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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

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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 concomitant 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 compatibility, 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/m^2 [33]. For the best evidence synthesis, we looked at the highest level (i.e., BMI > 35 kg/m^2) compared to reference level (i.e., BMI < 25 kg/m^2). We then assessed the consistency of the results within and across studies. If within a study, a marker was represented in multiple non-hierarchical 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 (general)	(worsening) Fatigue	1x positive association [22]		Moderate evidence of positive association
	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 (joints)	Arthralgia in women (not men)	1x positive association [22]		Moderate evidence of positive association
	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 (skin/nails)	Duration of Pso	1x no association [27]	1x positive association [28]	Conflicting evidence
	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]	1x positive association [28]	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]	1x no association [21]	Conflicting evidence
Intoxication	Alcohol consumption	3x no association [18–20] 1x mixed results [29]	3x no association [21, 28, 30]	Strong evidence of no association
	Current smoking	2x negative association [20, 31] 2x no association [18, 29]	1x negative association [28] 1x no association [32]	Conflicting evidence
	Past smoking	3x no association [18, 29, 31] 1x negative association [20]	2x no association [28, 32]	Strong evidence of no association
	Smoking intensity		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

Table 1 Best evidence synthesis of clinical markers *(Continued)*

Category	Marker	Good/fair quality studies	Poor quality studies	Evidence
				no association
	Methotrexate use	2x no association [18, 19]		Strong evidence of no association
	Retinoid use	1x positive association [18]		Moderate evidence of positive association
	Rubella vaccination	1x no association [20]	1x positive association [21]	Conflicting evidence
	Tetanus vaccination	1x no association [20]	1x no association [21]	Moderate evidence of no association
Patient characteristics	Age	4x no association [20, 22, 25, 27]		Strong evidence of no association
	BMI	3x no association [18, 22, 27] 2x positive association [29, 33]	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] 1x negative association [18]		Conflicting evidence
	Waist circumference		1x positive association [34]	Limited evidence of positive 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 positive association [36]	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 [22] 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

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 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
	Alkalic phosphate	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
	CPII:C2C	1x positive association [49]		Moderate evidence of positive association
	CTX		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] 3x no association [50, 51, 53]	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
Cytokines	(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 [62]	1x positive association [63] 1x no association [64]	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

Table 2 Best evidence synthesis of laboratory markers (Continued)

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-IFNy+		1x negative association [67]	Limited evidence of negative association
	CD4 + CD45RA-IL17+		1x positive association [67]	Limited evidence of positive association
	CD4 + T_{EM}CXCR3 + CCR4-		1x negative association [67]	Limited evidence of negative association
	CD4 + T_{EM}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_{CM}CD69+		1x positive association [67]	Limited evidence of positive association
	CD8 + T_{EM}IL17A+		1x positive association [67]	Limited evidence of positive association
	CD8 + T_{EMRA}CCR6 + CXCR3-CD69-		1x positive association [67]	Limited evidence of positive association
	CD8 + T_{EMRA}CXCR3 + CCR4-		1x negative association [67]	Limited evidence of negative association
	CD8 + T_{EMRA}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]1x no association [68]	Conflicting evidence
	Platelet to lymphocyte ratio		1x positive association [70]	Limited evidence of positive association
	White blood count		1x positive association [70] 1x no association [46]	Conflicting evidence
Inflammation marker	CRP	5x positive association [43, 49, 54, 66, 71] 1x no association [27]	8x positive association [44, 47, 53, 56, 70, 72–74] 4x no association [46, 58, 64, 75]	Strong evidence of positive association
	ESR	1x positive association [66] 1x no association [43]	5x positive association [44, 47, 56, 70, 74] 2x no association [62, 75]	Conflicting evidence
Lipid metabolism	Adiponectin	1x positive association [71]	1x negative association [64]	Conflicting evidence
	ApoA to ApoB ratio		1x positive association [76]	Limited evidence of positive association

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] 1x positive association [62]	Strong evidence of no association
	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] 1x no association [71]	2x no association [76, 77] 1x positive association [62]	Conflicting evidence
	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] 2x positive association [62, 72]	Strong evidence of no association
	VLDL		2x no association [62, 76]	Moderate evidence of no association
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
	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	CD5L	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

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

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]	Limited association of negative association
	K17		1x positive association [84]	Limited evidence of positive association
	M2BP	1x positive association [54]		Moderate 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 [87]	1x no association [88] 1x negative association [77]	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

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 rM12 protein		1x positive association [96]	Limited evidence of positive 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

ACPA anti citrullinated protein antibodies, *ADAMTS* a disintegrin and metalloproteinase with thrombospondin motifs; anti-CCP, anti-cyclic citrullinated protein; *Apo* apolipoprotein, *C16ORF61* endosomal protein sorting factor like (VSP35L), *C2C* collagen fragment neoepitopes Col2-3/4 (long mono), *CCL* C-C chemokine ligand, *CCR* C-C chemokine receptor, *CD*, cluster of differentiation, *CD5L* CD5 ligand, *CER* ceramide, *CM* central memory, *COMP* cartilage oligomeric matrix protein, *CPII* C-propeptide of type II collagen, *CPN2* carboxypeptidase N subunit 2, *CRP* C-reactive protein, *CTX* collagen type I C-telopeptide, *CX3CL* C-X3-C motif ligand, *CXCL* C-X-C motif ligand, *CXCR* C-X-C motif receptor, *DKK* Dickkopf, *EM* effector memory, *ESR* erythrocyte sedimentation rate, *FHL1* four and a half LIM domains, *GPS* G protein pathway suppressor, *HAT* human airway trypsin-like protein, *HDL* high-density lipoprotein, *Hp* hydroxyproline, *IFI* interferon-inducible protein, *IFN* interferon, *IgG* immunoglobulin G, *IL* interleukin, *IL23R* IL23 receptor, *ISG* interferon stimulated gene, *ITGB* integrin beta, K17, keratin 17, *LDL* low-density lipoprotein, *M2BP* Mac-2-binding protein, *M-CSF* macrophage colony-stimulating factor, *MCV* mutated citrullinated vimentin, *miRNA* micro RNA, *MMP* matrix metalloproteinase, *MPO* myeloperoxidase, *mRNA* messenger RNA, *OPG* osteoprotegerin, *POSTN* periostin, *PPP2R4* protein phosphatase 2 phosphatase activator (PTPA);PRL, prolactin, *RANKL* receptor activator of nuclear factor kappa-B ligand, *RNA* ribonucleic acid, *SETD* SET domain protein, *sIL-2R* soluble IL-2 receptor, *SNCA* synuclein alpha, *SRP* signal recognition particle, *SRPX* sushi repeat containing protein X-linked, *STAT* signal transducer and activator of transcription, *STIP* stress-inducible phosphoprotein, *SYK* spleen-associated tyrosine kinase, *TBX* T-box, *TNF* tumor necrosis factor, *VCP* valosin-containing protein, *VEGFR* vascular endothelial growth factor receptor, *VLDL* very low-density lipoprotein

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 entheseal 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 3 Best evidence synthesis of genetic markers

Category	Marker	Good/fair quality studies	Poor quality studies	Evidence
HLA	Haplotype B*08:01-C*07		1x positive association [97]	Limited evidence of positive association
	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*35-C*04-MICA*0201/020	1x negative association [98]		Moderate evidence of negative 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] 3x no association [100, 102, 103]	Conflicting evidence
	HLA-B*13		1x mixed results [101] 2x no association [102, 104]	Conflicting evidence
	HLA-B*18		1x positive association [97] 1x no association [100]	Conflicting evidence
	HLA-B*27		6x positive association [97, 99, 100, 103–105] 1x no association [102]	Moderate evidence of positive association
	HLA-B*37		1x negative association [97] 1x no association [102]	Conflicting evidence
	HLA-B*38		3x positive association [97, 99, 100] 1x no association [104] 1x mixed results [101]	Conflicting evidence
	HLA-B*39		1x positive association [100] 1x mixed results [97]	Conflicting evidence
	HLA-B*40		1x negative association [97]	Limited evidence of negative association
	HLA-B*44		1x negative association [97]	Limited evidence of negative association
	HLA-B*57		1x negative association [99] 3x no association [100, 102, 104]	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] 2x no association [102, 103]	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

Table 3 Best evidence synthesis of genetic markers *(Continued)*

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]	Moderate evidence of no association
	HLA-C*02		2x positive association [97, 99] 2x no association [100, 102]	Conflicting evidence
	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]	Conflicting evidence
	HLA-C*08		1x negative association [105]	Limited evidence of negative association
	HLA-C*12		1x positive association [100] 2x no association [99]	Conflicting evidence
	HLA-C amino acid position 305 Ala		1x positive association [102]	Limited evidence of positive association
	HLA-C rs10484554		1x positive association [110]	Limited evidence of positive association
	HLA-C rs12191877		1x negative association [111]	Limited evidence of negative association
	HLA-DQB1*02		1x mixed results [101] 1x no association [102]	Conflicting evidence
	HLA-DRB1*03		2x no association [101, 102]	Moderate evidence of no association
	HLA-DR*04		1x positive association [101]	Limited evidence of positive association
	HLA-DR*07		1x negative association [105]	Limited evidence of negative association
	HLA-DR*11		1x mixed results [101]	Conflicting evidence
Non-HLA	ADAMTS9-MAG1 deletion		1x positive association [112]	Limited evidence of positive association
	CCR2 rs1799864	1x positive association [113]		Limited evidence of positive association
	IL1RN rs397211		2x no association [111, 114]	Moderate evidence of no association
	IL12B rs2082412		2x negative association [111, 114]	Moderate evidence of negative association
	IL12B rs3212227	1x no association [115]	1x no association [109]	Moderate evidence of no association
	IL12B rs6887695	1x no association [115]	1x no association [109]	Moderate evidence of no association
	IL13 rs1800925	1x positive association [116]	1x positive association [117]	Moderate evidence of positive association
	IL13 rs20541		2x positive association [114, 117] 1x not associated [111]	Conflicting evidence
	IL13 rs848	1x positive association [116]		Moderate evidence of positive association
	IL17E rs79877597		1x positive association [118]	Limited evidence of positive association
	IL23A rs2066807		2x not associated [111, 114]	Moderate evidence of no association
	IL23R rs11209026	1x no association [115]	1x no association [109]	Moderate evidence of no association

Table 3 Best evidence synthesis of genetic markers *(Continued)*

Category	Marker	Good/fair quality studies	Poor quality studies	Evidence
	IL23R rs2201841		1x negative association [111] 1x not associated [114]	Conflicting evidence
	KIR2DS1 pos/C2 neg		1x positive association [119]	Limited evidence of positive association
	LOC100505817 rs4891505		1x positive association [120]	Limited evidence of positive association
	MICA*00701/026	1x positive association [98]		Moderate evidence of positive association
	MICA*00801	1x positive association [98]		Moderate evidence of positive association
	MICA*016	1x negative association [98]		Moderate evidence of negative association
	NFKBIA rs7152376	1x positive association [107]		Moderate evidence of positive association
	PTPN22 rs2476601		1x positive association [121]	Limited evidence of positive association
	TNFa-238		2x not associated [109, 122]	Moderate evidence of no association
	TNFa-308		2x not associated [109, 122]	Moderate evidence of no association
	TNFa-857		1x positive association [109]	Limited evidence of positive association
	TNFacd haplotype a6c1d3		1x positive association [123]	Limited evidence of positive association
	TNFAIP3 rs610604		2x not associated [111, 114]	Moderate evidence of no association
	TNIP rs17728338		2x not associated [111, 114]	Moderate evidence of no association
	TRAF3IP2 rs240993		1x not associated [114]	Limited evidence of no association
	TRAF3IP2 rs458017		1x not associated [110]	Limited evidence of no association
	TSC1 rs1076160		2x not associated [111, 114]	Moderate evidence of no association
	ZNF816A		1x negative association [114]	Limited evidence of negative 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.

ADAMTS a disintegrin and metalloproteinase with thrombospondin motifs, *Arg* arginine, *CCR* C-C motif receptor, *Glu* glutamic acid, *HLA* human leukocyte antigen, *IL* interleukin, *IL1RN* IL-1 receptor antagonist, *IL23R* IL-23 receptor, *KIR* killer-cell immunoglobulin-like receptor, *MAGI* membrane-associated guanylate kinase, *MICA* MHC class I polypeptide-related sequence A, *PTPN22* protein tyrosine phosphatase non-receptor type 22, *TNF* tumor necrosis factor, *TNFAIP* TNF alpha-induced protein, *TNIP* TNFAIP3-interacting protein, *TRAF* TNF receptor-associated factor, *TRAF3IP* TRAF3-interacting protein, *TSC1* tuberous sclerosis 1, *ZNF* zinc finger protein
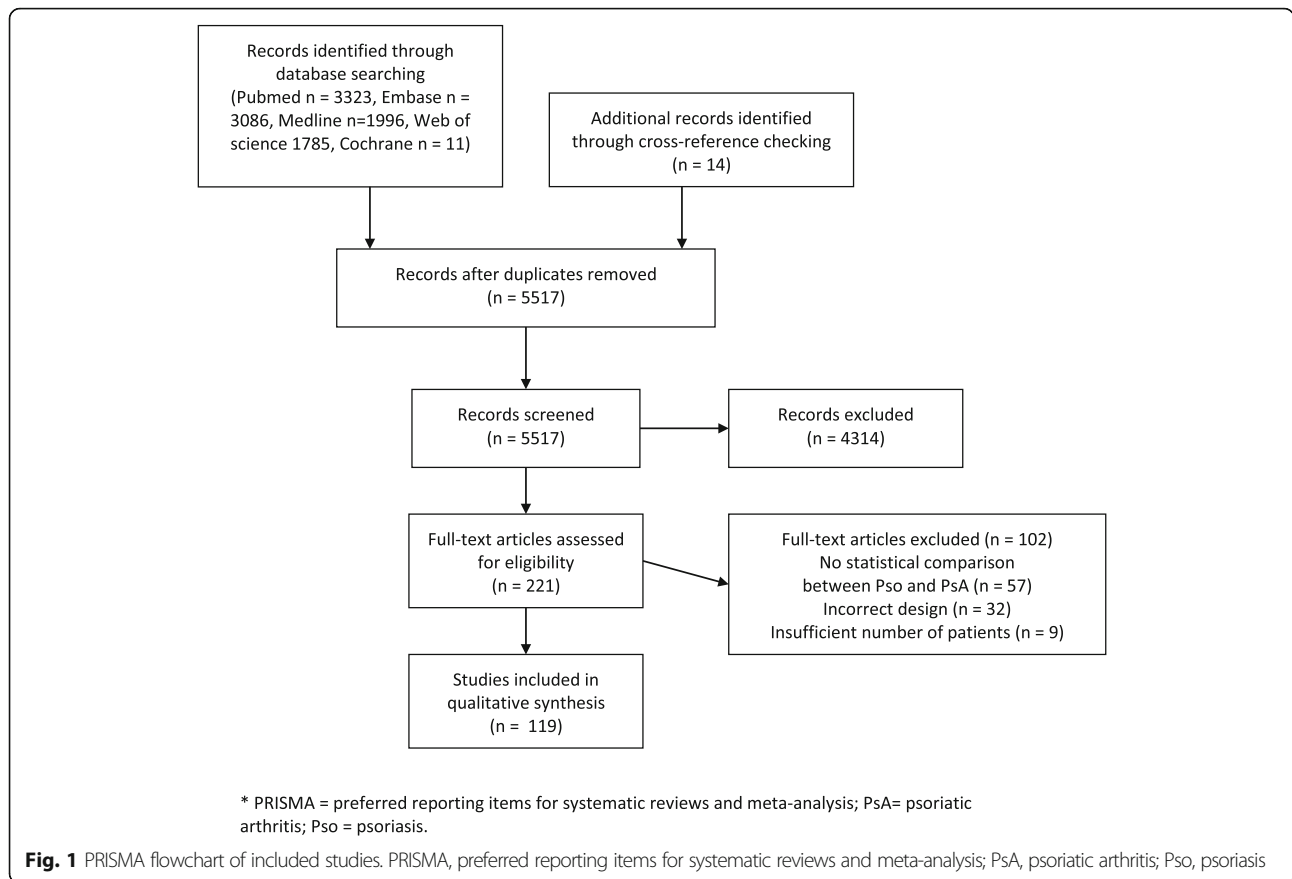
Conflicting evidence

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, 22, 27, 29, 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], anxiety/depression [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,

Fig. 1 PRISMA flowchart of included studies. PRISMA, preferred reporting items for systematic reviews and meta-analysis; PsA, psoriatic arthritis; Pso, psoriasis
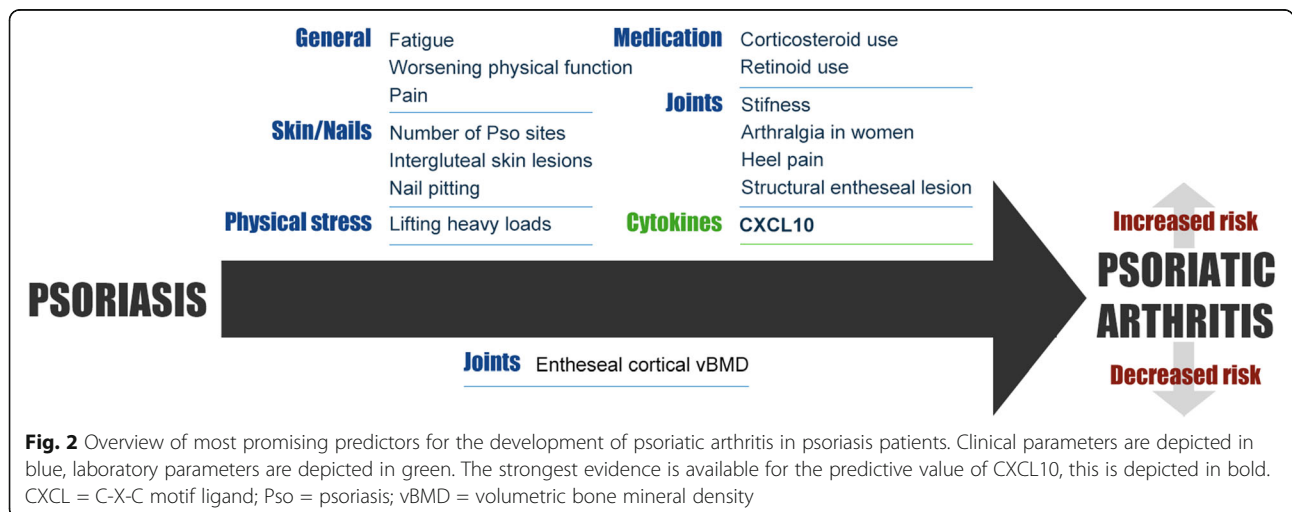
55], a higher level of interleukin 6 (IL-6) [61–64], and a higher level of C-reactive protein (CRP) [27, 43, 44, 47, 49, 53, 54, 56, 62, 64, 66, 70–75, 124, 130].

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, 53, 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.

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-34 [56, 66], 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 alkalic phosphate [43, 47, 48], serum calcium [47, 48], serum cartilage oligomeric matrix protein (COMP) [49, 50], serum phosphate [43, 47], serum collagen type I C-telopeptide (CTx) [47, 51], serum very low-density lipoprotein (VLDL) [62, 76], and serum creatinine [43, 53].

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 LL-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].

Conflicting evidence
Conflicting evidence was found for 17 of 71 genetic markers, of which 14 were investigated in more than one study. These were the presence of HLA-B*08 [97, 99, 100, 102, 103], HLA-B*13 [101, 102, 104], HLA-B*18 [97, 100], HLA-B*37 [97, 102], HLA-B*38 [97, 99–101, 104], HLA-B*39 [97, 100], HLA-C*02 [97, 99, 100, 102], HLA-C*07 [99, 100, 102], HLA-C*12 [99, 100], HLA-DQB1*02 [101, 102], the presence of glutamic acid (Glu) at HLA-B amino acid position 45 [102, 103, 106], the presence of arginine (Arg) at HLA-B amino position 97 [102, 103], the presence of SNP rs20541 in the *IL13* gene [111, 117, 135], and the presence of SNP rs2201841 in the *IL23R* gene [111, 135].

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 [29, 33]. 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 composure (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 Koebner phenomenon [140]. This phenomenon is comparable to the well-known Koebner phenomenon in the skin, where trauma can cause the appearance of new skin lesions. The theory on the deep Koebner 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.

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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 systematic 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, subsequentially 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.

lipoprotein; M-CSF: Macrophage colony-stimulating factor;
MMP3: Metalloproteinase 3; MPV: Mean platelet volume;
OPG: Osteoprotegrin; PsA: Psoriatic arthritis; Pso: Psoriasis; RANKL: Receptor
activator of nuclear factor kappa-B ligand; SNP: Single nucleotide
polymorphism; TNF: Tumor necrosis factor; TNFAIP: TNF alpha-induced pro-
tein; TNIP: TNFAIP3-interacting protein; TSC1: Tuberous sclerosis 1;
vBMD: Volumetric bone mineral density; VLDL: Very low-density lipoprotein

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-021-02545-4.

> **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.

Authors' contributions
MM, MW, JV were involved in study design. MM, TvH and JV were involved in data collection, under supervision of MW, HK, 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.

Availability of data and materials
The data underlying this article will be shared on reasonable request to the corresponding author.

Declarations

Ethics approval and consent to participate
Not required.

Consent for publication
Not applicable.

Competing interests
MM: non-financial support from UCB, outside the submitted work; TvH: per-sonal fees from Eli Lily, non-financial support from UCB, outside the submit-ted work; EdJ: research grants for the independent research fund of the department of dermatology of the Radboud University Medical Centre Nij-megen, the Netherlands from AbbVie, Pfizer, Novartis, Janssen Pharmaceu-tica, and Leo Pharma. Has acted as consultant and/or paid speaker for and/or participated in research sponsored by companies that manufacture drugs used for the treatment of psoriasis including AbbVie, Janssen Pharmaceutica, Novartis, Lily, Celgene, Leo Pharma, UCB, and Almirall. The other authors have nothing to disclose.

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