | HLA-B*13 | 1x mixed results [101] | Conflicting evidence |          |
|          | HLA-B*18 | 2x no association [102, 104] | Conflicting evidence |          |
|          | HLA-B*27 | 1x positive association [97] | Conflicting evidence |          |
|          | HLA-B*27 | 1x no association [100] | Conflicting evidence |          |
|          | HLA-B*27 | 6x positive association [97, 99, 100, 103–105] | Moderate evidence of positive association |          |
|          | HLA-B*27 | 1x no association [102] | Conflicting evidence |          |
|          | HLA-B*37 | 1x negative association [97] | Conflicting evidence |          |
|          | HLA-B*38 | 3x positive association [97, 99, 100] | Conflicting evidence |          |
|          | HLA-B*38 | 1x no association [104] | Conflicting evidence |          |
|          | HLA-B*38 | 1x mixed results [101] | Conflicting evidence |          |
|          | HLA-B*39 | 1x positive association [100] | Conflicting evidence |          |
|          | HLA-B*39 | 1x mixed results [97] | Conflicting evidence |          |
|          | HLA-B*40 | 1x negative association [97] | Limited evidence of negative association |          |
|          | HLA-B*40 | 1x no association [100, 102, 104] | Limited evidence of negative association |          |
|          | HLA-B*40 | 1x negative association [107] | Limited evidence of negative association |          |
|          | HLA-B*57 | 1x negative association [99] | Moderate evidence of no association |          |
|          | HLA-B*70 | 1x mixed results [101] | Conflicting evidence |          |
|          | HLA-B amino acid position 45 Glu | 1x positive association [106] | Conflicting evidence |          |
|          | HLA-B amino acid position 95 Leu | 1x positive association [102] | Limited evidence of positive association |          |
|          | HLA-B amino acid position | 1x mixed results [103] | Conflicting evidence |          |
| Category | Marker | Good/fair quality studies | Poor quality studies | Evidence |
|----------|--------|---------------------------|----------------------|----------|
| 97 Arg   |        | 1x no association [102]   |                      |          |
| HLA-C*01|        | 1x positive association [99] | 3x no association [97, 100, 102] |          |
| HLA-C*02|        | 2x positive association [97, 99] | 2x no association [100, 102] |          |
| HLA-C*06| 1x negative association [107] | 7x negative association [97, 99, 102–105, 108] | 2x no association [100, 109] | 1x mixed results [101] | Moderate evidence of negative association |
| HLA-C*07|        | 1x positive association [99] | 2x no association [100, 102] |          |
| HLA-C*08|        | 1x negative association [105] |                      |          |
| HLA-C*12|        | 1x positive association [100] | 2x no association [99] |          |
| HLA-C amino acid position 305 Ala | | 1x positive association [102] |                      |          |
| HLA-C rs10484554 | | 1x positive association [110] |                      |          |
| HLA-C rs12191877 | | 1x negative association [111] |                      |          |
| HLA-DQB1*02 | | 1x mixed results [101] | 1x no association [102] |          |
| HLA-DRB1*03 | | 2x no association [101, 102] |                      |          |
| HLA-DR*04 | | 1x positive association [101] |                      |          |
| HLA-DR*07 | | 1x negative association [105] |                      |          |
| HLA-DR*11 | | 1x mixed results [101] |                      |          |
| Non-HLA | ADAMTS9-MAG1 deletion | 1x positive association [112] |                      |          |
| CCR2 rs1799864 | | 1x positive association [113] |                      |          |
| IL1RN rs397211 | | 2x no association [111, 114] |                      |          |
| IL12B rs2082412 | | 2x negative association [111, 114] |                      |          |
| IL12B rs3212227 | | 1x no association [115] | 1x no association [109] |          |
| IL12B rs6887695 | | 1x no association [115] | 1x no association [109] |          |
| IL13 rs1800925 | | 1x positive association [116] | 1x positive association [117] |          |
| IL13 rs20541 | | 2x positive association [114, 117] | 1x not associated [111] |          |
| IL13 rs848 | | 1x positive association [116] |                      |          |
| IL17E rs79877597 | | 1x positive association [118] |                      |          |
| IL23A rs2066807 | | 2x not associated [111, 114] |                      |          |
| IL23R rs11209026 | | 1x no association [115] | 1x no association [109] |          |
Conflicting evidence was available for 13 of 51 clinical markers. These markers included several disease characteristics: younger age at Pso onset [23–25], longer duration of Pso [27, 28], presence of scalp lesions [25, 27], more severe Pso [18, 20, 22, 25, 27, 28], and higher BMI [18, 20, 22, 27, 28, 33, 34]. Conflicting evidence was also found for infection requiring antibiotics [18, 20], pregnancy [19–21], current smoking [18, 20, 28, 29, 31, 32], rubella vaccination [20, 21], university or high school level of education [18, 20, 21, 36], and moving to a new home [20, 21].

**Laboratory markers**

**Strong level of evidence**

Strong evidence was available for nine of 137 investigated laboratory markers. CXCL10 (C-X-C motif ligand 10) was the only laboratory marker which showed a positive association with the development of PsA in Pso patients. It was also the only laboratory marker studied in a longitudinal design.

Four markers showed a strong level of evidence for a positive association with the presence of PsA in Pso: a higher level of matrix metalloproteinase 3 (MMP3) [49, 51, 52, 54], a higher level of osteoprotegerin (OPG) [49–53,
55], a higher level of interleukin 6 (IL-6) [61–64], and a higher level of C-reactive protein (CRP) [27, 43, 44, 47, 49, 53, 54, 56, 62, 64, 66, 70–75, 124, 130].

Five markers showed a strong level of evidence for no association with PsA in PsO: vitamin D [42–45, 130], serum glucose [42, 62, 71, 76, 77, 130], serum triglycerides [42, 46, 62, 71, 72, 76, 77], serum high-density lipoprotein (HDL) [42, 62, 71, 72, 77], and serum low-density lipoprotein (LDL) [42, 50, 51, 55, 62, 71, 72, 76, 130].

**Moderate level of evidence**

Moderate evidence was available for 56 of 137 investigated laboratory markers. Fourteen of these 56 have been investigated in more than one study.

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**Fig. 1** PRISMA flowchart of included studies. PRISMA, preferred reporting items for systematic reviews and meta-analysis; PsA, psoriatic arthritis; PsO, psoriasis.

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**Fig. 2** Overview of most promising predictors for the development of psoriatic arthritis in psoriasis patients. Clinical parameters are depicted in blue, laboratory parameters are depicted in green. The strongest evidence is available for the predictive value of CXCL10, this is depicted in bold. CXCL = C-X-C motif ligand; PsO = psoriasis; vBMD = volumetric bone mineral density.
Of those 14 markers, six showed a positive association with the presence of PsA in Pso: the presence of anti-citrullinated protein antibodies (ACPA) [37–40], a higher level of IL-12/23 p40 [49, 56], a higher level of tumor necrosis factor alpha (TNFα) [56, 64], a higher mean platelet volume (MPV) [68, 69], a higher LDL:HDL ratio [62, 64, 71, 76], and the presence of microRNA miR-146a-50 [78, 79].

Only one of the 14 markers which were investigated more than once showed moderate evidence of a negative association with the presence of PsA in Pso: a lower ratio of OPG to receptor activator of nuclear factor kappa-B ligand (RANKL) was associated with the presence of PsA in Pso [50, 56].

There was moderate evidence for no association for seven laboratory markers: serum alkaline phosphate [43, 47, 48], serum calcium [47, 48], serum cartilage oligomeric matrix protein (COMP) [49, 50], serum phosphate [51, 52, 53], serum cholesterol [42, 64, 66, 70, 74, 75], and antibodies against LL-37 [82, 95].

Conflicting evidence
Conflicting evidence was available for 14 of 137 laboratory markers: markers of bone metabolism (Dickkopf (DKK1) [52, 53]; RANK-L [49–51, 53, 56, 57]), markers of lipid metabolism (serum leptin [64, 71]; total serum cholesterol [42, 62, 71, 76, 77]; total cholesterol: HDL ratio [42, 76]; serum triglycerides [42, 71, 72, 76, 77, 130]), inflammation markers (erythrocyte sedimentation rate (ESR) [43, 44, 47, 56, 62, 66, 70, 74, 75], cell numbers (platelet count [68, 70]; white blood cell count [70, 130]), cell phenotype (IL-17 secretion [58, 59]), cytokine levels (IL-12/23 p40 [49, 56]; macrophage colony-stimulating factor (M-CSF) [52, 53]), uric acid [77, 86–88], and antibodies against IL-37 [82, 95].

Genetic markers

Strong level of evidence
There were no genetic markers which reached a strong level of evidence for a positive, negative, or no association with the presence of PsA.

Moderate level of evidence
Moderate evidence was available for 30 of 71 investigated genetic markers. Twenty-two of those 31 have been investigated in more than one study.

Of these 22 markers, six showed a positive association with the presence of PsA in Pso: the presence of haplotype B*27–C*01 [97, 99], haplotype B*27–C*02 [97, 99, 100], haplotype B*38–C*12 [97, 99, 100], haplotype B*39–01–C*12 [97, 100], the presence of HLA-B*27 [97, 99, 100, 102–105], and the presence of the single nucleotide polymorphism (SNP) rs1800925 in the IL13 gene [116, 117].

Moderate evidence of a negative association was available for three markers: the presence of haplotype B*57–C*06 [97, 99], the presence of HLA-C*06 [97, 99–105, 107–109], and the presence of the SNP rs2082412 in the IL12B gene [111, 135].

There was moderate evidence for no association for 13 genetic markers: the presence of HLA-B*57 [99, 100, 102, 104], HLA-C*01 [97, 100, 102], HLA-DRB1*03 [101, 102], the presence of the SNP rs397211 of IL1RN [111, 135], the presence of the SNP’s rs3212227 [109, 115] and rs6887695 in the IL12B gene [109, 115], the presence of the SNP rs2066807 in IL23A [111, 135], the presence of the SNP rs11209026 in IL23R [109, 115], the presence of the SNP rs610604 in TNFAIP3 (TNF alpha-induced protein 3) [111, 135], the presence of the SNP rs17728338 in TNIP (TNFAIP3-interacting protein) [111, 135], the presence of the SNP rs1076160 in TSC1 (tuberous sclerosis 1) [111, 135], and the presence of TNFa-238 [109, 122] and TNFa-308 [109, 122].

Discussion
In this review, we summarized the available evidence for possible markers for the onset or presence of PsA in a Pso patient population in a systematic way. Thereby, we provide an update and addition to a recent narrative review regarding this subject by Scher et al. [10]. When looking at clinical markers, we found only strong evidence for markers which were not associated with the development of PsA. Regarding laboratory markers, there was strong evidence for the predictive value of (a change in) CXCL10 serum titers [27, 60]. There was also strong evidence for the association with (but not prediction of) PsA of several markers related to bone metabolism [49–55] and inflammation [27, 43, 44, 47, 49, 53, 54, 56, 58, 61–64, 66, 70–75, 130]. With respect to genetic markers, we found no markers which reached a strong level of evidence for the association with PsA.
In line with previous beliefs on possible clinical risk factors [10, 140], we found moderate evidence for a positive association of gluteal fold lesions [25] and nail pitting for the onset of PsA [18]. However, for nail involvement in general (e.g., distal onycholysis, oil drop phenomenon and crumbling), there was strong evidence of no association [18, 19, 25, 27]. Therefore, this relationship seemed to be restricted to this specific nail feature.

Notably, we found conflicting evidence for the predictive value of obesity [18, 20, 22, 27, 29, 33, 34] and psoriasis severity [18, 20, 22, 25, 27, 28] for the development of PsA in Pso patients. These studies may also be prone to bias because patients with severe Pso differ from patients with mild Pso in several aspects. For instance, when looking at Pso severity in particular, one can argue that more severe skin involvement is treated more intensively, thereby possibly suppressing concomitant arthritis. These kinds of bias may be the reason why these frequently reported markers reach conflicting evidence when all the studies are taking into account in a systematic way.

When looking at BMI at one unspecified timepoint, this marker shows conflicting evidence for a relationship with the development of PsA. In three out of five high/fair quality studies, there was no association [18, 22, 27], while two out of five showed a positive association [25, 29]. Even when taking into account that the before mentioned three studies are performed in a partially overlapping cohort, this marker does not reach the 75% agreement level we consider necessary for a conclusive result. Therefore, BMI at any unspecified timepoint may not be specific enough for prediction of PsA. Interestingly, more specified markers of weight and body composition (e.g., recent weight gain, BMI at younger age or abdominal adiposity) showed a positive association with the development of PsA in Pso but were only investigated in one study of poor quality [34]. Increasing the evidence in a more detailed way may be more valid and relevant.

The association of trauma and psoriatic arthritis was theorized to be due to a deep Koeber phenome non [140]. This phenomenon is comparable to the well-known Koeber phenomenon in the skin, where trauma can cause the appearance of new skin lesions. The theory on the deep Koeber phenomenon is based on a study of Thorarensen et al., who used diagnostic codes to establish two comparable cohorts (Pso with and without PsA) [35]. However, when forming cohorts in this way, there is a higher risk of misclassification in either cohort. This study is in disagreement with two other papers with higher diagnostic certainty [19, 20]. Therefore, we concluded that there is currently strong evidence that physical trauma is not associated with a higher rate of PsA in Pso patients.

The relationship between smoking and PsA development has been described previously as the “smoking paradox” [31]. This entails the fact that smoking appears to be a risk factor for PsA when looking at the general population, but this association disappears when only looking at psoriasis patients. This paradox may be explained by collider bias: bias resulting from correcting for a variable which is a common effect of the exposure and outcome [10]. In our review, we found conflicting evidence for an effect of (current) smoking [18, 20, 28, 29, 31, 32]. However, due to this collider bias, it is hard to determine if smoking leads to additional risk for the development of PsA in a PsO population, unrelated to its effect on the development of PsO. Studies focusing on a change in smoking status after the development of PsO may shed a light on this enigma, as suggested by Nguyen [31].

With regard to laboratory markers, only CXCL10 was studied longitudinally. This cytokine was described in two good/fair quality studies; both found an association between CXCL10 and PsA. Pso patients who developed PsA had a higher CXCL10 serum level at baseline [27]. It was also shown that during the evolution to arthritis the serum level of CXCL10 diminished: a larger negative change was associated with a higher risk of PsA [60]. The reason why CXCL10 levels decreased towards the development of PsA is still unknown. One hypothesis could be that the psoriasis patient group with a high level of CXCL10 is more prone to develop arthritis due to its chemoattractant properties on CXCR3+ CD4+ and CD8+ T cells [141]. In the evolution towards clinical manifest PsA, locally produced CXCL10 might get depleted by these infiltrating and locally expanding inflammatory cells, subsequently lowering circulating CXCL10 levels over time. However, since these two studies were published by the same research group, results may be based on (partially) overlapping patient groups. Therefore, the predicting value of CXCL10 should be interpreted cautiously.

With regard to cross-sectional studies, and markers that may indicate the presence of PsA in Pso patients, we found strong evidence for a positive association with PsA in Pso for markers of inflammation and bone. CRP is a well-known, widely used inflammatory marker. We found strong evidence that the CRP level in PsA patients was higher than in patients with Pso only [27, 43, 44, 47, 49, 53, 54, 56, 64, 66, 70–75, 124, 130]. We argue that the co-appearance of joint inflammation is responsible for this observation. However, we found no articles which studied the level of CRP before the start of PsA in Pso. Therefore, it is unknown whether it can be used as a predictive marker. Also, a clear CRP cutoff value for the presence of PsA (and therefore, specificity and sensitivity) is lacking.
Other markers for which strong evidence of a positive association with the development of PsA in Pso exist were IL-6, MMP3, and OPG. IL-6 is widely regarded as a marker for systemic inflammation and an important contributor to the production of CRP by the liver. MMP3 and OPG are associated with bone metabolism; one of the hallmark signs of PsA is new bone formation [142]. Also, untreated arthritis can lead to irreversible erosions [4]. Therefore, it is not surprising that MMP and OPG showed an association with the presence of PsA in our review. In line with CRP, the predictive value of these markers is unknown, because longitudinal studies are not performed yet.

Laboratory markers for cardiovascular disease are studied extensively in psoriatic disease [42, 46, 62, 64, 71, 72, 76, 77, 130]. From these findings, we can conclude with strong evidence that these levels do not differ between psoriasis patients with and without arthritis. This is in contrast to a recent review which showed that the prevalence of cardiovascular comorbidities is higher in patients with PsA when compared to Pso [143]. This suggests that there are additional factors (e.g., systemic inflammation) that play a role in cardiovascular morbidity in PsA.

With respect to genetic markers, we focus here on the most important HLA-markers for PsO and PsA, and the IL-12 – IL-23 – IL-17 axis. The most important genetic marker for psoriasis is HLA-C*06, also known as PSOR1 [144]. This marker is responsible for up to 50% of PsO heritability in the healthy population. It is associated with type-I (early onset) psoriasis, as well as a guttate phenotype [145]. Interestingly, our review shows that, when looking within the population of Pso patients, patients with the HLA-C*06 marker were less likely to also have PsA. Despite multiple studies investigating this marker, high-quality studies are needed to confirm the robustness of the negative relationship between HLA-C*06 and the onset of PsA.

We found a moderate level of evidence for the presence of concomitant PsA in Pso for HLA-B*27, known for its high prevalence (90%) in ankylosing spondylitis (AS) [146]. In other diseases of the spondyloarthritis spectrum, the presence of HLA-B*27 is still higher than in the general population, but less than in AS. Our review showed that the presence of HLA-B*27 was higher in the Pso patients who developed arthritis than in the Pso patients who did not. This could indicate that HLA-B*27 may be able to differentiate between Pso patients who do or do not have PsA, which is also considered a part of the spondyloarthritis spectrum.

When looking at the IL-17/IL-23 axis from a genetic viewpoint, there was moderate evidence that there are no SNPs in the IL23 gene for which the presence differs significantly between PsA and Pso patients [109, 111, 114, 115, 147]. We found limited evidence that the presence of rs79877597 in the IL17 gene was more common in PsA versus Pso patients [118]. With regard to the common IL-12/IL-23 pathway, there was moderate evidence regarding several SNPs in the IL12 gene [148]. We found that the presence of one SNP in IL12 (rs2082412) was lower in PsA versus Pso patients, while other SNPs in this gene showed no difference [109, 111, 114, 115]. While the IL-17/IL-23 axis may be important for the development of psoriatic disease in the general population, these results may indicate that it is of limited importance in the development of PsA in Pso.

The strengths of this study include the extensiveness and systematic way of the search with respect to markers for PsA in patient cohorts with Pso, subsequently providing a comprehensive overview of the available evidence. Also, the intertwining of clinical, laboratory, and genetic markers in a systematic way is unique. By conducting a best evidence synthesis, taking the study quality into account, we made a qualitative overview of the extensive data.

The limitations of this systematic review are mostly due to the limitations of the included studies. Since there were (almost) no prospective/longitudinal studies looking at genetic and laboratory markers, we could only summarize the level of evidence with regard to the relationship between laboratory and genetic markers with the presence of PsA in patients with Pso (i.e., only one predictive factor could be identified). The level of evidence was limited by a paucity of high or fair quality studies. Mostly, this was because of a lack of appropriate definition of patient and control groups, in addition to not adjusting for possible confounders.

Conclusion
This comprehensive systematic review on clinical, laboratory, and genetic markers for PsA in patients with Pso revealed that a useful set of markers is not established yet. There were no clinical or genetic markers with strong evidence which could predict the development of PsA in Pso cohorts. There was strong evidence that laboratory markers related to bone metabolism and inflammation were associated with the presence of PsA. Promising is CXCL10, which reached a strong level of evidence for predicting development of PsA in a Pso population [27, 60]. The importance of timely detecting PsA in a Pso population, and finding more (bio)markers contributing to early detection, remains high.

Abbreviations
ACPA: Anti-citrullinated protein antibodies; Arg: Arginine; AS: Ankylosing spondylitis; BES: Best evidence synthesis; BMI: Body mass index; COMP: Cartilage oligomeric matrix protein; CRP: C-reactive protein; CTx: Collagen type I C-telopeptide; CXCL: C-X-C motif ligand; DKK1: Dickkopf 1; ESR: Erythrocyte sedimentation rate; Glu: Glutamic acid; HDL: High-density lipoprotein; HLA: Human leukocyte antigen; IL: Interleukin; LDL: Low-density lipoprotein; IL12: Interleukin 12; IL17: Interleukin 17; MMP: Matrix metalloproteinase; NA: Non-availability; OPG: Osteoprotegerin; Pso: Psoriasis; PsA: Psoriatic arthritis; PsOR1: Psoriasis 1; PsT1: Psoriasis type 1; Pso: Psoriasis; SNP: Single nucleotide polymorphism; TNF: Tumor necrosis factor; T1: Tumor necrosis factor alpha; TNF-R: Tumor necrosis factor receptor; U: Unavailable; V: Very little; W: Weak; X: X-linked; Y: Strong; Z: Z-linked.
lipoprotein; M-CSF: Macrophage colony-stimulating factor; MMP3: Metalloproteinase 3; MPV: Mean platelet volume; OPG: Osteoprotegrin; PsA: Psoriatic arthritis; PsCS: Psoriasis; RANKL: Receptor of nuclear factor kappa-B ligand; SNP: Single nucleotide polymorphism; TNF: Tumor necrosis factor; TNFαIP: TNF-α-induced protein; TNFIP3: TNF-α-interacting protein; TSC1: Tuberous sclerosis 1; vBMD: Volumetric bone mineral density; VLDL: Very low-density lipoprotein

Supplementary Information
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Additional file 1: Supplementary table 1. Search strategy.
Additional file 2: Supplementary table 2. Characteristics of included studies (n = 119).
Additional file 3: Supplementary table 3. Statistical significance and effect sizes of clinical markers.
Additional file 4: Supplementary table 4. Statistical significance and effect sizes of laboratory markers.
Additional file 5: Supplementary table 5. Statistical significance and effect sizes of genetic markers.
Additional file 6: Supplementary table 6. Quality assessment of cohort studies.
Additional file 7: Supplementary table 7. Quality assessment of case control studies.

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Authors’ contributions
MM, MW, JV were involved in study design. MM, TVH and JV were involved in data collection, under supervision of MW, HK, EdJ, JvdR and JV. MM and TVH performed the data analysis, under supervision of MW, HK, EdJ, EdJ, JvdR and JV. All authors were involved in writing, revision and final approval of the manuscript. MM is the study guarantor.

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Availability of data and materials
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Declarations
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Not required.

Consent for publication
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References
1. Mease PJ, Gladman DD, Papp KA, Khashim MI, Thaci D, Behrens F, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. J Am Acad Dermatol. 2013;69(5):279–35.
2. Tilliet W, Charlton R, Nightingale A, Snowball J, Green A, Smith C, et al. Interval between onset of psoriasis and psoriatic arthritis comparing the UK Clinical Practice Research Datalink with a hospital-based cohort. Rheumatology (Oxford). 2017;56(12):2109–13.
3. Kane D, Stafford L, Bresnihan B, Fitzgerald O. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. Rheumatology (Oxford). 2003;42(12):1460–8.
4. Haroon M, Gallagher P, FitzGerald O. Diagnostic delay of more than 6 months contributes to poor radiographic and functional outcome in psoriatic arthritis. Ann Rheum Dis. 2015;74(6):1045–50.
5. Coates LC, Moverley AR, McInland L, Doherty M, Khamashta MA, O’Dwyer JL, et al. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a UK multicentre, open-label, randomised controlled trial. Lancet. 2015;386(10012):2489–98.
6. Ibrahim GH, Buch MH, Lawson C, Watan X, Rellwell P. Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: the Psoriasis Epidemiology Screening Tool (PEST) questionnaire. Clin Exp Rheumatol. 2009;27(3):469–74.
7. Coates LC, Aslam T; AI BF, Burden AD, Burden-Te M, Caperon AR, et al. Comparison of three screening tools to detect psoriatic arthritis in patients with psoriasis (CONTEST study). Br J Dermatol. 2013;168(4):802–7.
8. Chimenti MS, Triggianese P, De Martino E, Conigliaro P, Fonti GL, Sunzini F, et al. On the pathogenesis of psoriatic arthritis and potential therapeutic targets. Expert Rev Clin Immunol. 2019;15(8):823–36.
9. Solmaz D, Erler Z, Aydin SZ. Update on the epidemiology, risk factors, and therapeutic targets. Expert Rev Clin Immunol. 2019;15(8):823–36.
10. Scher J, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. Nat Rev Rheumatol. 2019;15(3):153–66.
11. Rahmani S, Tioi L, O’Reilly D, Chanudet V, Rahmani P. Characteristics in genetics of psoriatic arthritis. Curr Rheumatol Rep. 2020;22(4):10.
12. Villanova F, Di Meo E, Cinquiglio P, Fonti GL, Sunzini F, et al. An update on the pathogenesis of psoriatic arthritis. Ann Rheum Dis. 2013;72(Suppl 2):ii104–10.
13. Villanova F, Di MP, Nestle FO. Biomarkers in psoriasis and psoriatic arthritis. Ann Rheum Dis. 2013;72(2):104–10.
14. Generali E, Scire CA, Favalieri E, Selmi C. Biomarkers in psoriatic arthritis: a systematic literature review. Expert Rev Clin Immunol. 2016;12(6):651–60. https://doi.org/10.1586/1744666X.2016.1147954.
15. Shamsaee I, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g5647.
16. Wells GA, Shea B, O’Connel D, Peterson L, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
17. Sackett DL. Evidence-based medicine: how to practice and reach EBM: 2nd edition ed. New York: Churchill Livingstone; 2000.
18. Eder L, Haddad A, Rosen CF, Lee KA, Chandran V, Cook R, et al. The incidence and risk factors for psoriatic arthritis in patients with psoriasis: a prospective cohort study. Arthritis Rheumatol. 2016;68(4):915–23.
19. Thumboo J, Kishimoto K, Shibeer MI, Ofallon WM, Crowson CS, Gibson LE, et al. Risk factors for the development of psoriatic arthritis: a population based nested case control study. J Rheumatol. 2002;29(4):577–62.
81. Pollock RA, Abji F, Liang K, Chandran V, Pellett FJ, Virtanen C, et al. Gene expression differences between psoriasis patients with and without inflammatory arthritis. J Invest Dermatol. 2015;135(2):620–3. https://doi.org/10.1038/jid.2014.414.

82. Frasca L, Palazzo R, Chimenti MS, Alvineini S, Tolusso B, Bui L, et al. Anti-LL37 antibodies are present in psoriatic arthritis (PsA) patients: new biomarkers in PsA. Front Immunol. 2018;9:1936.

83. De Andrea M, De Santis M, Caneparo V, Generali E, Sirotti S, Isailovic N, et al. Serum IFI16 and anti-IFI16 antibodies in psoriatic arthritis. Clin Exp Immunol. 2020;2019(11):889–96. https://doi.org/10.1111/cei.13376.

84. Maejima H, Nagashio R, Yanagita K, Harnada Y, Amoh Y, Sato Y, et al. Moein and stress-induced phosphoprotein-1 are possible sero-diagnostic markers of psoriasis. PLoS One. 2014(9)(7):e101773. https://doi.org/10.1371/journal.pone.0101773.

85. Husakova M, Lippert J, Stofa J, Sedova L, Arenderberger P, Lacinova Z, et al. Elevated serum procalcitonin levels as a marker of inflammatory arthritis in psoriasis vulgaris. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2015;159(4):562–6.

86. Tsutura N, Imakuku S, Narisawa Y. Hyperuricemia is an independent risk factor for psoriatic arthritis in psoriatic patients. J Dermatol. 2017;44(12):1349–52.

87. Barba aproja N, Arslas de la Rosa I, Lopez-Medina C, Camacho-Sanchez MDR, Gomez-Garcia I, Velazquez AJ, et al. Cardiovascular risk factors in psoriatic disease: psoriasis versus psoriatic arthritis. Ther Adv Musculoskelet Dis. 2019;11:175920X19880702.

88. Yilmaz E, Tamer E, Artuz F, Kucu Caliskan S, Kookturk F. Evaluation of serum uric acid levels in psoriasis vulgaris. Turk J Med Sci. 2017;47(2):531–4. https://doi.org/10.3906/sag-1512-5.

89. Maejima H, Kobayashi M, Yanagita K, Harnada Y, Nagashio R, Sato Y, et al. Valosin-containing protein is a possible sero-diagnostic marker of psoriatic arthritis. Biomed Res (India). 2017;28(4):442–4.

90. Hong X, Jiang S, Mannoleko N, Vangipuram R, Ramos-Rojas E, Yuan Y, et al. Serum vascular endothelial growth factor receptor 3 as a potential biomarker in psoriasis. Exp Dermatol. 2018;27(9):1053–7.

91. Jensen P, Well C, Mittling K, Poggenborg RP, Ostergaard M, Johansen JS, et al. Plasma YNL-40: a potential biomarker for psoriatic arthritis? J Eur Acad Dermatol Venereol. 2013;27:1815–9.

92. Cretu D, Liang K, Saran F, Batruch I, Diamantis EP, Chandran V. Quantitative tandem mass-spectrometry of skin tissue reveals putative psoriatic arthritis biomarkers. Clin Proteomics. 2015;12(1):1. https://doi.org/10.1186/s12302-015-0027-4.

93. Abdelshaal NH, Elhafawy NG, Abdullahm SM, Sayed S, Saleh NA, Saleh MA. Evaluation of the expression of the stromal cell-derived factor-1 alpha (CXCL-12) in psoriatic patients after treatment with methotrexate. J Dermatol. 2020;19(1):253–8.

94. El-Leithy S, Sherif N, El-Arousy NH, El-Hilaly R, Shakweer MM. Cutaneous immunohistochemical expression of interleukin-23 receptor (IL-23R) in psoriasis and psoriatic arthritis patients: relation to musculoskeletal ultrasound findings. Egypt Rheumatol. 2020;42(4):313–18.

95. Yuan Y, Qiu J, Lin ZT, Wu LW, Cai M, Mui UN, et al. Identification of novel autoantibodies associated with psoriatic arthritis. Arthritis Rheumatol. 2019;71(6):941–51. https://doi.org/10.1002/art.40830.

96. Muto M, Date Y, Ichimiya M, Moriwaki Y, Moni K, Kamiakwai J, et al. Significance of antibodies to streptococcal M protein in psoriatic arthritis and their association with HLA-A*0207. Tissue Antigens. 1999;54(1):175–92.

97. Aterido A, Canete JD, Tornero J, Ferrandiz C, Pinto JA, Gratacos J, et al. Genetic variation at the glycosaminoglycan metabolism pathway
contributes to the risk of psoriatic arthritis but not psoriasis. Ann Rheum Dis. 2019;78(3):x21458. https://doi.org/10.1136/annrheumdis-2018-21458.

103. Bowers J, Ashcroft J, Dand N, Jalali-Najafabadi F, Bellou E, Ho P, et al. Cross-phenotype association mapping of the MHC identifies genetic variants that differentiate psoriatic arthritis from psoriasis. Ann Rheum Dis. 2017;76(10):1774–9.

104. Pollock RA, Chandran V, Pellett FJ, Thavaneswaran A, Eder L, Barrett J, et al. The functional MICA-129 polymorphism is associated with skin but not joint manifestations of psoriatic disease independently of HLA-B and HLA-C. Tissue Antigens. 2013;82(1):43–7.

105. Liao HT, Lin KC, Chang YT, Chen CH, Liang TH, Chen WS, et al. Evidence to support the association with psoriatic arthritis. Hum Immunol. 2005;66(7):836–41.

106. Bostoen J, Van PL, Brochez L, Mielants H, Lambert J. A cross-sectional study on the prevalence of metabolic syndrome in psoriasis compared to psoriatic arthritis. J Eur Acad Dermatol Venereol. 2014;28(4):507–11. https://doi.org/10.1111/jdv.12071.

107. Calabava-Pinto PG, Francescini F, Manera C, Zane C, Prati E, Cretti L, et al. Antiperinuclear factor in psoriatic arthropathy. J Am Acad Dermatol. 1999;40(1 Pt 1):910–3.

108. Eder L, Jayakar J, Shankmugarajah S, Thavaneswaran A, Pereira D, Chandran V, et al. The burden of carotid artery plaques is higher in patients with psoriatic arthritis compared with those with psoriasis alone. Ann Rheum Dis. 2013;72(5):715–20.

109. Engin B, Tanakol A, Bülut H, Songur A, Vedih HE, Gokalp E, et al. Changes in serum TNF-like weak inducer of apoptosis (TWEAK) levels and Psoriasis Area Severity Index (PASI) scores in plaque psoriasis patients treated with conventional versus anti-TNF treatments. Int J Dermatol. 2020;59(2):207–15.

110. Li X, Xiao X, Wang H, Wang Y, Li F, Yang Q, et al. Association of serum uric acid levels in psoriasis: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95(19):e3676.

111. Nair RP, Duffin KC, Helms C, Ding J, Stuart PE, Goldgar D, et al. Genome-wide association study identifies genetic variants in the TNF-alpha gene that may not contribute to the risk of psoriasis. J Investig Dermatol. 2018;138(5):1228–35.

112. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: development of new criteria from among Turkish psoriatic patients. Egyptian Rheumatologist. 2016;38(4):313–7.

113. Kohler T, Grossmann S, Straßmann-Bellinghausen B, Kaluwa W, Reuss E, et al. Differential association of polymorphisms in the TNF-alpha region with psoriatic arthritis but not psoriasis. Ann Rheum Dis. 2002;61(3):213–8.

114. Rentzsch J, Van PL, Brochez L, Mielants H, Lambert J. A cross-sectional study on the prevalence of metabolic syndrome in psoriasis compared to psoriatic arthritis. J Eur Acad Dermatol Venereol. 2014;28(4):507–11. https://doi.org/10.1111/jdv.12071.

115. Calabava-Pinto PG, Francescini F, Manera C, Zane C, Prati E, Cretti L, et al. Antiperinuclear factor in psoriatic arthropathy. J Am Acad Dermatol. 1999;40(1 Pt 1):910–3.

116. Eder L, Jayakar J, Shankmugarajah S, Thavaneswaran A, Pereira D, Chandran V, et al. The burden of carotid artery plaques is higher in patients with psoriatic arthritis compared with those with psoriasis alone. Ann Rheum Dis. 2013;72(5):715–20.

117. Engin B, Tanakol A, Bülut H, Songur A, Vedih HE, Gokalp E, et al. Changes in serum TNF-like weak inducer of apoptosis (TWEAK) levels and Psoriasis Area Severity Index (PASI) scores in plaque psoriasis patients treated with conventional versus anti-TNF treatments. Int J Dermatol. 2020;59(2):207–15.

118. Li X, Xiao X, Wang H, Wang Y, Li F, Yang Q, et al. Association of serum uric acid levels in psoriasis: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95(19):e3676.

119. Mavropoulos A, V missing data and weakened the association between the polymorphism and the risk of psoriasis. J Dermatolog Therapeut. 2017;39(1):25–31. https://doi.org/10.1007/s12300-016-0088-7.

120. Kajewska-Wlodarczyk M, Owczarczyk-Szczotnek A, Placek W. Changes in body composition and bone mineral density in postmenopausal women with chondroitis. Reumatol. 2017;55(5):215–21.

121. Bartosinska J, Kuratk J, Kowal M, Michalak-Stoma A, Krasowska D, Chodorowska G, et al. The expression of selected molecular markers of immune tolerance in psoriatic patients. Adv Clin Exp Med. 2018;27(6):721–5.

122. Eder L, Jayakar J, Shankmugarajah S, Rosén CF, et al. IL13 gene polymorphism is a marker for psoriatic arthritis among psoriasis patients. Ann Rheum Dis. 2011;70(9):1594–8.

123. Bowes J, Ashcroft J, Dand N, Jalali-Najafabadi F, Bellou E, Ho P, et al. Evidence to support the risk of psoriatic arthritis but not psoriasis. Ann Rheum Dis. 2011;70(6):1016–9. https://doi.org/10.1136/ard.2010.143123.

124. Bostoen J, Van PL, Brochez L, Mielants H, Lambert J. A cross-sectional study on the prevalence of metabolic syndrome in psoriasis compared to psoriatic arthritis. J Eur Acad Dermatol Venereol. 2014;28(4):507–11. https://doi.org/10.1111/jdv.12071.

125. Calabava-Pinto PG, Francescini F, Manera C, Zane C, Prati E, Cretti L, et al. Antiperinuclear factor in psoriatic arthropathy. J Am Acad Dermatol. 1999;40(1 Pt 1):910–3.

126. Eder L, Jayakar J, Shankmugarajah S, Thavaneswaran A, Pereira D, Chandran V, et al. The burden of carotid artery plaques is higher in patients with psoriatic arthritis compared with those with psoriasis alone. Ann Rheum Dis. 2013;72(5):715–20.

127. Engin B, Tanakol A, Bülut H, Songur A, Vedih HE, Gokalp E, et al. Changes in serum TNF-like weak inducer of apoptosis (TWEAK) levels and Psoriasis Area Severity Index (PASI) scores in plaque psoriasis patients treated with conventional versus anti-TNF treatments. Int J Dermatol. 2020;59(2):207–15.

128. Li X, Xiao X, Wang H, Wang Y, Li F, Yang Q, et al. Association of serum uric acid levels in psoriasis: a systematic review and meta-analysis. Medicine (Baltimore). 2016;95(19):e3676.
143. Puig L. Cardiometabolic comorbidities in psoriasis and psoriatic arthritis. Int J Mol Sci. 2017;19(1):58. https://doi.org/10.3390/ijms19010058.

144. Boehncke WH, Schon MP. Psoriasis. Lancet. 2015;386(9997):983–94. https://doi.org/10.1016/S0140-6736(14)61909-7.

145. Chen L, Tsai TF. HLA-Cw6 and psoriasis. Br J Dermatol. 2018;178(4):854–62. https://doi.org/10.1111/bjd.16083.

146. Bowness P. HLA-B27. Annu Rev Immunol. 2015;33:29–48.

147. Suzuki E, Mellins ED, Gershwin ME, Nestle FO, Adamopoulos IE. The IL-23/IL-17 axis in psoriatic arthritis. Autoimmun Rev. 2014;13(4-5):496–502. https://doi.org/10.1016/j.autrev.2014.01.050.

148. Aggeletopoulou I, Assimakopoulos SF, Konstantakis C, Triantos C. Interleukin 12/interleukin 23 pathway: Biological basis and therapeutic effect in patients with Crohn’s disease. World J Gastroenterol. 2018;24(36):4093–103. https://doi.org/10.3748/wjg.v24.i36.4093.

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