Infections and the Risk of Psoriatic Arthritis Among Psoriasis Patients

A Systematic Review

Telma Þrastardóttir

**Thesis for Masters Degree (30 ECTS)
University of Iceland
Faculty of Medicine
Department of Public Health Sciences
School of Health Sciences**

HÁSKÓLI ÍSLANDS

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Telma Þrastardóttir

Thesis for the degree of Master of Public Health Sciences

Supervisor: Þorvarður Jón Löve, MD, PhD

Faculty of Medicine

Department of Public Health Sciences

School of Health Sciences

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**Sýkingar og áhættan á
sóragigt hjá sórasjúklingum
*kerfisbundið yfirlit***

Telma Þrastardóttir

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Ágrip

Sóri og sóragigt eru skyldir bólgusjúkómar sem hafa sameiginlega erfða- og umhverfis tengda áhættuþætti. Fyrri rannsóknir hafa gefið til kynna að umverfisþættir, m.a. sýkingar, geti átt þátt í að sórasjúklingar fái sóragigt. Þær takmörkuðu rannsóknir sem hafa verið gerðar gefa vísbendingar um tengsl við sýkingar en hvort að tengslin séu raunveruleg er ennþá á huldu þar sem úrtökin hafa verið lítil og rannsóknirnar byggja aðallega á þversniðs- og aftursýnum gögnum.

Markmið þessarar ritgerðar var að skoða með kerfisbundnum hætti þær rannsóknir sem þegar hafa verið gerðar á tengslum sýkinga við sóragigt og draga niðurstöður þeirra saman í kerfisbundnu yfirliti. Enn fremur sem undirmarkmið að skoða hvort að tengslin virðast vera við bakteríusýkingar, veirusýkingar eða hvoru tveggja. Markmiðið er að undirbúa þannig um leið frekari rannsóknir á þessum mögulegu tengslum og skýra hvert ætti helst að beina þeim.

Kerfisbundin leit var framkvæmd á Cochrane Library, PubMed, Scopus og Web Of Science þann 16. mars 2017 í samæmi við PRISMA viðmiðin. Eftirfarandi leitarorð voru notuð ásamt „psoriatic arthritis“: „infections“, „risk“, „bacteria“ og „virus“. Ágrip voru yfirfarin og niðurstöður sem uppfylltu eftirfarandi skilyrði teknar saman yfirlitið: (I) Athugunar rannsóknir á sóra- og sóragigtar sjúklingum, þ.e. tilfella-viðmiðs-, feril- og vistfræði rannsóknir og (II) innihalda frumgögn um tengsl sýkinga við PsA.

Tuttugu og sjö rannsóknir með frumgögn um sýkingar hjá sóragigtar sjúklingum uppfylltu skilyrðin. Af þeim sýndu 8 rannsóknir tölfraðilega marktæk tengsl milli sýkinga og sóragigtar. Til viðbótar sýndu 7 rannsóknir blandaðar niðurstöður með einhverjum tölfraðilega marktækum tengslum og 5 rannsóknir fundu ekki tölfraðilega marktæk tengsl. Þetta voru rannsóknir á bæði bakteríu- og veirusýkingum, en einnig sýkingum almennt. Þær 7 rannsóknir sem eftir stóðu, skorti gögn til að meta tölfraðilega marktækni.

Þó að rannsóknirnar sem eru teknar saman í þessu yfirliti gefi ekki allar vísbendingar um tengsl sýkinga og sóragigtar, komu fram ákveðnar línur sem gefa tilefni til frekari rannsókna til þess að byggja ofan á þessar niðurstöður. Niðurstöður þeirra rannsókna sem eru teknar saman hér ættu að leiðbeina um hvert ætti helst að beina frekari rannsóknum.

Lykilorð: Sóragigt, sóri, sýkingar og áhætta.

Abstract

Psoriasis and psoriatic arthritis (PsA) are related inflammatory diseases that share genetic and environmental risk factors. Previous studies have suggested that environmental factors, including infections, can trigger the development of PsA among psoriasis patients. Studies completed to date suggest a role for infections as an environmental trigger, but whether there is a true association remains unclear as they are based on small samples and rely mainly on cross-sectional and retrospective data.

The aim of this thesis project was to examine available data evaluating the effects of infections on the risk of developing PsA and to summarize the results in a systematic review article. Further, a secondary aim was to examine whether any observed associations are found with bacterial or viral pathogens, or both. This could then inform further studies on this suggested association, i.e. which subject they should initially focus on.

A systematic search of the Cochrane Library, PUBMED, Scopus and Web of Science was conducted on March 16, 2017, in accordance with the PRISMA statement. The following search terms were used along with „psoriatic arthritis“: „infections“, „risk“, „bacteria“ and „virus“. Abstracts were reviewed and publications meeting the following criteria included: (I) Observational studies on psoriasis and PsA patients, including case-control, cohort or ecologic studies and (II) presenting original data on the association between infections and PsA.

Twenty-seven original studies presenting data on infections among PsA patients were included. Thereof, 8 showed a statistically significant association between infections and PsA. Additionally, 7 studies reported mixed result with some statistically significant associations and 5 studies did not report statistically significant associations. This included both viral and bacterial pathogens in addition to infections in general. The remaining 7 studies lacked data to determine statistical significance.

While the studies summarized did not all provide evidence supporting an association between infections and PsA, certain trends emerged. Further studies are required to build upon these findings. The results reviewed here should guide the focus of future studies.

Keywords: Psoriatic arthritis, psoriasis, infections and risk.

Þakkir

Ég þakka öllum sem aðstoðuðu, studdu og leiðbeindu við verkefnið og ritgerðarskrifin. Fyrst og fremst leiðbeinanda mínum, Þorvarði Jón Löve, fyrir góða leiðsögn, fagleg ráð og lærdómsríkt og skemmtilegt samstarf. Einnig er ég honum afar þakklát fyrir að veita mér þetta tækifæri og leyfa mér að ganga til liðs við hóp rannsakenda sóragigtar í deild lýðheilsuvísinda við Háskóla Íslands.

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List of abbreviations

AHA	American Heart Association
AS	Ankylosing Spondylitis
ASCVD	Atherosclerotic Cardiovascular Disease
B19	Parvovirus B19
BMI	Body Mass Index
CASPAR	Classification Criteria for Psoriatic Arthritis
CD	Celiac Disease
CF	Campylobacter Foetus
CI	Confidence Interval
CI	Campylobacter Intestinalis
CJ	Campylobacter Jejuni
CMV	Cytomegalovirus
CMV-EA	Cytomegalovirus Early Antigen
CP	Chlamydophila Psittaci
CPN	Chlamydophila Pneumonia
CRA	Chronic, treated Rheumatoid Arthritis
CRP	C-reactive Protein
CT	Chlamydia Trachomatis
CVD	Cardiovascular Disease
DIP	Distal Interphalangeal
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic Acid
DVI	Double Virus Infection
EBV	Epstein - Barr Virus
ESR	Erythrocyte Sedimentation Rate
FRS	Framingham risk score
GAS	Group A Streptococci
GBS	Group B Streptococci
GI	Gastrointestinal
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HBDs	Healthy Blood Donors
HCV	Hepatitis C Virus
HD	Healthy Donors
HDL-C	High-density Lipoprotein Cholesterol
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HLT	Healthy Controls
HR	Hazard Ratio
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
IFN- α	Interferon- α
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IRR	Incidence Rate Ratio

LOD	Logarithm of the Odds
LPS	Lipopolysaccharides
NAP	Non-arthritic Psoriasis
NHANESIII	Third National Health and Nutrition Examination Survey
NHS	Nurses' Health Study
NHLBI	National Heart, Lung, and Blood Institute
NORA	New-onset Rheumatoid Arthritis
OA	Osteoarthritis
OR	Odds Ratio
PASI	Psoriasis Area and Severity Index
PBL	Peripheral Blood Lymphocytes
PBMC	Peripheral Blood Mononuclear cells
PG	Peptidoglycan
PGA	Psoriasis Global Assessment
PG-PS	Peptidoglycan-Polysaccharide
PIP	Proximal Interphalangeal
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Psoriasis
PsA	Psoriatic Arthritis
PV	Psoriasis vulgaris
RA	Rheumatoid Arthritis
ReA	Reactive Arthritis
ReA/S	Reactive Arthritis/synovitis
RR	Relative Risk
rRNA	Ribosomal Ribonucleic Acid
RS	Reiter's Syndrome
SCW	Streptococcal Cell Wall preparation
SEA	Staphylococcal enterotoxin A
SEB	Staphylococcal enterotoxin B
SEC1	Staphylococcal enterotoxin C1
SF	Synovial Fluid
SFL	Synovial Fluid Lymphocytes
SNSA	Seronegative Spondyloarthropathy Arthritis
SpA	Spondyloarthropathies
SVI	Single Virus Infection
THIN	The Health Improvement Network
TLR	Toll-like Receptor
YEC	Yersinia Enterocolitica
YPT	Yersinia Pseudotuberculosis

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List of papers

This thesis is based on the following original publication:

Thrastardottir T., Jon Love T. Infections and the risk of psoriatic arthritis among psoriasis patients: a systematic review. Rheumatol Int. 2017 Nov 9. doi: 10.1007/s00296-017-3873-4. [Epub ahead of print]: <https://link.springer.com/article/10.1007/s00296-017-3873-4/fulltext.html>

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1 Introduction

Over 80 chronic autoimmune human diseases have been described to date, which are caused by abnormal response of the immune system to healthy cells and tissues¹. Their prevalence is rising and patients have to deal with lifetime illness, treatment, debilitating symptoms, loss of organ functions, reduced productivity and high medical expenses¹. In addition to personal difficulties, they unavoidably create a burden on society due to the loss of contribution from affected individuals. Generally, the cause of these diseases remains unclear but genetic and environmental factors are known to play a role in their susceptibility and some of them may be triggered by environmental exposures¹. The heritability of autoimmune diseases ranges from 0.008 to 1, with median value of ~0.60². However, increasing interest in environmental factors in susceptibility of autoimmunity is evidenced by the 7% annual increase of environmental trigger publications since 1997². While scientists have tools to analyze genes that are involved in the pathogenesis of diseases, the tools available to examine environmental factors are limited and less advanced¹.

Psoriasis is an autoimmune chronic inflammatory skin disease affecting 2-3% of the population and is therefore considered a common disorder³. Predominately the skin is affected, but psoriasis can be associated with inflammation of other organ systems; such as the musculoskeletal system, the gastrointestinal system and eyes⁴. Less common, but closely linked to psoriasis is the inflammatory joint arthritis, psoriatic arthritis (PsA), which 5-42% of psoriasis patients develop⁵. Psoriasis and PsA share some genetic and environmental risk factors. Furthermore, it has been hypothesized that psoriasis patients with predisposing genetic factors may develop PsA after exposure to an environmental trigger⁶. The particulars, including effect sizes, remain largely unclear. One environmental risk factor suggested in prior research includes infections. Finally, emerging trends and evidence highlight that infectious agents, as triggers of autoimmune disease, may have a larger role in the pathogenesis of PSA than previously imagined¹.

This master thesis summarizes the current literature on the association of infections and the development of PsA among psoriasis patients.

1.1 Psoriasis

Psoriasis skin disease is associated with increased morbidity and has a major impact on health and quality of life⁴. Psoriasis is more frequent in certain racial groups and geographical areas, being more common among Caucasians and in colder northern climates than in tropical ⁷. The mean age of onset is around 28 years' age and both genders are equally affected. Yet, women tend to have an earlier onset^{7, 8}. The pathogenesis of psoriasis involves abnormal activation of the immune system in the skin where T cells are triggered and cytokines released. The classic psoriatic plaques are well defined erythematous lesions with sharp borders. Phenotypes of psoriasis can present as acute with sudden outbreak of lesion within a short time (days) or chronic where lesions persist unchanged for months or even years⁹.

Several tools have been developed to evaluate the severity of the disease. The psoriasis area and severity index (PASI) score is commonly used and results in a single score indicating the severity of

the disease from 0-72¹⁰. The PASI score is based on assessment of four body regions (head, trunk, upper and lower extremities) of erythema, infiltration and desquamation, and body surface involvement¹⁰. The degree of severity per body region gets a score from 0 for no symptoms to 4 when involvement of the body region is very marked. Likewise, the surface involved per body region gets a value from 1 when the surface involved is <10% up to 6 when the surface involved is 90-100%¹⁰. More tools have been developed, like the psoriasis global assessment (PGA) which is more intuitive than PASI and assigns a single estimate of overall severity of the disease in a seven-point scale from clear (no signs of psoriasis) to severe (very marked)¹⁰.

1.1.1 Association of arthritis with psoriasis

The association of arthritis with psoriasis was first described by the French Jean Lous Alibert in 1818 and represents the first disease association observed in dermatology⁹. Psoriasis typically precedes joint manifestations, by 10 years on average, but joint manifestations can also occur before skin symptoms; this is the case in about 10% of patients^{11, 12}. The true prevalence of PsA is uncertain and might be underestimated since some psoriasis patients are unaware of their PsA and have not been diagnosed, e.g. by a rheumatologist. This was illustrated in a German study of 2009 psoriasis patients where 19% of the patients had a probable or confirmed PsA diagnosis, 7.7% had unspecific joint symptoms which could not be clearly attributed to PsA and 4.2% patients were diagnosed for the first time with PsA during the study¹¹. The prevalence of undiagnosed PsA among psoriasis patients seeing dermatologists was recently analyzed in a meta-analysis of 12 studies and the point prevalence of PsA was found to be 15.5%, 95% confidence interval (CI) 11.5-19.5, among the psoriasis patients¹³. As the authors rightly point out, this evaluation of undiagnosed PsA does not apply to the general population, only to psoriasis patients who are already seeing a dermatologist. Since the majority of patients initially show skin symptoms, there is an opportunity for dermatologists to look out for and be aware of joint symptoms among their psoriasis patients¹¹.

All patterns of psoriasis, from small patches to widespread, may be observed in association with arthritis but the risk of PsA may increase with more extensive and severe psoriasis^{11, 14}. In a population based cohort study by Wilson et al., which followed 1,593 psoriasis patients over a 30-year period, the risk of PsA was significantly increased with scalp psoriasis lesions having a hazard ratio (HR) of 3.89 (95% CI 2.18-6.94), nail dystrophy with a HR of 2.93 (95% CI 1.68-5.12), interguteal/perianal psoriasis lesions with a HR of 2.35 (95% CI 1.32-4.19) and patients with ≥ 3 psoriasis lesions¹⁵. Furthermore, nail involvement seems to be a predicting factor for PsA as was concluded by Langenbruch et al. in a retrospective study of 4,146 psoriasis patients with an odds ratio (OR) of 2.93 (95% CI 2.51-3.42, $p < 0.001$)¹⁶. Inpatient hospital treatment due to psoriasis at least once in the last five years was also found to be a predicting factor for PsA with an OR of 1.63 (95% CI 1.38-1.93, $p < 0.001$) while scalp involvement was not found to be significant in that study¹⁶.

1.2 Psoriatic arthritis

Psoriatic arthritis (PsA) is an inflammatory arthritis which belongs to a group of diseases known as seronegative spondyloarthropathies (SpAs). It is usually negative for rheumatoid factor or in about

95% of cases¹². This spondyloarthritides are characterized by involvement of the spine, peripheral arthritis and enthesitis¹⁷. In addition to PsA, SpAs include ankylosing spondylitis (AS), reactive arthritis (ReA), enteropathic, and undifferentiated SpA.

PsA can begin in early childhood but the mean age of onset is 36 years¹². Both genders are equally affected with a male to female ratio close to 1:1¹². Nonetheless, some studies have suggested that PsA is more common among women as indicated in a study by Love et al. where the female to male ratio approached 2:1 among 156 PsA patients⁸. Like psoriasis, PsA is associated with increased morbidity compared to the general population and has a major impact on patients' health and quality of life^{18, 19}. Compared to psoriasis, PsA has even larger effects on patient quality of life as evidenced by the results of a prospective cross-sectional study of 1,511 psoriasis and 312 PsA patients. The PsA patients had lower quality of life with a mean dermatology life quality index (DLQI) of 11.6 compared to 7.7 among the psoriasis patients ($p < 0.0001$)²⁰. The DLQI measures how much the skin problem is affecting the individuals life and consists of ten items which give a total score from 0-1 for no effect to 21-30 for extremely large effect on patients life²¹. PsA patients were also more likely to have been hospitalized due to psoriasis within the last five years or 42.6% vs. 22.6% ($p < 0.0001$)²⁰. Additionally, the number of patients with lost work days and the number of work days lost in the last 12 months were higher among the PsA patients compared to the psoriasis patients, 10.1% vs. 37.4% ($p < 0.0001$) and a mean of 9.5 days vs. 2.6 days ($p < 0.0001$)²⁰.

1.2.1 Clinical characteristics

Clinical characteristics of PsA include peripheral arthritis involving few small joints in asymmetrical fashion, involvement of distal interphalangeal (DIP) joints, sausage digits, arthritis mutilans, ankylosing spondylitis, and higher incidence of nail involvement than occurs in uncomplicated psoriasis¹⁴. The original diagnostic criteria for PsA were published by Moll & Wright in 1973. Their criteria, often referred to as the Moll & Wright criteria, are as follows:

- Inflammatory arthritis, spinal arthritis (sacroiliitis or spondylitis) as well as peripheral arthritis
- Presence of psoriasis
- Negative serologic test for rheumatoid factor (usually)¹⁴

Further, five clinical subtypes of PsA have been defined. The oligoarticular type affecting fewer than four joints, the polyarticular type affecting four or more joints, the distal type affecting DIP joints of the hands and/or feet, arthritis mutilans which involves marked bone resorption or osteolysis and finally the axial or spondyloarthritis type which primarily involves the spine and sacroiliac joints¹². Enthesitis is reported in 30-50% of patients and dactylitis in 40-50%, most prevalent in the third and fourth toes but may also involve fingers. Peripheral joints are affected in 96% of PsA cases and axial joints in 50% of cases¹². Spinal involvement is present in more than 40% of PsA patients, i.e. in the sacroiliac joint or the lumbar, thoracic or cervical spine¹². Since the Moll & Wright criteria were published, several classification criteria have been proposed and used. The most recent and commonly applied today are

the classification criteria for psoriatic arthritis (CASPAR) criteria which was constructed from an international study of observed data from 13 countries, including 588 cases and 536 controls with RA (n=384), AS (n=72), undifferentiated arthritis (n=38), connective tissue disorder (n=14) and other diseases (n=28)²². This criteria involves inflammatory articular disease with at least three points from the following:

- Current psoriasis (2 points)
- History of psoriasis, unless current psoriasis was present (1 point)
- A family history of psoriasis, unless current psoriasis was present or there was a history of psoriasis (1 point)
- Dactylitis (1 point)
- Juxta articular new bone formation (1 point)
- Rheumatoid factor negativity (1 point)
- Nail dystrophy (1 point)

The CASPAR criteria are simple and highly specific but less sensitive compared to others. Unsurprisingly, the single most important clinical feature of PsA is the presence of psoriasis¹⁷, hence it is one third of the items in the Moll & Wright criteria and the only item which scores two points in CASPAR. Both mentioned criteria, Moll & Wright and CASPAR, involve a negative of rheumatoid factor as supporting evidence for PsA but a positive rheumatoid factor does not exclude PsA diagnosis¹⁷.

The joints that are most frequently the initial sites for PsA are small joints, the proximal interphalangeal (PIP) joints and DIP joints of the hands¹⁴. The terms „sausage fingers“ or „sausage digits“ are sometimes used to describe a diffuse uniform swelling of an entire finger or toe²³. Results from a study using Doppler ultrasound to examine extra synovial involvement in PsA patients, compared to that seen in fingers of RA patients, suggest that while like in RA the finger of a PsA patient has involvement of the synovial membrane PsA patients also have enthesopathy with inflammation of the fibrous skeleton. Further, that involvement of the fibrous skeleton might be used to distinguish PsA from RA²³. Small joint involvement has also been found to be associated with onycholysis, among PsA patients with an OR of 3.42 (95% CI 1.41-8.92)¹⁵. Onycholysis is a subtype of nail changes in psoriasis, characterized by loosening or separation of the nail plate from the nail bed, and manifests as a whitish discoloration of the nail²⁴. In fact, nail changes are common among PsA patients and are therefore commonly discussed as a clinical feature of PsA.

1.2.1.1 *Nail changes*

Nail changes or nail dystrophy can be found in up to 50% of psoriasis patients but are seen in up to 85% of PsA patients^{25 24}. As previously mentioned, nail dystrophy has been found to be a predicting factor for the development of PsA among psoriasis patients, as psoriasis patients with nail dystrophy are nearly three times more likely to develop PsA compared to psoriasis patients without nail dystrophy¹⁵. Types of nail changes involve nail pitting, discoloration, onycholysis, subungual

hyperkeratosis and splinter hemorrhages²⁴. Since nail lesions are uncommon in other forms of spondyloarthritis, i.e. AS, ReA and inflammatory bowel disease (IBD) associated arthritis, they are considered characteristic for PsA¹².

Types of nail changes among 1,116 psoriasis patients were analyzed in a cross-sectional study by Love et al. Altogether 139 of the 183 PsA cases returned for further participation in the study and were followed and evaluated for up to six years. Association was found with onycholysis in a multivariate analysis with OR 2.05, $p < 0.001$ ²⁶ suggesting that onycholysis is the form of nail change which is most closely associated with PsA. Regarding nail pitting, previous studies have shown mixed results. Some suggests that nail pitting is less specific for psoriatic disease while other suggest an association. Nail pits are superficial depressions within the nail plate which can vary in morphology and distribution²⁴. A recent prospective cohort study of 464 psoriasis patients, free from PsA at baseline, which were followed up for eight years found an association between nail pitting and the development of PsA with a relative risk (RR) of 2.5 (95% CI 1.37-4.49, $p = 0.002$)²⁷. Unlike the previously mentioned study, their data did not support a statistically significant association with onycholysis.

Though it is unclear why nail dystrophy is associated with a higher risk of developing PsA, and the underlying mechanisms are not known, it has been speculated that inflammation of enthesal complexes may link the fingernail and the synovium. Regardless of the mechanism involved the data clearly support nail changes as a predictor for the development of PsA¹⁵.

1.3 Comorbidities

Like psoriasis, PsA is associated with increased morbidity compared to the general population¹⁹. Psoriasis and PsA have some common comorbidities and therefore it can be complicated to separate the effects of the skin disease from the effects of PsA.

1.3.1 Cardiovascular and associated risk factors

A meta-analysis of 75 studies, involving 503,686 cases and 29,686,694 controls, showed an association of psoriasis with cardiovascular disease (CVD) with a combined OR of 1.4 (95% CI 1.2-1.7)²⁸. Association of psoriasis with cardiovascular associated risk factors were also found: diabetes with OR 1.9 (95% CI 1.5-2.5), hypertension with OR 1.8 (95% CI 1.6-2.0), dyslipidemia with OR 1.5 (95% CI 1.4-1.7), obesity by BMI with OR 1.8 (95% CI 1.4-2.2), obesity by abdominal fat with OR 1.6 (95% CI 1.2 – 2.3) and the metabolic syndrome with OR 1.8 (95% CI 1.2 – 2.8)²⁸. Even stronger associations were found in this study with PsA compared to psoriasis, but this was not described further numerically in the report. The authors point out that PsA may reflect a more severe disease or that joint pain causes immobility and therefore a more sedentary lifestyle. No association between psoriasis and cerebrovascular disease or cardiovascular mortality was found. Therefore, psoriasis patients seem to have a higher risk of cardiovascular disease despite it not being their cause of death.

Other studies have focused on patients with PsA. A population based cohort study by Ernste et al. reported on the associations of CVD with PsA. The prevalence of CVD risk factors and CVD events in a cohort of 158 newly diagnosed PsA patients who fulfilled the CASPAR criteria in 1989-2008 were examined and followed until April 10, 2013. The 10-year cumulative incidence of CVD events was

17% (95% CI 10-14%) in this cohort²⁹. Compared with the 9.7% cumulative 10-year incidence of CVD events predicted by the Framingham Risk Score (FRS), the observed incidence was nearly double that, suggesting the FRS is not able to accurately predict the risk of CVD among patients with PsA. The association of hypertension with psoriasis and PsA was analyzed in a meta-analysis of 24 observational studies with approximately 2.7 million participants, thereof 309,460 psoriasis patients. A random effects model yielded an OR of 1.30 (95% CI 1.15-1.47) for hypertension among psoriasis with mild psoriasis and an OR of 1.49 (95% CI 1.20-1.86) for hypertension among patients with severe psoriasis, compared to controls³⁰. The odds were even greater for PsA patients with a pooled OR of 2.07 (95% CI 1.41-3.04) for hypertension³⁰.

A survey of 5,604 psoriasis patients conducted by the National Psoriasis Foundation from 2003 – 2011 found that patients with more severe psoriasis have an increased risk of diabetes with an OR of 1.5 (95% CI 1.01-2.24) compared to patients with mild to moderate psoriasis³¹. An increased risk of diabetes has likewise been found among PsA patients. The incidence of diabetes among PsA patients was examined in a population-based cohort study, using data from the health improvement network (THIN), representative of the UK population. The study cohort consisted of 4,196 PsA patients, 59,281 psoriasis patients and 11,158 RA patients who were age, sex and cohort entry matched with up to 10 individuals and followed until diagnosis of diabetes, death or the end of follow up time. Increased risk of diabetes was found among the PsA patients with a HR of 1.72 (95% CI 1.46-2.02) and 1.43 (95% CI 1.2-1.7) for the psoriasis patients³². When adjusted for BMI, smoking and alcohol the HR remained significant but attenuated to 1.43 (95% CI 1.2-1.7) for PsA and 1.24 (95% CI 1.18-1.31) for psoriasis³². The authors point out that lifestyle factors and obesity can partially explain the increased risk of diabetes among PsA and psoriasis patients³². In addition to an increased risk of diabetes, insulin resistance has been found to be associated with more severe PsA with an OR of 3.49 (p=0.03), even after adjusting for presence of the metabolic syndrome³³.

Previous studies have found an association of PsA with the metabolic syndrome which predisposes to an increased risk of diabetes and atherosclerotic cardiovascular disease (ASCVD). The prevalence was determined in a retrospective analysis of 105 PsA patients where the metabolic syndrome was defined using the criteria of the American Heart Association (AHA) and National Heart, Lung, and Blood Institute (NHLBI). According to those criteria the metabolic syndrome is diagnosed if three of the five following features are present:

- Elevated waist circumference: ≥ 102 cm (40 inches) in men and ≥ 88 cm (35 inches) in women
- Elevated triglycerides: ≥ 150 mg/dl (1.7 mmol/L) or drug treatment for elevated triglycerides
- Reduced High-density lipoprotein cholesterol (HDL-C): < 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.3 mmol/L) in women, or drug treatment for reduced HDL-C
- Elevated blood pressure: ≥ 130 mmHg systolic blood pressure or ≥ 85 mmHG diastolic blood pressure or antihypertensive drug therapy

- Elevated fasting glucose: ≥ 100 mg/dL or drug treatment for elevated glucose³⁴

The results showed a very high prevalence of the metabolic syndrome among the PsA patients or 58.1% compared to 35.2% reported in data from the third national health and nutrition examination survey (NHANESIII)³⁵. The most common feature of metabolic syndrome among the PsA patients were elevated triglycerides (54.3%), reduced HDL-C (51.4%) and elevated blood pressure (56.2%)³⁵. As with insulin resistance, the metabolic syndrome has been found to be associated with more severe PsA with an OR of 4.47 ($p < 0.001$)³³.

In summation, there is strong evidence for an association between psoriatic disease in general and PsA in particular on the one hand and cardiovascular risk factors and cardiovascular disease on the other. This suggests that there is a good reason to screen psoriasis and PsA patients for these comorbidities. Lifestyle interventions or drugs might be appropriate to manage these risk factors.

1.3.1 Gastrointestinal

Association of common gastrointestinal (GI) diseases with PsA was evaluated in a large retrospective study of 3,161 PsA patients and 31,610 randomly selected patients (10 for each PsA case), matched for age and sex, between 2002 and 2013. Adjustments for known risk factors were made and association found with Crohn's disease with an OR of 2.2 (95% CI 1.59-3.03, $p < 0.0001$), ulcerative colitis with an OR of 1.9 (95% CI 1.21-3.00, $p = 0.005$), reflux esophagitis with an OR of 1.5 (95% CI 1.31-1.63, $p < 0.0001$), and peptic ulcer disease with an OR of 1.3 (95% CI 1.12-1.47, $p < 0.0001$)³⁶. Association with irritable bowel syndrome (IBS) did not reach statistical significance when adjusted for known risk factors. Association with celiac disease (CD) was examined but did not reach statistical significance ($p = 0.22$)³⁶. Substantially stronger association of Crohn's disease with PsA was found in a study analyzing 174,476 US women enrolled in the Nurses' Health Study (NHS). Women with psoriasis had significantly increased risk of developing Crohn's disease with a RR of 3.86 (95% CI 2.23-6.67) and higher risk when concomitant PsA was present with a RR of 6.43 (95% CI 2.04-20.32)³⁷.

Concerning CD, some previous studies have found association with psoriasis. Bastiani et al. assessed the prevalence of CD in a multicenter primary care setting and the response to gluten-free diet in a study of 218 psoriasis patients and 264 controls. Nine (4.1%) of the psoriasis patients had positive anti-tissue transglutaminase antibodies and confirmed diagnosis histologically, compared to one among the controls and calculated an OR of 2.03 (95% CI 1.42-90.11, $p < 0.05$)³⁸. All the nine psoriasis patients diagnosed with CD adhered to gluten-free diet and completed a 6 month follow up. Interestingly, all patients showed significant improvements in PASI after 3 months on gluten-free diet and all had negative results for CD serological screening after 6 months. The improvement in PASI was maintained in all but one patients who experienced worsening. A larger study from Sweden also focusing on psoriasis linked nationwide biopsy data on CD with data on psoriasis and found an increased risk of psoriasis among patients with CD, both before and after the diagnosis of CD. A total of 28,958 CD patients diagnosed between 1969 and 2008 were linked and compared with 143,910 age and sex matched controls. Celiac disease was found to be a risk factor for future psoriasis with a

HR of 1.72 (95% CI 1.54-1.92) and before the diagnosis of CD with an OR of 1.91 (95% CI 1.58-2.31)³⁹.

1.3.2 Psychological

Psoriasis and PsA also have an effect on patients' psychical health. The risk of depression was examined in a prospective cohort study of 50,750 US female nurses, from the NHS. The nurses were free of depression at baseline in the year 2000 and retrospectively asked in 2008 if they had been diagnosed with psoriasis or PsA. Depression was defined as self-report of clinician diagnosis of depression or regular use of antidepressant medication. Cox proportional hazard models adjusting for BMI, physical activity, smoking, and the presence of major chronic conditions found an increased risk of depression with a RR of 1.29 (95% CI 1.10-1.52) for women with psoriasis and 1.52 (95% CI 1.06-2.19) for women with PsA compared to women without psoriasis⁴⁰. Of note, the study cohort is a sample of educated health care nurses and might therefore not accurately represent the general population but certainly gives a clue.

A recent population-based cohort study further examined the mental health of psoriasis and PsA patients in comparison with the general population. The study cohort consisted of 36,214 psoriasis patients, 5,138 PsA patients, and 1,878 AS patients who were frequency matched with a cohort from the general population. Annual incidence rates were calculated and adjusted for age, sex, smoking status, obesity, diabetes, presence of cardiovascular disease or risk, autoimmune disease, cancer, calendar visit quarter, and diagnosis year. Increased risk of depression was found among the three cohorts with an adjusted incidence rate ratio (IRR) of 1.14 (95% CI 1.11-1.17) for the psoriasis patients and 1.22 (95% CI 1.16-1.29) for the PsA patients⁴¹. No significantly increased risk of suicidal ideations or suicides attempts was observed in this study.

1.4 Heritability

As with psoriasis, disease susceptibility of PsA includes both genetic and environmental risk factors. The heritability of PsA seems to be stronger since it has a higher familial aggregation, that is clustering of cases in families⁴². A strong heritability of PsA was recently demonstrated in a convincing Icelandic study of all known PsA cases (n=220) in Reykjavík, which were linked to the genealogy database of deCODE Genetics. First to fourth degree relatives of patients with PsA had a risk ratio of 39, 12, 3.6 and 2.3, respectively (all p-values<0.0001) reflecting a strong familial risk⁴³. Some shared susceptibility genes have already been identified but the challenge is to differentiate genes that confer a risk for PsA from those who have been found to be associated with psoriasis. So far only a few genes specific for PsA have been identified⁴². Many studies have been conducted on the genetic factors underlying psoriasis and PsA and they warrant a brief discussion on their main findings.

1.4.1 Human leucocyte antigen

Certain human leucocyte antigen (HLA) alleles have been found to confer susceptibility for psoriasis and PsA and some have been found to be PsA specific. These genes are part of the major histocompatibility complex (MHC) region on 6p which contains more than 160 genes, both HLA and

non-HLA genes⁴². Many of them have been implicated in autoimmune diseases and they have an important role in the regulation of immune responsiveness.

A population based case-control study of 712 PsA patients, 335 psoriasis patients and 713 healthy controls found that four HLA alleles were associated with PsA compared to psoriasis patients: B*08 with an OR of 1.61 ($p=0.009$), B*27 with an OR of 5.17 ($p<0.0001$), B*38 with an OR of 1.65 ($p=0.026$), and C*06 with an OR of 0.58 ($p=0.0002$)⁴². Further, when PsA patients were compared to healthy controls higher frequencies of three alleles were seen: HLA-B*27 with an OR of 3.05 ($p<0.0001$), HLA-B*38 with an OR of 5.9 ($p<0.0001$) and HLA-C*06 with an OR of 1.71 ($p<0.0001$)⁴². In addition to the genes belonging to MHC, several additional genes outside of this area have been identified⁴².

1.4.2 Paternal transmission

An interesting form of genomic imprinting called the parent-of origin effect has been demonstrated in several autoimmune diseases⁴⁴. This phenomenon results in differential transmission and expression of the disease depending on the sex of the affected parent. It has been suggested that paternal transmission might apply to PsA, with the disease passing from father to offspring. Differences in parental and offspring transmission of PsA were examined in a study of 508 PsA probands attending the University of Toronto PsA clinic, including 228 females and 280 males. Ninety-five had an affected parent, 65% had an affected father and 35% an affected mother. The proportion of paternal transmission was significantly greater than expected, or 0.65 vs. 0.5 ($p=0.001$) meaning that the probands were much more likely to have an affected father⁴⁴. The age of onset and the severity of PsA were similar in both groups, maternally and paternally transmitted. Further evidence of this interesting imprinting was illustrated in an Icelandic genome-wide linkage scan study. From 907 psoriasis patients, 178 PsA patients were identified and a linkage scan performed to map genes contributing to PsA. Linkage with chromosome 16q was found with a logarithm of the odds (LOD) score of 2.17, a statistical estimate used to measure whether genes are near each other on a chromosome and therefore inherited. Moreover, when conditioned to paternal transmission to affected individual a LOD score of 4.19 was found compared to only 1.03 when conditioned to maternal transmission, suggesting that a gene in this area of the genome contributes to paternal inheritance of PsA⁴⁵.

1.4.3 Twin studies

The heritability of psoriasis and PsA has been studied in twin sample studies, using proband-wise concordance rates. A population based twin sample of 10,725 twin pairs aged 20-71 years from the Danish Twin Registry was collected to estimate the heritability of psoriasis via questionnaire survey. The concordance for psoriasis was found to be larger in the monozygotic twins, compared to the dizygotic twins, 0.33 vs. 0.17⁴⁶. The authors conclude that genetic factors explain about 68% (60-75%) of the variation in the susceptibility to psoriasis and the rest is explained by non-shared environmental factors⁴⁶. The Danish Twin Registry was likewise used to analyze the heritability of PsA but it suffered from a lack of statistical power. Three nationwide cohorts of twins, a total of 83,806 twin individuals,

were asked by questionnaire if they had PsA and those who replied they did were invited to further clinical examination. A total of 228 twin individuals reported PsA and the diagnosis was validated in 164 individuals (70%). One of the 10 monozygotic twin pairs and one of the 26 dizygotic twin pairs were concordant for PsA. In addition, five of the 10 monozygotic and four of the 26 dizygotic twin pairs were concordant for psoriasis. These results suggest that the genetic contribution to PsA is less prominent, compared to psoriasis, since the concordance rates were almost identical for PsA among the monozygotic and dizygotic twins⁴⁷. Again, this study lacks statistical power and should be interpreted carefully when considering the heritability of PsA.

By gaining greater understanding of the contributing genetics factors, there is an opportunity to identify psoriasis patients which are more genetically susceptible to the development of PsA. Strong heritability is seen in PsA and specific HLA antigens appear to confer susceptibility but genetic factors do not account for all cases^{43, 48}. The effects of causal environmental factors remain largely unclear but it has been suggested that psoriasis patients with predisposing genetic factors may develop PsA after exposure to triggering environmental factors⁶.

1.5 Environmental risk factors

Triggering environmental factors which have been shown to be associated with psoriasis are streptococcal pharyngitis, stressful life events, humidity, HIV infection, parvovirus B19 infection, trauma, smoking, drugs, cold weather, diet and obesity^{7, 49, 50}. Some of them overlap with the environmental risk factors which have been shown to be associated with PsA but they include obesity, trauma, moving home, physically demanding occupations, lifting heavy weights, steroid use, use of systemic retinoid medication, uveitis, recurrent oral ulcers, rubella vaccination, HIV infection and other infections^{27, 51-56}.

A population-based study of 75,395 psoriasis patients on the effects of obesity on the risk for PsA showed increasing risk with increasing Body Mass Index (BMI). The RR for developing PsA among psoriasis patients was 1.09 for BMI from 25-29.9, 1.22 for BMI from 30-34.9 and 1.48 for BMI over 35, compared to psoriasis patients with BMI < 25⁵². The association of obesity and PsA was further analyzed in a recent case-control study of 314 PsA patients and 498 psoriasis patients. First, obesity was more frequent among the PsA patients, compared to the psoriasis patients, with an OR of 1.77 ($p=0.002$)⁵⁷. Higher BMI was also found to be associated with late onset of PsA and psoriasis, $p<0.001$ and $p=0.0009$ respectively⁵⁷. Further, this association was found to be related to the HLA-B*27 allele and potentially different effects of obesity on the risk of PsA. Normal weight and earlier onset was associated with the presence of HLA-B*27 ($p=0.002$), but the association between obesity and PsA was seen in HLA-B*27 negative patients with an OR of 2.39 ($p<0.001$)⁵⁷.

The association of trauma and psoriasis was first described in the 18th century by Heinrich Koebner⁵⁸. When psoriasis develops following an injury to previously healthy and normal looking skin it's called Koebner phenomenon, after Heinrich. Unsurprisingly, psoriasis often begins on elbows and knees, places that are commonly exposed to trauma⁵⁹. Several studies have found an association of trauma with the development of PsA. A recent longitudinal matched cohort study used data from THIN and matched 15,416 psoriasis patients exposed to physical trauma recorded in primary care to 55,230

unexposed patients. During a total of 425,120 person years, 1,010 PsA cases were identified and physical trauma found to be associated with the onset of PsA among psoriasis patients with a multivariate HR of 1.32 (95% CI 1.13-1.54). Sub analysis showed a HR of 1.46 (95% CI 1.04-2.04) for bone trauma and 1.50 (95% CI 1.19-1.90) for joint trauma⁵⁵. Nerve and skin trauma did not reach statistical significance. Another study, by Eder et al., of 159 PsA patients and 159 psoriasis control, found an association of injuries with the development of PsA among psoriasis patients with an OR of 2.1 (95% CI 1.11-4.01)⁵¹. These variable injuries included cuts, falls, burns and blunt penetrating trauma. Lastly, environmental risk factors were examined in a case-control study by Pattison et al. of 98 PsA patients and 163 psoriasis controls. The strongest association was found with trauma or injury sufficient to require medical consultation with an OR of 2.53 (95% CI 1.1-6.0). The PsA cases were also more likely to have experienced a fractured bone requiring hospital admission, 50% vs. 9%, $p=0.040$ ⁶⁰.

The possible association of emotional stress or psychological trauma with PsA is less well known. The study by Eder et al. mentioned above did not find a significant association with the emotional stress associated with the death of a close family member, divorce/separation, moving house, changing job, becoming unemployed or undergoing treatment for depression or anxiety⁵¹. However, moving house was found to be associated with the PsA in a study by Pattison et al. study with an OR of 2.3 (95% CI 1.2-4.4) but none of the others psychological traumas were examined in their study⁶⁰. Occupations involving lifting heavy weights, at least 100 pounds/hour, were found to be associated with an increased risk of PsA with an OR of 2.8 (CI 1.51-5.05)⁵¹.

A lower level of education, which has been considered a marker of lower socioeconomic status, was found to be predictive of the development of PsA in a recent prospective cohort study of 464 psoriasis patients which were followed up for eight years. During the follow up time, 51 patients developed PsA and a lower level of education was associated with PsA in a multivariate regression analysis comparing university/college vs. high school incomplete with a RR of 0.22 (95% CI 0.08-0.62, $p=0.005$), and high school graduate vs. high school incomplete with a RR of 0.30 (95% CI 0.09-0.99, $p=0.049$)²⁷.

Other environmental factors found to be associated with the risk of PsA are recurrent oral ulcers with an OR of 4.2 (95% CI 2.0-9.0), rubella vaccination with an OR of 12.4 (95% CI 1.2 -122), uveitis with a RR of 31.5 ($p=0.0002$), use of systemic retinoid medication with a RR of 3.42 (95% CI 1.24-9.44, $p=0.02$) and the use of corticosteroids with an OR of 5.54 (95% CI 1.54-19.87, $p=0.009$)^{27, 53, 56}. While adding to the list of potential risk factors for PsA, some of these studies have a small sample size and often the participants were recruited from dermatology clinics and should be interpreted with caution until more data is presented.

Controversially, an inverse association of smoking with the risk of PsA has been revealed. A case-control study of 159 PsA patients with recent onset and 159 psoriasis patients found an inverse association of smoking with the developing of PsA with an OR of 0.6 (95% CI 0.36-0.89)⁵¹. As suggested by the authors, the proportion of current and past smokers was lower in the PsA group in this study which could explain this significant association observed. This association was further analyzed in a case-control study with a larger sample of patients which also tested an interaction

between HLA-C*06 allele and smoking. Higher proportions of current and past smokers were found in the group of 404 psoriasis patients compared to the 728 PsA patients, current smokers 26.7% vs. 22.3% and past smokers 30.2% vs. 23.4%, $p=0.001$. Smoking remained inversely associated with PsA in a multivariate analysis, being a current smoker vs. lifetime non-smoker with an OR of 0.57, $p=0.002$. Being a past smoker vs. lifetime non-smoker did not reach statistical significance⁶¹. Interaction between smoking, ever smoked vs. lifetime non-smoker, and the HLA-C*06 allele was significant, $p=0.01$, so the effects of smoking seem to be modified in the presence of this allele. The inverse associations between smoking and PsA applied to patients who were negative for HLA-C*06 but were not significant among HLA-C*06 positive patients⁶¹. Further studies are needed to analyze this gene-environment interaction further. Consumption of alcohol has been examined in previous studies but an association has not been found⁶⁰.

Pregnancy in the two years before the onset of psoriasis and through the development of PsA has been found to decrease the risk of developing PsA with an OR of 0.19 (95% CI 0.04-0.95) when adjusted for gender, age, duration of psoriasis and corticosteroid use⁵⁶. There were few occurrences of pregnancy in this study but the association seems plausible because of immunosuppressing during pregnancy.

In addition to these environmental risk factors, previously published data have also suggested that exposure to infection related triggers for PsA might be of relevance^{51, 53}.

1.5.1 Infections

The idea of a possible triggering role of infections in PsA is anything but novel. A case report from 1979 discussed a patient with a history of Varicella virus infection 2 weeks before the onset of PsA, which the authors suggested might have triggered the arthritis⁶². Another case report from 2000 suggested a role for bacterial infection as a trigger, reporting that a psoriasis patient in remission for five years developed severe PsA within two weeks of a *Salmonella typhimurium* infection⁶³. Previous studies which have suggested a triggering role for infections in psoriasis and PsA, have studied both bacterial- and viral infections in addition to infections in general. Unfortunately, most of them rely on cross-sectional or retrospective data.

Musculoskeletal manifestation have been described in HIV positive patients, including psoriatic arthritis⁶⁴. These patients apparently tend to have more progressed HIV infection, and are more likely to experience progression to clinical acquired immunodeficiency or death⁶⁵. Therefore, it has been suggested that rheumatic symptoms may be a predicting factor for poor prognosis for HIV patients. The frequency of rheumatological manifestations among HIV positive patients was analyzed in a study by Buskila et al. Of 52 consecutive HIV patients attending an HIV clinic in Canada 65.3% reported rheumatic manifestation and thereof 5.7% had PsA⁶⁶. Similar frequency was found in a study by Berman et al. who analyzed consecutive HIV patients attending a clinic for immunodeficiency and sexually transmitted diseases in Argentina. Of the 89 HIV positive patients, 66% had rheumatic manifestations compared to 6% of the 80 HIV negative controls⁶⁷. An even higher incidence among HIV positive individuals has been reported in data from sub-Saharan Africa but PsA was infrequently reported prior to the HIV pandemic, suggesting that there may be an association between HIV

infection and PsA. Clinical characteristics of PsA and its association with HIV infection was assessed in a cohort study of black Zambians. A total of 702 new inflammatory arthritis patients with psoriasis lesions attending an arthritis clinic in a 40-month period were assessed. Altogether, 405 had SpA (spondyloarthropathies) and thereof 28 patients had PsA. Of the 28 PsA patients, 27 were HIV-positive⁶⁸. Notably, the prevalence of PsA in this study seems to be 25-fold higher than in usual European populations. However, there is a lack of studies with an unexposed control group without HIV infection from the same area, making interpretation more difficult. Furthermore, these studies are certainly biased because of limited access to healthcare contingent on personal finances in this region.

A triggering role for human parvovirus B19 has been suggested both for psoriasis and PsA. A case-control study by Yazici et al. found that human parvovirus B19 DNA was present in a higher proportion of 47 psoriasis patients compared to controls (20 blood donors) or in 38% vs. 0%, $p=0.01$ ⁶⁹. Another case-control study by Mehraein et al. focused on autoimmune chronic arthritis, including PsA. A significantly higher proportion of cases expressing human parvovirus B19 virus protein in immune-related arthritis was found, especially RA (89.7%) and PsA (66%), compared to reactive arthritis and synovitis (38.5%)⁷⁰.

Previous studies have suggested that the hepatitis C virus (HCV) might be involved in the pathogenesis of psoriasis and moreover to be a triggering factor for PsA. This has been described in hepatitis C patients who are being treated with IFN- α . A higher prevalence of HCV infections among PsA patients compared to the general population was described in a case-control study by Taglione et al.⁷¹. Anti-HCV antibodies were detected in the sera of 12% of 50 PsA patients, significantly higher than in the general population where the prevalence is 3.2% (referring to historical data on the prevalence in the Italian population)⁷¹. They also detected anti-HCV antibodies in 10% of 50 psoriasis patients and 5.2% of 76 RA patients (control) but neither group was statistically significantly different from the general population. Conversely, a case-control study by Palazzi et al. did not find a significant difference in anti-HCV antibody prevalence among 100 consecutive PsA patients compared to 100 consecutive controls with peripheral osteoarthritis (OA) or sciatica due to L4-L5 or L5-S1 herniated disc⁷².

Some previous studies have explored a variety of environmental factors, including infections in general. Eder et al. explored the association between environmental factors and the onset of PsA among psoriasis patients in a case-control study where the history of exposure was recorded with a standardized questionnaire. The study population consisted of 159 PsA patients with recent onset and 159 psoriasis patients without arthritis who were asked to report whether they had been exposed to hypothesized triggers, including infections, in the previous 10 years. Infections that required antibiotics were associated with PsA among the psoriasis patients with an OR of 1.7 (CI 1.00-2.77)⁵¹. Severe infections that required hospitalization were also more common among the PsA patients, 7.2% vs. 0%, $p<0.001$. Infectious diarrhea was more common among the PsA cases but this observation did not reach statistical significance, 12.7% vs. 7%, $p=0.19$. Types of infections were also noted in this study, which included lower respiratory tract infections (11%), upper respiratory tract infections (22.2%), urinary tract infections (8.3%), skin and soft tissue infections (25%), sinus infections (8.3%), sepsis

(2.8%), hepatitis B or C (8.3%) and other types of infections (13.9%)⁵¹. Of note, this type of study design entails a risk of recall bias as recalling 10 years of history of exposure may not be completely reliable.

Another common drawback of previous studies of the role of infections in the onset of PsA is that PsA patients are rarely the primary focus of these studies. Instead, they are included as controls or part of the control group or data on them is reported as a side note in a study with a different focus. Therefore, the results for PsA patients are sometimes not specifically presented and no useful data included. As an example, Soderlin et al. carried out a population based cohort study exploring whether infections preceded early arthritis. Of the 72 arthritis patients who had disease duration of less than 3 months, 45% had infection preceding the arthritis⁷³. Whether the four PsA patients included in this study had preceding infection was not stated.

1.6 Summary

Psoriatic Arthritis, an inflammatory joint disease which up to 30% psoriasis patients develop, has a major impact on patient health and quality of life. Several comorbidities exist, including cardiovascular, gastrointestinal and psychological. Both genetic and environmental risk factors contribute to disease susceptibility. Specific genes have been identified, but genetic factors do not account for all diseases pathogenesis. A clearer picture of environmental risk factors will help in the understanding of the interaction between genetic and environmental factors. Some environmental risk factors have been identified but the potential role of infections remains to be elucidated.

2 Aims

Based on the background presented, the main aim of this study was to systematically review available data evaluating the effects of infections on the risk of developing PsA among psoriasis patients. A secondary aim was to examine whether any observed associations are found with bacterial or viral pathogens, or both.

Hypothesis: There are indications in the medical literature that infections can trigger PsA.

3 Methods

3.1 Systematic literature search

A systematic search of the Cochrane Library, PUBMED, Scopus and Web of Science was conducted on March 16 2017, in accordance with the PRISMA (Preferred reporting items for systematic review and meta-analysis) guidelines⁷⁴. The following search terms were used along with „psoriatic arthritis“: „infections“, „risk“, „bacteria“, and „virus“. The search was further limited to publications with available abstracts and published in English. No time frame was fitted for the search nor regarding the publication status. As an example, the search strategy employed was as follows: (((psoriatic arthritis AND infections)) OR (psoriatic arthritis AND risk)) OR (psoriatic arthritis AND bacteria)) OR (psoriatic arthritis AND virus).

3.2 Article selection

Duplicate publications were removed and abstracts and titles of the remaining publications screened for eligibility. Full texts of articles were obtained for all publications that appeared to meet the inclusion criteria, likewise if there was any uncertainty. All abstracts were reviewed and publications meeting the following criteria were included:

- (I) Observational studies on psoriasis and PsA patients, including case-control, cohort or ecologic studies.
- (II) Presenting original data on the association between infections and PsA.

Publications including data on five or fewer PsA patients were excluded from the review as they share more features with case reports than observational studies. Figure 1 shows the PRISMA flow diagram of the progression of the database search and study selection. Included studies were parsed to categories of bacterial infections, viral infections and infections in general.

Figure 1: PRISMA flow diagram of the literature search and study selection.

3.3 Data extraction

Data were extracted directly from each eligible study. Data extracted included information about study design, study groups, how the exposure to infection was examined, adjusted covariates and the result. When p-values were published in comparison between groups, they were likewise extracted. All data were extracted with a predefined structured form.

3.4 Statistical analysis

When P-values were missing for comparison between groups, they were calculated by Fisher's exact test if sufficient data were available in the published article. Calculations were performed on

<http://vassarstats.net/>.

4 Results

4.1 Search results

The search yielded 4,747 publications, after the removal of duplicates. No additional publications were identified from other sources. Altogether 4,579 publications with no data on the associations between infections and PsA were excluded after the screening of title and abstract, as well as 88 publications that did not present original data. Thirty-eight case reports and studies including five or fewer PsA cases were also excluded from the review but are briefly described for completeness.

Therefore, 27 original studies presenting data on infections among PsA patients were included: six case-control studies, twenty cross-sectional studies and one cohort study. Study design, country, source of information for exposure (i.e. infection), number of PsA patients and controls and risk estimates/results for the included studies are summarized in tables 1-3, parsed into categories of bacterial infections, viral infections and infections in general. The total number of included patients in all studies was 933 PsA patients and 1611 controls. Overall there are indications in previous studies of a possible role for infections in the pathogenesis of PsA and it is very relevant to examine this hypothesis further.

4.2 Bacterial infections

Seventeen included studies examined bacterial infections and six of them found an association with PsA (table 1). Additionally, five studies reported mixed results with some statistically significant associations. Those studies examined both gram positive and gram-negative bacteria. The most common subject were Streptococcal infections, which are gram positive.

4.2.1 Gram positive bacterial infections

Streptococcal infections were the subject of six studies and were found to be associated with the development of PsA in four⁷⁵⁻⁷⁸. Vasey et al. found that 51% of 49 PsA cases were anti-DNase-B positive compared to 10% among normal controls, $p < 0.0001$ ⁷⁷. Increased reactivity among peripheral PsA as compared to axial PsA was also described, $p < 0.05$. Three studies found an association between PsA and *Streptococcus pyogenes*. Higher immune responses to *Streptococcus pyogenes* rM12 protein (AB and C regions) and IgG antibody levels against each region were observed in 31 PsA patients compared to 88 psoriasis vulgaris patients, six Rheumatoid Arthritis (RA) patients and 77 healthy controls by Muto et al.⁷⁵. Wang et al. similarly demonstrated higher levels of 16S rRNA of *Streptococcus pyogenes* in the blood of 19 PsA patients compared to 17 RA patients and 10 other arthritis patients⁷⁸. Rantakokko et al. measured IgM, IgA and IgG serum antibodies against peptidoglycan-polysaccharide (PG-PS) and peptidoglycan (PG) from *Streptococcus pyogenes* in 38 PsA patients and 34 controls and found statistically significant association with IgA-PG-PS⁷⁶.

Two of the six studies exploring associations between PsA and streptococcal infections found no statistically significant connection^{56, 79}. Thumbor et al's. population based nested case-control study matched 60 PsA patients with 120 psoriasis controls. The PsA patients were not more likely to have had a positive streptococcal culture within a period beginning 2 years before the onset of psoriatic

disease, $p=0.528$ (95% CI 0.29-1.90)⁵⁶. Likewise, responses to three streptococcal antigens were not statistically significantly different between 21 PsA cases and 15 age matched controls in a study by Grinlinton et al.⁷⁹.

Two studies demonstrated an association between staphylococcal super antigens and PsA^{80, 81}. Rahman et al. measured serum antibody levels to staphylococcal antigens in 110 patients with various diseases and found statistically significantly higher titers among 22 PsA patients compared to 16 psoriasis patients⁸⁰, while Yamamoto et al. found a statistically significant difference in mononuclear cell responses in eleven PsA patients compared to normal controls⁸¹.

4.2.2 Gram negative bacterial infections

A possible role for *Chlamydia trachomatis* (CT) infections was explored in two studies^{82, 83}. Silveira et al. collected urethral and endocervical specimens for detection of CT, along with serum for determination of IgG and IgM antibodies. Although focused on reactive arthritis, of 18 patients with PsA 22.2% had a positive culture for CT but no control group was available. Furthermore, of 14 PsA patients tested 35.7% had serum IgG and 14.3% IgM antibodies, which was not statistically significantly different from a control group of 60 individuals, $p=0.06$ and 0.09 ⁸³. Lapadula et al. found that 22 PsA patients had statistically significantly higher titers of anti-CT antibodies compared to 22 healthy controls, as well as higher antibodies for all four additional pathogens tested for:

Campylobacter foetus, *Campylobacter jejuni*, *Yersinia enterocolitica*, and *Yersinia pseudotuberculosis*⁸². Previously, Lapadula et al. studied the occurrence of anti-bacterial antibodies among seronegative spondyloarthropathy (SNSA) patients. Sera from 101 patients with different rheumatic diseases were compared, including seven PsA patients, to sera from 31 healthy donors. Statistically significant difference in antibody production against *Yersinia enterocolitica*, *Campylobacter intestinalis* and *Yersinia pseudotuberculosis* between the healthy donors and the seronegative polyarthritis patients was found⁸⁴. All the studies on antibody titers were cross-sectional, and no data presented on the temporal relationship between measured antibody titers and onset of disease.

In a study focused on psoriasis by Stinco et al., *Chlamydophila psittaci* DNA positive samples were not statistically significantly more common among 12 PsA patients than in the general population with an OR of 20.36 (95% CI 1.2 – 347.6), $p=0.1$ ⁸⁵. On the other hand, in a study by Fabris et al. *Chlamydophila psittaci* infections were associated with PsA with an OR of 44.8 (95% CI 5.21–385.2), $p<0.0001$ ⁸⁶. Trull et al. focused on ankylosing spondylitis (AS) patients but included PsA patients, RA patients and healthy controls as comparison. IgA levels for *Klebsiella pneumoniae* was measured but no difference found between the 35 PsA patients and 57 normal controls⁸⁷.

One study compared gut bacteria from patients with NORA (new-onset rheumatoid arthritis), CRA (chronic, treated rheumatoid arthritis), PsA and healthy controls. The prevalence of *P. copri* among the 16 PsA patients included was 37.5% compared to 21.4% among the healthy controls, $p=0.3032$ ⁸⁸.

4.2.3 Non-type specific bacterial infections

Two studies were not specific for type of bacterial infections. Moen et al. examined oral bacterial DNA based on the hypothesis that bacteria may perpetuate autoimmunity in joint disease. Statistically

significantly higher numbers of bacterial species and higher concentrations were found in the PsA and RA groups compared to controls⁸⁹. Finally, association of recent infection requiring antibiotics was examined in a prospective cohort study of 464 psoriasis patients. The patients had not been diagnosed with PsA at the study enrollment and were followed up for eight years. In that time, a total of 51 patients developed PsA. Association with recent infection requiring antibiotics was not found in analysis controlled for age at onset of psoriasis and stratified by sex (RR 0.88, CI 0.39-1.98)²⁷.

Table 1: Main characteristics of the 17 included studies presenting data on bacterial infections, by publication year.

Reference, Country	Study Design, Groups, Exposure	Adjusted Covariates	N(PsA)/ Controls	Results
Vasey et al. (1982) ⁷⁷ ; USA – Florida.	Cross-sectional study, PsA and PS vs. RA, other form of dermatitis and normal controls, serum anti-DNase-B.	Age matching.	49/59	Positive, PsA vs. controls: 51% of all PsA patients vs. 10%, p<0.0001. 62% of PsA-peripheral, vs. 10%, p<0.001. 27% of PsA-central vs. 10%, p=0.04.
Trull et al. (1983) ⁸⁷ ; England – London.	Cross-sectional study, PsA vs. AS, RA, and healthy controls, serum IgA antibodies to <i>Klebsiella pneumonia</i> .	None.	21/57	Antibody titers: PsA 7.97±0.72. Controls: 10.00±0.64.
Lapadula et al. (1988) ⁸⁴ ; Italy.	Cross-sectional study, PsA vs. HD, serum antibodies against YEC, YPT, CJ, CI, and CT.	Sex, age and disease duration were comparable between cases and controls.	7/31	Positive test, PsA vs. controls: YEC 42.86% vs. 3.13%, p=0.015. YPT 42.86% vs. 3.13%, p=0.015. CI 57.14% vs. 31.25%, p=0.39. CJ 28.57% vs. 9.38%, p=0.22. CT 57.14% vs. 0.00%, p=0.00047.
Rahman et al. (1990) ⁸⁰ ; USA – Pennsylvania and Philadelphia.	Cross-sectional study, PsA vs. PS, serum antibody titers to soluble peptidoglycan from <i>Staphylococcus aureus</i> .	No correlation with age, sex, duration, severity of disease or number and type of joints involved.	22/16	Antibody titers, PsA vs. Ps: 82±25 vs. 32±21, p<0.0001.
Lapadula et al. (1992) ⁸² ; Italy.	Cross-sectional study, PsA vs. HD, RA and PS, serum antibodies against YEC, YPT, CJ and CF. Anti-CT antibody titers.	None.	22/22	Positive test, PsA vs. controls: YEC 23% vs. 6%, p=0.19. YPT 18% vs. 6%, p=0.34. CJ 55% vs. 36%, p=0.36. CF 86% vs. 50%, p=0.02.
Grinlinton et al. (1993) ⁷⁹ ; New Zealand.	Cross-sectional study, PsA vs. RA and healthy controls, proliferative responses of PBL and SFL to 3 streptococcal antigens.	Age matching.	21/15	PBL proliferation, PsA vs. healthy controls, median (range): Strep 1: 10.8 (1.4-159.0) vs. 8.5 (0.5-40.2), p>0.05. Strep 2: 19.7 (3.5-391.0) vs. 11.6(4.3-132.0), p>0.05. SCW: 3.8(0.6-13.8) vs. 1.8(0.3-10.3), p>0.05. SFL proliferation, PsA vs. RA, median (range): Strep 1: 11.6(1.6-24.7) vs. 14.7(7.-30.5). Strep 2: 6.2(3.5-33.6) vs. 5.0(2.6-11.8).

Silveira et al. (1993) ⁸³ ; USA – New Orleans, Louisiana.	Cross-sectional study, consecutive SNSA (AS, RS and PsA) patients vs. HBDs, self-questionnaire, self-evaluation and physical examination by rheumatologist. Specimen samples from Urethral and endocervical swabs. Serum for determination of IgG and IgM antibodies against CT.	None.	18/60	Positive test, PsA vs. controls: CT 22.2% vs. 0%, p=0.002. IgG 35.7% vs. 8.3%, p=0.02. IgM 14.3% vs. 1.8%, p=0.04.
Muto et al. (1996) ⁷⁵ ; Japan.	Cross-sectional study, PsA vs. PV, RA and healthy controls, <i>in vivo</i> immune response to <i>Streptococcus pyogenes</i> , rM12 protein (AB and C regions) and IgG antibody level against each region measured.	None.	31/77	Mean antibody levels to C region: PsA 20.193±3.285 (reference). Controls 3.417±395 (p<0.001). Mean antibody levels to AB region: PsA 2.172±468 (reference). Controls 1.510±253. No statistically significant difference of the responses to the AB region.
Rantakokko et al. (1997) ⁷⁶ ; Finland.	Case-control study, PsA, NAP and RA vs. healthy controls, IgM, IgA and IgG class serum antibodies against PG-PS and PG from GAS (<i>Streptococcus Pyogenes</i>). Data also collected regarding recent infections, antibiotic treatments and exacerbations of PS and/or arthritis.	The RA patients were matched with the PsA patients by sex, age and duration of the arthritis.	38/34	Antibody response, PsA vs. controls: IgA - PG-PS 28.8(0-148) vs. 15.1(1-74), p<0.05. IgG - PG-PS 24.5(6-170) vs. 15.8(2-142). IgG - PG 18.6(2-75) vs. 17.8(4-78). Only PsA cases had slightly increased, but not statistically significantly increased values for the IgA class.
Wang et al. (1999) ⁷⁸ ; USA – Florida.	Cross-sectional study, PsA vs. RA and other arthritis controls (RS, AS, OA and IBD), detection of 16S ribosomal RNA of GAS (<i>Streptococcus pyogenes</i>), GBS (<i>Streptococcus agalactiae</i>) and <i>Streptococcus pneumoniae</i> in peripheral blood and SF.	None.	19/27	Positive test, PsA vs. controls: GAS 7 vs. 1, p=0.006. GBS 2 vs. 2, p=1. <i>Streptococcus pneumoniae</i> was absent from all specimens.
Yamamoto et al. (1999) ⁸¹ ; Japan.	Cross-sectional study, PsA vs. PV patients and normal controls, response of PBMC to Staphylococcal super antigens, SEA, SEB and SEC1.	None.	11/19	PBMC responses, PsA vs. controls: SEA 31.819±812dpm vs. 21.989±427dpm, p<0.05. SEB 38.715±719dpm vs. 23.708±466dpm, p<0.05. SEC1 29.740±633dpm vs. 20.291±582dpm, p<0.05.
Thumboo et al. (2002) ⁵⁶ ; USA – Minnesota.	Population based nested case-control study, PsA vs. PS, medical records and patient survey information from the Rochester Epidemiology Project.	Each case of PsA was matched with 2 PS controls with age, gender and PS duration/date of onset.	60/120	PsA vs. controls: <i>Streptococcal</i> infection 16.7% vs. 20%, p=0.528 (OR 0.74 95% CI 0.29-1.90). Use of corticosteroid 16.7% vs. 5%, p=0.015 (OR 4.33 95% CI 1.34-14.02), p=0.009 (OR 5.54 95% CI 1.54-19.87) after adjusting for the influence of gender, age and duration of PS.
Moen et al. (2006) ⁸⁹ ; Norway.	Cross-sectional study, PsA vs. RA and osteoarthritis controls, serum and SF samples extracted for oral bacterial DNA detection of 40 different bacteria.	None.	14/9	Number of species in serum, PsA vs. controls: 5.4 (±2.7 SD) vs. 2.1 (±1.7 SD), p=0.009. Number of species in SF, PsA vs. controls: 19.4 (±7.1 SD) vs. 4.0 (±1.7 SD), p<0.001. Higher means of DNAs were found in PsA SF compared to PsA serum, p<0.001.

				Higher concentrations of bacterial DNAs were found in RA and PsA compared to controls.
Fabris et al. (2011) ⁸⁶ ; <i>Italy</i> .	Cross-sectional study, PsA vs. HBDs, presence of CP DNA assessed in PBMC.	No difference in age, sex, disease duration and undergoing therapies were noticed between CP-positive and CP-negative patients, nor between seropositive and seronegative patients.	36/225	Positive test, PsA vs. HBD: 16.7% vs. 0.4%, p=0.0001 (OR 44.8 95% CI 5.21-385.2).
Stinco et al. (2012) ⁸⁵ ; <i>Italy</i> .	Cross-sectional study, PsA and PS vs. healthy controls, bacterial DNA of CP, CPN and CT extracted from PBMC.	CP positive and negative patients did not differ statistically significantly in age, sex and disease duration.	12/225	Positive test, PsA vs. controls: CP 8% vs. 0.4%, p=0.099. All patients and controls were negative for CPN and CT.
Scher et al. (2013) ⁸⁸ ; <i>United States</i> .	Case-control study, PsA, RA vs. HLT, 16S ribosomal RNA gene sequencing on stool samples.	None.	16/28	Prevalence of <i>P. copri</i> , PsA vs. HLT: 37.5% vs. 21.4%, p=0.3032. ESR (mm/h, mean): 19.7 vs. 10.2. CRP (mg/l, mean): 7.6 vs. 1.1.
Eder et al. (2016) ²⁷ ; <i>Canada - Toronto</i> .	Cohort study of 464 PS patients followed up for 8 years, information collected from patients.	Analyses controlled for age at onset and stratified by sex.	51	Recent infection requiring antibiotics (within 1 year): RR 0.88 (CI 0.39 – 1.98, p=0.75).

Abbreviations: **AS:** Ankylosing spondylitis, **ESR:** Erythrocyte sedimentation rate, **CF:** *Campylobacter fetus*, **CJ:** *Campylobacter jejuni*, **CI:** *Campylobacter intestinalis*, **CP:** *Chlamydomphila psittaci*, **CPN:** *Chlamydomphila pneumonia*, **CRP:** C-reactive protein, **CT:** *Chlamydia trachomatis*, **GAS:** Group A streptococci, **GBS:** Group B streptococci, **HBDs:** Healthy blood donors, **HD:** Healthy donors, **HLT:** Healthy controls, **IBD:** Inflammatory bowel disease, **NAP:** Non-arthritis psoriasis, **OA:** Osteoarthritis, **PBL:** Peripheral blood lymphocytes, **PBMC:** Peripheral blood mononuclear cells, **PG:** Peptidoglycan, **PG-PS:** Peptidoglycan-polysaccharide, **PsA:** Psoriatic arthritis, **PS:** Psoriasis, **PV:** Psoriasis vulgaris, **RA:** Rheumatoid arthritis, **RR:** Relative risk, **RS:** Reiter's syndrome, **SCW:** Streptococcal cell wall preparation, **SEA:** Staphylococcal enterotoxin A, **SEB:** Staphylococcal enterotoxin B, **SEC1:** Staphylococcal enterotoxin C1, **SF:** Synovial fluid, **SFL:** Synovial fluid lymphocytes, **SNSA:** Seronegative spondyloarthropathy arthritis, **YEC:** *Yersinia enterocolitica* and **YPT:** *Yersinia pseudotuberculosis*.

4.3 Viral infections

Seven included studies examined viral infections, with Human Immunodeficiency Virus (HIV) infection being the most common subject (table 2).

4.3.1 Human Immunodeficiency virus (HIV) infections

HIV infections were the subject of three included studies^{68, 90, 91}. Louthrenoo et al. examined 100 HIV infected patients with musculoskeletal symptoms (including nine PsA patients) and found that the HIV infection had been documented before the development of musculoskeletal symptoms in thirty-one patients⁹⁰. HIV antibodies were measured in 595 new consecutive attendees in an arthritis clinic in Zambia by Njobvu et al. The prevalence of HIV infection among the 13 PsA cases was 92% compared to approximately 50% among hospital outpatients and 30% of the adult urban population during the period⁹¹. Another report by Njobvu and McGill described that among 702 inflammatory arthritis patients

attending an arthritis clinic in Zambia, 28 had PsA of whom 96% had HIV⁶⁸. These two studies from Zambia appear to be partially based on the same patient pool. The authors note that the prevalence of PsA in their study appeared to be 25-fold higher than in European populations, in areas where PsA was previously rare, and that it appears to be linked to HIV infection which is more common in this area.

4.3.2 Hepatitis C virus (HCV) infections

Two studies explored HCV infection. Taglione et al. found anti-HCV antibodies in the sera of 12% of PsA cases compared to 5.2% in RA and 3.2% reported in the general population in another study⁹², $p=0.11$ and 0.0004 respectively⁷¹. However, Palazzi et al. found no statistically significant difference in the prevalence of HCV antibodies between 100 PsA patients and 100 controls with Osteoarthritis (OA) or sciatica⁷².

4.3.3 Viruses in synovium

Mehraein et al. have published two reports on viruses in the synovium of patients with inflammatory arthritis, with data on *Parvovirus B19*, *Cytomegalovirus* (CMV), and *Epstein-Barr* virus (EBV)^{70, 93}. Patients with PsA and RA were found to be more likely to have evidence of replicating *Parvovirus B19* in their synovium than patients with reactive arthritis/synovitis (ReA/S)⁷⁰. The proportion of patients expressing B19 virus protein was especially high among the RA patients (89.7%) and to a lesser extent among the PsA patients with 66% compared to 38.5% among the ReA/S patients. The proportion was higher among the six PsA patients compared to the two normal controls or 66% vs. 50%, $p=1.000$ ⁷⁰. CMV-DNA was detected in 50% of PsA patients, and 31% of RA patients vs. 11.6% in the ReA/S patients. Compared to normal controls the proportion was higher among the PsA patients or 50% vs. 0%, $p=0.46$. Finally, the PsA and RA patients were more likely than ReA/S patients to have more than one of these viruses simultaneously present⁹³. Of note, none of these differences reached statistical significance.

Table 2: Main characteristics of the 7 included studies presenting data on virus infections, by publication year.

Reference, Country	Study Design, Groups, Exposure	Adjusted Covariates	N(PsA)/ Controls	Results
Louthrenoo (1997) ⁹⁰ ; Thailand.	Cross-sectional study, 100 consecutive HIV patients with musculoskeletal symptoms, detection of HIV antibodies.	None.	9	9 PsA patients.
Njobvu et al. (1998) ⁹¹ ; Africa – Zambia.	Cross-sectional study, 595 new consecutive attendees in arthritis clinic in a 30-month period, presence of antibodies to HIV.	None.	13	Positive test: PsA 92%.

Taglione et al. (1999) ⁷¹ ; <i>Italy</i> .	Case-control study, PsA vs. PS, RA and general Italian population, detection of anti-HCV antibodies in sera.	None.	50/76	Positive test: PsA 12% (95% CI 4.73-25.25) (reference). General Italian population 3.2% p=0.015.
Njobvu and McGill (2000) ⁶⁸ ; <i>Zambia</i> .	Cross-sectional study, 702 new inflammatory arthritis patients attending arthritis clinic in 40-month period, presence of antibodies to HIV.	None.	28	Positive test: PsA 96.4%.
Mehraein et al. (2003) ⁷⁰ ; <i>Germany – Homburg</i> .	Cross-sectional study, PsA, RA, ReA/S vs. normal, detection of B19 capsid protein in synovial specimens.	None.	6/2	Positive test, PsA vs. controls: 66% vs. 50%, p=1.000.
Mehraein et al. (2004) ⁹³ ; <i>Germany</i> .	Cross-sectional study, PsA, RA, ReA/S vs. normal, CMV-DNA and EBV positive cells in synovial specimens.	None.	6/2	Positive test, PsA vs. controls: CMV-DNA 50% vs. 0%, p=0.46. CMV-EA 33.3% vs. 0%, p=1.000. EBV 50% vs. 0%, p=0.46. EBV latent 16.7% vs. 0%, p=1.000. B19 33.3% vs. 50 %, p=1.000. SVI 66.7% vs. 50%, p=1.000. DVI 66.7% vs. 0%, p=0.43.
Palazzi et al. (2005) ⁷² ; <i>Italy</i> .	Cross-sectional study, consecutive PsA vs. consecutive OA or sciatica patients, detection of anti-HCV antibodies.	None.	100/100	Positive test, PsA vs. controls: HCV 1% vs. 4%, p=0.68.

Abbreviations: **B19:** Parvovirus B19, **CMV:** Cytomegalovirus, **CMV-EA:** Cytomegalovirus early antigen, **DVI:** Double virus infection, **EBV:** Epstein-Barr virus, **HCV:** Hepatitis C virus, **HIV:** Human immunodeficiency virus, **OA:** Peripheral osteoarthritis, **PsA:** Psoriatic arthritis, **PS:** Psoriasis, **RA:** Rheumatoid arthritis, **ReA/S:** Reactive arthritis/synovitis and **SVI:** Single virus infection.

4.4 Infections in general

Four of the included studies were not pathogen specific but explored infections in general (table 3). Pattison et al. studied 98 PsA cases and found a statistically significant association between PsA and recurrent oral ulceration with an OR of 4.2 (95% CI 1.96-9.0), which the authors suggest may be a proxy for recent exposure to infection⁶⁰. No association was found with infective diarrhea or conjunctivitis in this study. Eder et al. explored the association between environmental factors and the onset of PsA among psoriasis patients. The study population consisted of 159 patients with recent onset PsA and 159 psoriasis patients without arthritis who were asked if they had been exposed to hypothesized triggers, including infections, in the previous 10 years. Statistically significant association with infections that required antibiotics was found with an OR of 1.7 (95% CI 1.00-2.77)⁵¹. No association was found with infectious diarrhea in this study. Brzewski et al. collected data from consultations to examine the role of focal infections in psoriasis and urticaria. Laryngeal foci of infection were found to be more common among 16 PsA patients compared to 85 psoriasis patients, 43.75% vs. 17.65%, p=0.028 while the rates of gynecological foci of infection were similar⁹⁴. Finally, Eder et al. published the results of a prospective cohort study of 464 psoriasis patients where 51 patients developed PsA during 8 years of follow-up. Association with recent infection was not statistically significant with a RR of 0.96 (CI 0.52-1.77) in an analysis controlled for age at onset of psoriasis and stratified by sex²⁷.

Table 3: Main characteristics of the 4 included studies presenting data on infections in general, by publication year.

Reference, Country	Study Design, Groups, Exposure	Adjusted Covariates	N(PsA)/ Controls	Results
Pattison et al. (2008) ⁶⁰ ; <i>United Kingdom – Manchester.</i>	Case-control study, PsA vs. PS, self-completion questionnaire.	Age and gender.	98/163	PsA vs. controls: Infectious diarrhea 2.3% vs. 8.7%, p=0.035 (OR 0.23 95% CI 0.05-1.06). Conjunctivitis 11% vs. 5.3%, p=0.15 (OR 2.1 95% CI 0.78-5.74). Recurrent oral ulceration 25.3% vs. 8.9%, p=0.0006 (OR 4.20 95% CI 1.96-9.0).
Eder et al. (2011) ⁵¹ ; <i>Canada – Toronto.</i>	Case-control study, PsA vs. PS, standardized questionnaire.	Age, sex, education level, duration and severity of PS.	159/159	PsA vs. controls: Infective diarrhea 12.7% vs. 7%, p=0.68 (OR 1.7 95% CI 0.76-3.79). Infections requiring antibiotics 34.4% vs. 23.7%, p=0.05 (OR 1.7 95% CI 1.00-2.77). Infections that required hospitalization 7.2% vs. 0%, p<0.001.
Brzewski et al. (2013) ⁹⁴ ; <i>Poland – Krakow.</i>	Cross-sectional study, PsA, PS and patients with chronic urticaria, results from consultation and CRP value.	None.	16/85	PsA vs. PS: Laryngological foci of infection 43.75% vs. 17.65%, p=0.028. Gynecological foci of infection 14.29% (1/7 women) vs. 14.81% (4/27 women), p=1.000.
Eder et al. (2016) ²⁷ ; <i>Canada – Toronto.</i>	Cohort study of 464 PS patients followed up for 8 years, information collected from patients.	Analyses controlled for age at onset and stratified by sex.	51	Recent infection (within 1 year): RR 0.96 (CI 0.52 – 1.77, p=0.89).

Abbreviations: CRP: C-reactive protein, PsA: Psoriatic arthritis, PS: Psoriasis and RR: Relative risk.

4.5 Case reports and studies with five or fewer PsA patients

Case reports and studies including five or fewer PsA patients were excluded from the review but warrant a brief mention. Most considered the same pathogens as the included studies, i.e. CT, *staphylococcus*, *streptococcus*, EBV, HCV, HIV, CMV and *Parvovirus B19*. Schaeffer et al. collected 209 synovial fluid samples over a 30-month period, half from inflammatory rheumatic disease patients and the remaining from patients with other conditions. The samples were cultured for *Streptococcus Pyogenes*, *Mycobacterium* and *Mycoplasma*. *Mycoplasma* was detected in eight samples, most from RA patients, but one of the five included PsA patients had a positive culture for *Mycoplasma hominis*⁹⁵. Johnson et al. examined synovial fluid samples from 26 RA patients, 10 OA patients and eight patients with other inflammatory arthritis, including two PsA patients. *Mycoplasma fermentans* was found in nearly all (88%) of the non-rheumatoid inflammatory arthritis cases, including one of the two PsA patients⁹⁶. One case report on *Salmonella typhimurium* described a PsA patient in remission for 5 years who developed severe PsA within 2 weeks of a *Salmonella typhimurium* infection⁶³.

5 Discussion

The studies included in this review suggest a triggering role for infections in the development of PsA, but further research is needed to elucidate the association. The review includes twenty-seven studies exploring this association. As PsA is an uncommon disease, most of the studies were cross-sectional in nature. Eight of the 27 studies showed a statistically significant association between infections and PsA. Additionally, seven studies were inconclusive as they reported mixed results with some statistically significant associations. Five studies did not find any statistically significant associations. This included studies of bacterial pathogens as well as viral infections and infections in general. Two studies presented data from Zambia. While the studies did not present statistical analysis to support an association between infections and PsA, the authors were of the belief that infections are linked with PsA. The five remaining studies neither presented a statistical analysis nor provided enough data to allow for the performance of such analyses. Ultimately, 15 of the 20 studies that presented enough data for statistical analysis showed some statistically significant associations between infections and PsA. The risk of publication bias cannot be excluded, that is a bias of more published data concerning positive results of association between infections and PsA.

In earlier studies, more evidence supported an association between PsA and exposure to Gram positive bacteria as compared to gram-negative bacteria. Notably, streptococcal infections were most often studied. Gram positive bacteria are known to trigger or exacerbate psoriasis and this association may explain why earlier studies homed in on studying gram positive bacteria⁹⁷. One of the studies reviewed includes data supporting a possible link between laryngeal infections and PsA⁹⁴. This is of particular interest given the literature on skin exacerbations linked to sore throat and streptococcal infections. Furthermore, there are reports on the benefit of tonsillectomy as a treatment for psoriasis^{97, 98}. Remarkably, a statistically significant association between PsA and infections was not found when prospectively studied, however an association was found when subjects were asked about past infections requiring antibiotics. Retrospective bias may explain why the retrospective study did find an association, but an alternative explanation worth considering is that antibiotic treatment could act as an effect modifier, highlighting a potential protective effect of infection. Based on these findings, future studies should consider the infectious agent, the location of the infection, and any treatment received when trying to ascertain the role of infection in PsA.

Included studies presenting data from sub-Saharan Africa suggest a role for HIV infection in the development of PsA. However, one limitation of these studies is the lack of an unexposed control group, i.e. without HIV infection. These studies are also hampered by the limited access to healthcare in this area.

5.1 Limitations of the study

This review is limited by both the quality of the available data as well as potential shortcomings of the review process. Preferably, a review of this nature would include meta-analyses but none were available. Moreover, the search was limited to publications with available abstracts published in English. Hence, published data in other languages may have been missed.

Studies presenting data on antibody titers were limited by their cross-sectional design. Hence, it is unclear whether exposure occurred before or after the onset of PsA in those studies. As the immune system of PsA patients may be somewhat stimulated at baseline as compared to controls, the antibody titers should be interpreted with caution. Of note, recall bias is a potential confounder as some studies require subjects to recall 10 or more years of exposure history. Perhaps the most obvious shortcoming of this review is the small number of PsA patients in most studies reviewed. Despite these limitations, the literature clearly suggests a triggering role for infections in the pathogenesis of PsA, particularly laryngeal and streptococcal infections.

5.2 Biological plausibility

PsA is believed to be caused by the dysregulation of the immune system and infections have a clear impact on the immune system. Hence, a potential role for infections in the development of PsA among psoriasis patients is biologically plausible.

5.2.1 Activation of toll-like receptors (TLRs)

Prior studies attempting to elucidate possible mechanism have suggested that gram-negative and gram-positive bacteria induce different patterns of immunoregulation which may be explained by the activation of different TLRs (Toll-like receptors)⁹⁹. TLRs activate different cell types and are highly expressed on most immune cells including fibroblasts, chondrocytes, keratinocytes and endothelial cells¹⁰⁰. Studies have shown that TLRs can modulate inflammatory responses¹⁰⁰. A total of 10 TLRs have been identified in humans. TLR2 and TLR4 are extracellular receptors which recognize lipid-based structures, like the lipopeptides and lipopolysaccharides (LPS) in both gram-positive and gram-negative bacteria¹⁰⁰. TLR2 and TLR4 can therefore activate innate immune cells in response to gram-positive and gram-negative bacteria, respectively¹⁰¹. Carrasco et al. assessed the expressions of membrane bound TLR2 and TLR4 on peripheral blood monocytes and neutrophils from 45 PsA patients and 32 healthy controls. They found that TLR2 was statistically significantly upregulated on monocytes in the PsA group compared to healthy controls. This suggests that gram-positive bacteria exposure could induce higher inflammatory responses in PsA¹⁰¹. The authors hypothesize that overexpression of TLR2 in the skin may be the mechanism linking bacterial exposure and cutaneous inflammation in PsA. With respect to the results of this review, some of the included studies established statistical significant association of gram-positive bacteria, *Streptococcal* and *Staphylococcal* infections, with the development of PsA. Both are part of normal human bacterial flora including the skin flora.

5.2.2 Involvement of CD8+ T cells

Previous studies suggest a role for HIV infection and/or related antigens in the pathogenesis of rheumatic manifestations based on the observation that approximately 65% of HIV positive patients have rheumatic manifestations⁶⁶. Further, there is clear evidence of exacerbation of psoriatic disease and increased prevalence among HIV patients¹⁰². The link between HIV infection and psoriatic disease might be explained by the pathogenesis of HIV, which involves a decreasing number of CD4⁺ T cells, but psoriatic disease is thought to be largely T-cell mediated¹⁰³. This could mean that HIV infections

create an environment conducive to psoriasis, i.e. by decreasing the number of CD4⁺ T cells and increasing the number of CD8⁺ T cells¹⁰³. Moreover, studies have indicated an involvement of CD8⁺ T cells in the pathogenesis of PsA since joints of PsA patients have been found to be enriched in IL-17⁺ CD8⁺ T cells. This was described in a study by Menon et al. which further found that the amount of the IL-17⁺ CD8⁺ T cells correlated with disease activity and progression of joint damage¹⁰⁴. Thus, the changes in T-cell mediated immunity associated with HIV may create an environment compatible with psoriatic disease. While included studies presenting data from sub-Saharan Africa suggest a dramatic role of HIV infection in the development of PsA, the data must be interpreted with caution as local control groups were not included.

5.3 Possible benefits

A better understanding of possible triggering environmental factors, e.g. infections, in the development of PsA among psoriasis patients is undoubtedly very relevant and could possibly bring forth great benefits. Patients may benefit from increased understanding and awareness e.g. how to decrease the risk of developing PsA as much as possible.

Obviously, dermatologists are in a great position to identify psoriasis patients at risk of developing PsA, since the skin lesions normally precede the joint symptoms. Dermatologists could have a chance to execute a preventive role to reduce the risk of psoriasis patients progressing to PsA in addition to their position to diagnose PsA at an early stage and initiate early treatment. Unfortunately, there seems to be a high prevalence of undiagnosed PsA cases among psoriasis patients seen by dermatologists²⁰. Dermatologists understandably focus on the patients' skin symptoms and symptoms of PsA may be overlooked. In a study by Reich et al. of 1,511 patients attending a dermatology clinic for a plaque-type psoriasis, the prevalence of PsA was 20.6% but 144 patients or 9.5% had suspected joint involvement and did not consult a rheumatologist so diagnosis of PsA was not confirmed in these cases²⁰. Therefore, psoriasis patients should be questioned about joint pain, morning stiffness, "sausage digits" (dactylitis) or sign of enthesitis¹².

Considering the possible association of infection with PsA, it is important to keep in mind that patients with autoimmune diseases, like psoriasis and PsA, are at increased risk of infections. The cause of the increased risk is multiplex, there is a loss of integrity of the skin barrier, the cellular immunity is altered and finally patients may receive immunosuppressive therapy e.g. with biologics. Association between infection and biologic treatment of psoriasis was confirmed in a recent longitudinal cohort study which examined the incidence and predictors of infections among psoriasis and PsA patients. During the follow up time, 498 infections were reported among the 695 PsA patients and 74 infections among the 509 psoriasis patients. The HR of the time to first infection in the PsA group vs. psoriasis group was 1.6, $p=0.002$. The risk was found to be higher in patients treated with biologics vs. non-biologics or 1.56 (95% CI 1.22-2.00) for PsA and 1.50 (95% CI 0.64-3.54) for psoriasis¹⁰⁵. Of the psoriasis patients with recorded infection during follow up, 83.9% had only one infection and 3.2% had more than 2 infections compared to the PsA patients where 46.6% had more than 1 infection and 27.7% had 3 or more infections¹⁰⁵. Therefore, the infection rate was

higher among the PsA patients compared to the psoriasis patients. A minority of the infections in this study required hospitalization.

While genetic therapy is not currently a focus for PsA treatment research, this may change in the future. But for now, the most obvious way to try to influence the risk of developing PsA is to find modifiable environmental risk factors. Studies of changes in genetic expression in response to environmental factors is one potential avenue of future studies which could inform preventive measures addressing both environmental and genetic risk.

5.4 Further studies

The association of infections with PsA requires further studies. Small sample sizes have been a limiting factor in earlier studies. Therefore, there is a need for more statistical power and a large-scale, prospective cohort study, directly generalizable to the general population to verify whether there is a significant association between infections and the development of PsA.

Prior studies which suggest a triggering role for infections include both bacterial and viral infections so both groups are possible causal factors and worth looking at in a large-scale population based cohort study. Further studies should evaluate the potentially differential effects of bacterial infections compared to viral infections. Moreover, it remains to be studied whether there are site-specific effects of infections i.e. if infections at a site such as the throat have an effect different from infections at other sites. Greater understanding and knowledge may aid clinicians with respect to treatment plans, preventative strategies and consultation.

6 Conclusions

This systematic review provides an overview of available data evaluating the effect of infections on the risk of developing PsA. The case reports, case-control, and retrospective studies completed to date suggest a role for infections but cannot be taken as adequate proof that there is a true association between infections and the development of PsA among psoriasis patients. There is a need for more statistical power and a large-scale, prospective cohort study, directly generalizable to the general population to verify whether there is a significant association between infections and the development of PsA. Such studies should initially focus on the infectious agents suggested by the results of the reports reviewed here, both bacterial and viral pathogens. Gram positive infections in general and streptococcal infections in particular seem most relevant. The link between HIV and PsA may provide insights into pathogenesis.

The main purpose of this systematic review was to prepare for further studies on this suggested association, specifically which subject they should initially focus. The intent is to continue researching infections as environmental risk factor for PsA and hopefully add to the knowledge pool. The most obvious next step based on these results is to study streptococcal throat infections.

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TITLE PAGE:

**Infections and the Risk of Psoriatic Arthritis among Psoriasis Patients:
A Systematic Review**

Authors

Telma Thrastardottir¹ (orcid.org/0000-0002-5997-3398) and

Thorvardur Jon Love^{1,2} (orcid.org/0000-0002-2680-6120).

Affiliations

1. Center of Public Health Sciences, Faculty of Medicine, University of Iceland.
2. The National University Hospital of Iceland.

Corresponding author

Thorvardur Jon Love, University of Iceland, Sturlugotu 8, 101 Reykjavik, Iceland.

thl@hi.is

Tel: [+354](tel:+3546950296) 6950296

Running title

Psoriatic Arthritis and infections.

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ABSTRACT

Background. Psoriasis and Psoriatic Arthritis (PsA) are related inflammatory diseases with some shared genetic and environmental risk factors. It has been suggested that environmental factors, including infections, can trigger the development of PsA among psoriasis patients. The aim of this review was to systematically examine available data evaluating the effect of infections on the risk of developing PsA.

Methods. A systematic search of the Cochrane Library, PUBMED, Scopus and Web of Science was conducted on March 16 2017, in accordance with the PRISMA statement. The following search terms were used along with „psoriatic arthritis“: „infections“, „risk“, „bacteria“, and „virus“. Abstracts were reviewed and publications meeting the following criteria included: (I) Observational studies on psoriasis and PsA patients, including case-control, cohort or ecologic studies and (II) presenting original data on the association between infections and PsA. The protocol for this systematic review was registered on PROSPERO (ID: 79432).

Results. Twenty-seven original studies presenting data on infections among PsA patients were included. Eight studies showed a statistically significant association between infections and PsA. Additionally, seven studies reported mixed result with some statistically significant associations and five studies did not find statistically significant associations. This included studies of bacterial as well as viral pathogens and of infections in general. The remaining seven studies lacked data to determine statistical significance. Out of all included studies, the total number of included patients was 933 PsA patients and 1611 controls.

Conclusion. While the studies summarized did not all provide evidence supporting an association between infections and PsA certain trends emerged. The available data are inconsistent and further studies are needed to verify or refute this purported association. In particular, laryngeal infections and infections involving streptococci should be studied more carefully.

Keywords: Psoriatic arthritis, infections, risk, and psoriasis.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease affecting 2-3% of the population [1]. The inflammatory joint arthritis Psoriatic Arthritis (PsA) is closely related to psoriasis and can be found in 5 - 42% of psoriasis patients [2]. PsA has a major impact on patient health and quality of life [3]. Strong heritability is seen in PsA and specific Human Leukocyte Antigen (HLA) antigens appear to confer susceptibility but genetic factors do not account for all cases [4,5]. It has been suggested that psoriasis patients with predisposing genetic factors may develop PsA after exposure to triggering environmental factors [6] but the particulars, including effect sizes, remain largely unclear.

Environmental factors associated with psoriasis include streptococcal pharyngitis, stressful life events, humidity, *Human Immunodeficiency Virus* (HIV) infection, trauma, smoking, drugs, cold weather, diet and obesity [7-10]. Similarly, studies have suggested PsA may be associated with Rubella vaccination, infections, HIV infection, obesity, smoking, recurrent oral ulcers, moving home, trauma, physically demanding occupations, and fractured bone requiring hospital admission [11-15]. Longitudinal population-based studies showed that the relative risk (RR) for developing PsA among psoriasis patients was 1.48 among those with a Body Mass Index (BMI) over 35 [14] and 6.46 in a study of women only [16]. In a longitudinal matched cohort study, physical trauma recorded in primary care was associated with PsA among psoriasis patients with a multivariate hazard ratio (HR) of 1.32 for any trauma, 1.46 for bone trauma and 1.50 for joint trauma [13]. Previously published data have also suggested that exposure to infection related triggers might be of relevance [15,12].

The principal aim of this study is to systematically review available data evaluating the effects of infections on the risk of developing PsA.

METHODS

Systematic literature search

A systematic literature search of the Cochrane Library, PUBMED, Scopus and Web of Science was conducted on March 16 2017, in accordance with the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines [17]. The following search terms were used along with „psoriatic arthritis“: „infections“, „risk“, „bacteria“, and „virus“. The search was further limited to articles with available abstracts and published in English. No time frame was fitted for the search nor regarding the publication status. As an example, the search strategy employed was as follows: (((psoriatic arthritis AND infections)) OR (psoriatic arthritis AND risk)) OR (psoriatic arthritis AND bacteria)) OR (psoriatic arthritis AND virus). The protocol for this systematic review was registered on PROSPERO (ID: 79432).

Study Selection

Duplicate publications were removed and abstracts and titles of the remaining publications screened for eligibility. Full texts of articles were obtained for all publications that appeared to meet the inclusion criteria, likewise if there was any uncertainty. Both authors screened the publications in terms of content. When uncertainty rose about whether a publication should be included or not, it was discussed by both authors. Publications meeting the following criteria were included: (I) Observational studies on psoriasis and PsA patients, including case-control, cohort or ecologic studies and (II) presenting original data on the association between infections and PsA. Articles including data on five or fewer PsA cases were excluded from the review as they share more features with case reports than observational studies. Figure 1 shows the progression of the database search and study selection. Included studies were parsed to categories of bacterial infections, viral infections

and infections in general.

Figure 1

Data extraction

Data was extracted directly from each eligible study. Data extracted included information about study design, study groups, how the exposure to infection was examined, adjusted covariates and the result. When p-values were published in comparison between groups, they were likewise extracted. All data were extracted with a predefined structured form. Both authors contributed to the work of clarifying the included studies.

Statistical analyses

When p-values were missing for comparison between groups, they were calculated by Fisher's exact test if sufficient data were available in the published article.

RESULTS

Search results

The search yielded 4,747 articles, after the removal of duplicates. No additional publications were identified from other sources. Altogether 4,579 articles with no data on the association between infection and PsA were excluded after screening of title and abstract, as well as 88 articles that did not present original data. Thirty-eight case reports and studies including 5 or fewer PsA cases were also excluded from the review but are briefly described for completeness.

Twenty-seven original studies presenting data on infections among PsA patients were included: 6 case-control studies, 20 cross-sectional studies and 1 cohort study. Study design, country, exposure (i.e. infection), number of PsA patients and controls, and risk

estimates/results for the included studies are summarized in tables 1-3, parsed into categories of bacterial infections, viral infections and infections in general. Out of all included studies, the total number of included patients was 933 PsA patients and 1611 controls.

Bacterial infections

Seventeen included studies examined bacterial infections and six of them found an association with PsA (table 1). Additionally, five studies reported mixed result with some statistically significant associations.

Gram Positive Bacterial Infections

Streptococcal infections were the subject of six studies and were found to be associated with the development of PsA in four [18-21]. Vasey and colleagues found that 51% of 49 PsA cases were anti-DNase-B positive compared to 10% among normal controls, $p < 0.0001$ [20]. They also described increased reactivity among peripheral PsA as compared to axial PsA, $p < 0.05$. Three studies found an association between PsA and *Streptococcus pyogenes*. Higher immune responses to *Streptococcus pyogenes* rM12 protein (AB and C regions) and IgG antibody levels against each region were observed in 31 PsA patients compared to 88 psoriasis vulgaris patients, 6 Rheumatoid Arthritis (RA) patients and 77 healthy controls by Muto and colleagues [18]. Wang and colleagues similarly demonstrated higher levels of 16S rRNA of *Streptococcus pyogenes* in the blood of 19 PsA cases compared to 17 RA patients and 10 other arthritis patients [21]. Rantakokko and colleagues measured IgM, IgA and IgG serum antibodies against peptidoglycan-polysaccharide (PG-PS) and peptidoglycan (PG) from *Streptococcus pyogenes* in 38 PsA cases and 34 controls and found statistically significant association with IgA-PG-PS [19].

Two of the seven studies exploring associations between PsA and streptococcal infections found no statistically significant connection [22,23]. Thumboo and colleagues' population based nested case-control study matched 60 PsA patients with 120 psoriasis controls and found PsA patients were not more likely to have had a positive streptococcal culture within a period beginning two years before the onset of psoriatic disease, $p=0.528$ (95% CI 0.29-1.90) [23]. Responses to three streptococcal antigens were not statistically significantly different between 21 PsA cases and 15 age matched controls in a study by Grinlinton and colleagues [22].

Two studies demonstrated an association between staphylococcal super antigens and PsA [24,25]. Rahman and colleagues measured serum antibody levels to staphylococcal antigens in 110 patients with various diseases and found statistically significantly higher titers among 22 PsA patients compared to 16 psoriasis patients [24], while Yamamoto and colleagues found a statistically significant difference in mononuclear cell responses in 11 PsA patients compared to normal controls [25].

Gram Negative Bacterial Infections

A possible role for *Chlamydia trachomatis* (CT) infections was explored in two studies [26,27]. Silveira and colleagues collected urethral and endocervical specimens for detection of CT, along with serum for determination of IgG and IgM antibodies. Although they focused on reactive arthritis, they found that of 18 patients with PsA 22.2% had a positive culture for CT but no control group was available. Furthermore, of 14 PsA patients tested 35.7% had serum IgG and 14.3% IgM antibodies, which was not statistically significantly different from a control group of 60 individuals, $p=0.06$ and 0.09 [27]. Lapadula and colleagues found that 22 PsA patients had statistically significantly higher titers of anti-CT antibodies compared to 22

healthy controls, as well as higher antibodies for all four additional pathogens tested for: *Campylobacter foetus*, *Campylobacter jejuni*, *Yersinia enterocolitica*, and *Yersinia pseudotuberculosis* [26]. Previously, Lapadula and colleagues studied the occurrence of anti-bacterial antibodies among seronegative spondyloarthritis (SNA) patients. They compared sera from 101 patients with different rheumatic diseases, including 7 PsA cases, to sera from 31 healthy donors. They found a statistically significant difference in antibody production against *Yersinia enterocolitica*, *Campylobacter intestinalis* and *Yersinia pseudotuberculosis* between the healthy donors and the seronegative polyarthritis patients [28]. All the studies on antibody titers were cross-sectional, and no data presented on the temporal relationship between measured antibody titers and onset of disease.

In a study focused on psoriasis by Stinco and colleagues, *Chlamydophila psittaci* DNA positive samples were not statistically significantly more common among 12 PsA patients than in the general population with an odds ratio (OR) of 20.36 (95% CI 1.2 – 347.6), $p=0.1$ [29]. On the other hand, in a study by Fabris and colleagues *Chlamydophila psittaci* infections were associated with PsA with an OR of 44.8 (95% CI 5.21–385.2), $p<0.0001$ [30]. Trull and colleagues focused on ankylosing spondylitis (AS) patients but included PsA patients, RA patients and healthy controls as comparison. They measured IgA levels for *Klebsiella pneumoniae* but found no difference between the 35 PsA patients and 57 normal controls [31].

One study compared gut bacteria from patients with NORA (new-onset rheumatoid arthritis), CRA (chronic, treated rheumatoid arthritis), PsA and healthy controls. The prevalence of *P.copri* among the 16 PsA cases included was 37.5% compared to 21.4% among the healthy controls, $p=0.3032$ [32].

Non-type Specific Bacterial Infections

Two studies were not specific for type of bacterial infections. Moen and colleagues examined oral bacterial DNA based on the hypothesis that bacteria may perpetuate autoimmunity in joint disease. Statistically significantly higher numbers of bacterial species and higher concentrations were found in the PsA and RA groups compared to controls [33]. Finally, association of recent infection requiring antibiotics as a possible risk factors was examined in a prospective cohort study of 464 psoriasis patients by Eder and colleagues. The patients had not been diagnosed with PsA at the study enrollment and were followed up for 8 years. A total of 51 patients developed PsA in the follow up time and association with recent infection requiring antibiotics was not statistically significant with a RR of 0.88 (CI 0.39-1.98) in an analysis controlled for age at onset of psoriasis and stratified by sex [34].

Table 1

Viral infections

Seven included studies examined viral infections, with HIV infection being the most common subject (table 2).

Human immunodeficiency virus (HIV) infection

HIV infections were the subject of three included studies [35-37]. Louthrenoo and colleagues examined 100 HIV infected patients with musculoskeletal symptoms (including 9 PsA patients) and showed that the HIV infection had been documented before the development of musculoskeletal symptoms in 31 patients [35]. HIV antibodies were measured in 595 new

consecutive attendees in an arthritis clinic in Zambia by Njobvu and colleagues. The prevalence of HIV infection among the 13 PsA cases was 92% compared to approximately 50% among hospital outpatients and 30% of the adult urban population during the period [37]. Another report by Njobvu and McGill described that among 702 inflammatory arthritis patients attending an arthritis clinic in Zambia, 28 had PsA of whom 96% had HIV [36]. These two studies from Zambia appear to be partially based on the same patient pool. The authors note that the prevalence of PsA in their study appeared to be 25-fold higher than in European populations, in areas where PsA was previously rare, and that it appears to be linked to HIV infection which is more common in this area.

Hepatitis C virus (HCV) infection

Two included studies explored *Hepatitis C virus* (HCV) infection [38,39]. Taglione and colleagues found anti-HCV antibodies in the sera of 12% of PsA cases compared to 5.2% in RA and 3.2% in historical controls in the general population reported in another study [40], $p=0.11$ and 0.0004 , respectively [39]. On the other hand, Palazzi and colleagues found no statistically significant difference in the prevalence of HCV antibodies between 100 PsA patients and 100 controls with Osteoarthritis (OA) or sciatica [38].

Viruses in synovium

Mehraein and colleagues have published two reports on viruses in the synovium of patients with inflammatory arthritis, with data on *Parvovirus B19*, *Cytomegalovirus* (CMV), and *Epstein-Barr virus* (EBV) [41,42]. They found that patients with PsA and RA were more likely to have evidence of replicating *Parvovirus B19* in their synovium than patients with reactive arthritis/synovitis (ReA/S) [42]. The proportion of cases expressing B19 virus protein was

especially high in the RA cases (89.7%) and to a lesser extent in the PsA cases with 66% compared to 38.5% in the ReA/S cases. The proportion was higher among the 6 PsA cases compared to the 2 normal controls or 66% vs. 50%, $p=1.000$ [42]. CMV-DNA was detected in 50% of PsA cases, and 31% of RA cases vs. 11.6% in the ReA/S cases. Compared to normal controls the proportion was higher among the PsA cases or 50% vs. 0%, $p=0.46$. Finally, they found that PsA and RA patients were more likely than ReA/S patients to have more than one of these viruses simultaneously present [41].

Table 2

Infections in general

Four of the included studies were not pathogen specific but explored infections in general (table 3). Pattison and colleagues studied 98 cases of PsA and found a statistically significant association between PsA and recurrent oral ulceration with an OR of 4.2 (95% CI 1.96-9.0), which the authors suggest may be a proxy for recent exposure to infection [12]. No association was found with infective diarrhea or conjunctivitis in this study. Eder and colleagues explored the association between environmental factors and the onset of PsA among psoriasis patients. The study population consisted of 159 patients with recent onset PsA and 159 psoriasis patients without arthritis who were asked if they had been exposed to hypothesized triggers, including infections, in the previous ten years. Statistically significant association with infections that required antibiotics was found with an OR of 1.7 (95% CI 1.00-2.77) [15]. No association was found with infective diarrhea. Brzewski and colleagues collected data from consultations to examine the role of focal infections in psoriasis and urticaria. Laryngeal foci of infection were more common among 16 PsA cases than among 85

psoriasis cases, 43.75% vs. 17.65%, $p=0.028$ while the rates of gynecological foci of infection were similar [43]. Finally, Eder and colleagues published the results of a prospective cohort study of 464 psoriasis patients where 51 patients developed PsA during 8 years of follow-up. Association with recent infection was not statistically significant with a RR 0.96 (CI 0.52-1.77) in an analysis controlled for age at onset of psoriasis and stratified by sex [34].

Table 3

Case reports and studies with 5 or fewer PsA cases

Case reports and studies including 5 or fewer PsA cases were excluded from the review but warrant a brief mention. Most considered the same pathogens as the included studies, i.e. CT, *staphylococcus*, *streptococcus*, EBV, HCV, HIV, CMV and *Parvovirus B19*. Schaefferbeke and colleagues collected 209 synovial fluid samples over a 30-month period, half from inflammatory rheumatic disease patients and the remaining from patients with other conditions. The samples were cultured for *Streptococcus Pyogenes*, *Mycobacterium* and *Mycoplasma*. They detected *Mycoplasma* in 8 samples, most from RA patients, but one of the 5 included PsA patients had a positive culture for *Mycoplasma hominis* [44]. Johnson and colleagues examined synovial fluid samples from 26 RA patients, 10 OA patients and 8 patients with other inflammatory arthritis, including 2 PsA cases. They found *Mycoplasma fermentans* in nearly all (88%) of the non-rheumatoid inflammatory arthritis cases, including 1 of the 2 PsA cases [45]. One case report on *Salmonella typhimurium* described a PsA patient in remission for 5 years who developed severe PsA within 2 weeks of a *Salmonella typhimurium* infection [46].

DISCUSSION

The idea of a possible triggering role for infections in the pathogenesis of PsA is anything but novel. A case report from 1979 discussed a patient with a history of *Varicella* virus infection two weeks before the onset of PsA, which might have triggered the arthritis [47]. The studies reviewed here suggest a role for infections but whether there is a true association between infections and the development of PsA among psoriasis patients remains to be determined.

This review describes 27 studies exploring this purported association. As PsA is an uncommon disease, unsurprisingly most of the studies were cross-sectional. Eight of the 27 studies showed a statistically significant association between infections and PsA.

Additionally, seven studies reported mixed result with some statistically significant associations. Five studies did not find statistically significant associations. This included studies of bacterial pathogens as well as viral infections and infections in general. Two studies presented data from in Zambia which in the view of their authors support the hypothesis that infections are linked with PsA but did not present statistical analysis to support those claims. The remaining five studies neither presented a statistical analysis, nor enough data to allow readers to perform such analyses. Thus, 15 of the 20 studies that presented enough data for statistical analysis support a statistically significant association between infections and PsA. The risk of publication bias cannot be excluded, that is a bias of published data concerning positive results of association between infections and PsA.

There was more evidence for an association between PsA and exposure to Gram positive bacteria than to gram-negative bacteria. Notably, streptococcal infections were often studied, perhaps due to their better described association with skin psoriasis, where they are known to trigger or exacerbate psoriasis [48]. One of the studies reviewed here included data supporting a possible link between laryngeal infections and PsA [43]. This is particularly

interesting given the literature on skin exacerbations linked to sore throat and streptococcal infections [48] as well as reports on the benefit of tonsillectomy as a treatment for psoriasis [49]. Interestingly, Eder and colleagues found an association between infections and PsA when subjects were asked about past infections requiring antibiotics, but when they studied the question prospectively a protective effect emerged, although it did not reach statistical significance. Possible explanations include retrospective bias in the first study, but it would be wise to also consider the possibility that antibiotic treatment could modify the effect otherwise associated with sore throat, creating the appearance of a protective effect of infection. Based on these findings, future studies should therefore consider the infectious agent, the location of infection, and any treatment received when trying to decipher the role of infection in PsA.

Included studies presenting data from sub-Saharan Africa suggest a dramatic role for HIV infection in the development of PsA. However, there is a lack of studies with an unexposed control group, i.e. without HIV infection. These studies are also hampered by the limited access to healthcare in this area which is contingent on personal finances. These issues aside, PsA seems to be rare in HIV-negative individuals in sub-Saharan Africa, thus supporting the claim that the observed rates among HIV infected patients are indeed increased [36]. This possible link between HIV infection and PsA is more likely to provide insights into the pathogenesis of this disorder than to provide opportunities for public health interventions, as the treatment and eradication of HIV from human populations is pressing regardless of the presence of autoimmune disease.

Biological plausibility

The potential for infections to play a role in the development of PsA among psoriasis patients is biologically plausible, as PsA is thought to be caused by dysregulation of the immune system and the balance of the immune system is upset by infection. More specifically, Toll like receptors (TLRs) play a role in immunoregulation in bacterial infection and TLR2 and TLR4 can activate innate immune cells in response to gram-positive and gram-negative bacteria, respectively [50]. Monocytes in PsA patients have an increased number of TLR2 receptors compared to healthy controls, suggesting that gram-positive bacteria exposure could induce a more pronounced inflammatory response in PsA [50]. On the other hand, psoriasis and PsA patients are at increased risk of infection. The increased risk is multiplex, there is a loss of integrity of the skin barrier, cellular immunity is altered, and many patients receive immunosuppressive therapy e.g. with biologics.

There is clear evidence of exacerbation of psoriatic disease among HIV patients. Likewise, mounting evidence suggests that the prevalence of psoriatic disease is increased among HIV patients [51]. The link between HIV infection and psoriatic disease might be explained by the pathogenesis of HIV, which involves decreasing number of CD4⁺ T cells, but psoriatic disease is thought to be largely T-cell mediated [52]. It has been suggested that HIV infection creates an environment conducive to psoriasis, i.e. by decreasing the number of CD4⁺ T cells and increasing the number of CD8⁺ T cells [52]. Joints of PsA patients have been found to be enriched in IL-17⁺ CD8⁺ T cells, and the amount of these cells detected seems to correlate with disease activity and progression of joint damage [53]. Thus, the changes in T-cell mediated immunity associated with HIV may create an environment compatible with psoriatic disease.

Limitations and avenues for further investigation

This review is limited both by the quality of the available data as well as some shortcomings of the review process. Ideally, this paper would include a meta-analysis but the available data did not allow for one. The search was limited to publications with available abstracts published in English, so published data in other languages may have been missed.

Studies presenting data on antibody titers were limited by their cross-sectional design which prevented them from determining if exposure occurred before or after the onset of PsA. Furthermore, as the immune system may be somewhat stimulated at baseline in PsA patients resulting in higher antibody titers in general, such results must be interpreted with caution. Some included studies entail a risk of recall bias when subjects recall 10 years or more of history of exposure. Perhaps the most obvious shortcoming is the small number of PsA cases in most studies reviewed.

Despite these limitations there are clear suggestions of an association in several studies exploring laryngeal and streptococcal infections as a possible pathogenic factor for the onset of PsA and these merit further study

CONCLUSION

This systematic review provides an overview of available data evaluating the effect of infections on the risk of developing PsA. The data summarized here do not provide evidence of a clear association between infections in general and the development of PsA. However, the data were inconsistent and suggest that some types of infection merit further study. Future studies should focus on the site of infection and its treatment, as well as on the infectious agent.

Author contribution

TJL was the guarantor of the review. Both authors contributed to the development of the search strategy and inclusion criteria. TP performed the search of the databases and removed the duplications. Both authors screened the publications in terms of content. When uncertainty arose about whether a publication should be included or not, it was discussed by both authors. TJL provided expertise in rheumatology. Both authors contributed to the work of clarifying the included studies. Both authors read, provided feedback and approved the final manuscript.

Conflict of interest

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Tables

Table 1: Main characteristics of the 17 included studies presenting data on bacterial infections, by publication year.

Reference, Country	Study Design, Groups, Exposure	Adjusted Covariates	N(PsA)/ Controls	Results
Vasey and colleagues (1982) [20]; USA – Florida.	Cross-sectional study, PsA and PS vs. RA, other form of dermatitis and normal controls, serum anti-DNase-B.	Age matching.	49/59	Positive, PsA vs. controls: 51% of all PsA patients vs. 10%, $p<0.0001$. 62% of PsA-peripheral, vs. 10%, $p<0.001$. 27% of PsA-central vs. 10%, $p=0.04$.
Trull and colleagues (1983) [31]; England – London.	Cross-sectional study, PsA vs. AS, RA, and healthy controls, serum IgA antibodies to <i>Klebsiella pneumonia</i> .	None.	21/57	Antibody titers: PsA 7.97 ± 0.72 . Controls: 10.00 ± 0.64 .
Lapadula and colleagues (1988) [28]; Italy.	Cross-sectional study, PsA vs. HD, serum antibodies against YEC, YPT, CJ, CI, and CT.	Sex, age and disease duration were comparable between cases and controls.	7/31	Positive test, PsA vs. controls: YEC 42.86% vs. 3.13%, $p=0.015$. YPT 42.86% vs. 3.13%, $p=0.015$. CI 57.14% vs. 31.25%, $p=0.39$. CJ 28.57% vs. 9.38%, $p=0.22$. CT 57.14% vs. 0.00%, $p=0.00047$.
Rahman and colleagues (1990) [24]; USA – Pennsylvania and Philadelphia.	Cross-sectional study, PsA vs. PS, serum antibody titers to soluble peptidoglycan from <i>Staphylococcus aureus</i> .	No correlation with age, sex, duration, severity of disease or number and type of joints involved.	22/16	Antibody titers, PsA vs. Ps: 82 ± 25 vs. 32 ± 21 , $p<0.001$.
Lapadula and colleagues (1992) [26]; Italy.	Cross-sectional study, PsA vs. HD, RA and PS, serum antibodies against YEC, YPT, CJ and CF. Anti-CT antibody titers.	None.	22/22	Positive test, PsA vs. controls: YEC 23% vs. 6%, $p=0.19$. YPT 18% vs. 6%, $p=0.34$. CJ 55% vs. 36%, $p=0.36$. CF 86% vs. 50%, $p=0.02$.
Grinlinton and colleagues (1993) [22]; New Zealand.	Cross-sectional study, PsA vs. RA and healthy controls, proliferative responses of PBL and SFL to 3 streptococcal antigens.	Age matching.	21/15	PBL proliferation, PsA vs. healthy controls, median (range): Strep 1: 10.8 (1.4-159.0) vs. 8.5 (0.5-40.2), $p>0.05$. Strep 2: 19.7 (3.5-391.0) vs. 11.6(4.3-132.0), $p>0.05$. SCW: 3.8(0.6-13.8) vs. 1.8(0.3-10.3), $p>0.05$. SFL proliferation, PsA vs. RA, median (range): Strep 1: 11.6(1.6-24.7) vs. 14.7(7.-30.5). Strep 2: 6.2(3.5-33.6) vs. 5.0(2.6-11.8).
Silveira and colleagues (1993) [27]; USA – New Orleans, Louisiana.	Cross-sectional study, consecutive SNSA (AS, RS and PsA) patients vs. HBDs, self-questionnaire, self-evaluation and physical examination by rheumatologist. Specimen samples from Urethral and endocervical swabs. Serum for determination of IgG and IgM antibodies against CT.	None.	18/60	Positive test, PsA vs. controls: CT 22.2% vs. 0%, $p=0.002$. IgG 35.7% vs. 8.3%, $p=0.02$. IgM 14.3% vs. 1.8%, $p=0.04$.
Muto and colleagues (1996) [18]; Japan.	Cross-sectional study, PsA vs. PV, RA and healthy controls, <i>in vivo</i> immune response to <i>Streptococcus pyogenes</i> , rM12 protein (AB and C regions) and	None.	31/77	Mean antibody levels to C region: PsA 20.193 ± 3.285 (reference). Controls 3.417 ± 395 ($p<0.001$). Mean antibody levels to AB region: PsA 2.172 ± 468 (reference).

	IgG antibody level against each region measured.			Controls 1.510±253. No statistically significant difference of the responses to the AB region.
Rantakokko and colleagues (1997) [19]; <i>Finland</i> .	Case-control study, PsA, NAP and RA vs. healthy controls, IgM, IgA and IgG class serum antibodies against PG-PS and PG from GAS (<i>Streptococcus Pyogenes</i>). Data also collected regarding recent infections, antibiotic treatments and exacerbations of PS and/or arthritis.	The RA patients were matched with the PsA patients by sex, age and duration of the arthritis.	38/34	Antibody response, PsA vs. controls: IgA - PG-PS 28.8(0-148) vs. 15.1(1-74), p<0.05. IgG - PG-PS 24.5(6-170) vs. 15.8(2-142). IgG - PG 18.6(2-75) vs. 17.8(4-78). Only PsA cases had slightly increased, but not statistically significantly increased values for the IgA class.
Wang and colleagues (1999) [21]; <i>USA – Florida</i> .	Cross-sectional study, PsA vs. RA and other arthritis controls (RS, AS, OA and IBD), detection of 16S ribosomal RNA of GAS (<i>Streptococcus pyogenes</i>), GBS (<i>Streptococcus agalactiae</i>) and <i>Streptococcus pneumoniae</i> in peripheral blood and SF.	None.	19/27	Positive test, PsA vs. controls: GAS 7 vs. 1, p=0.006. GBS 2 vs. 2, p=1. <i>Streptococcus pneumoniae</i> was absent from all specimens.
Yamamoto and colleagues (1999) [25]; <i>Japan</i> .	Cross-sectional study, PsA vs. PV patients and normal controls, response of PBMC to Staphylococcal super antigens, SEA, SEB and SEC1.	None.	11/19	PBMC responses, PsA vs. controls: SEA 31.819±812dpm vs. 21.989±427dpm, p<0.05. SEB 38.715±719dpm vs. 23.708±466dpm, p<0.05. SEC1 29.740±633dpm vs. 20.291±582dpm, p<0.05.
Thumboo and colleagues (2002) [23]; <i>USA – Minnesota</i> .	Population based nested case-control study, PsA vs. PS, medical records and patient survey information from the Rochester Epidemiology Project.	Each case of PsA was matched with 2 PS controls with age, gender and PS duration/date of onset.	60/120	PsA vs. controls: <i>Streptococcal</i> infection 16.7% vs. 20%, p=0.528 (OR 0.74 95% CI 0.29-1.90). Use of corticosteroid 16.7% vs. 5%, p=0.015 (OR 4.33 95% CI 1.34-14.02), p=0.009 (OR 5.54 95% CI 1.54-19.87) after adjusting for the influence of gender, age and duration of PS.
Moen and colleagues (2006)[33]; <i>Norway</i> .	Cross-sectional study, PsA vs. RA and osteoarthritis controls, serum and SF samples extracted for oral bacterial DNA detection of 40 different bacteria.	None.	14/9	Number of species in serum, PsA vs. controls: 5.4 (±2.7 SD) vs. 2.1 (±1.7 SD), p=0.009. Number of species in SF, PsA vs. controls: 19.4 (±7.1 SD) vs. 4.0 (±1.7 SD), p<0.001. Higher means of DNAs were found in PsA SF compared to PsA serum, p<0.001. Higher concentrations of bacterial DNAs were found in RA and PsA compared to controls.
Fabris and colleagues (2011) [30]; <i>Italy</i> .	Cross-sectional study, PsA vs. HBDs, presence of CP DNA assessed in PBMC.	No difference in age, sex, disease duration and undergoing therapies were noticed between CP-positive and CP-negative patients, nor between seropositive and	36/225	Positive test, PsA vs. HBD: 16.7% vs. 0.4%, p=0.0001 (OR 44.8 95% CI 5.21-385.2).

		seronegative patients.		
Stinco and colleagues (2012) [29]; <i>Italy</i> .	Cross-sectional study, PsA and PS vs. healthy controls, bacterial DNA of CP, CPN and CT extracted from PBMC.	CP positive and negative patients did not differ statistically significantly in age, sex and disease duration.	12/225	Positive test, PsA vs. controls: CP 8% vs. 0.4%, p=0.099. All patients and controls were negative for CPN and CT.
Scher and colleagues (2013) [32]; <i>United States</i> .	Case-control study, PsA, RA vs. HLT, 16S ribosomal RNA gene sequencing on stool samples.	None.	16/28	Prevalence of <i>P. copri</i> , PsA vs. HLT: 37.5% vs. 21.4%, p=0.3032. ESR (mm/h, mean): 19.7 vs. 10.2. CRP (mg/l, mean): 7.6 vs. 1.1.
Eder and colleagues (2016) [34]; <i>Canada - Toronto</i> .	Cohort study of 464 PS patients followed up for 8 years, information collected from patients.	Analyses controlled for age at onset and stratified by sex.	51	Recent infection requiring antibiotics (within 1 year): RR 0.88 (CI 0.39 – 1.98, p=0.75).

Abbreviations: AS: Ankylosing spondylitis, ESR: Erythrocyte sedimentation rate, CF: *Campylobacter foetus*, CJ: *Campylobacter jejuni*, CI: *Campylobacter intestinalis*, CP: *Chlamydomydia psittaci*, CPN: *Chlamydomydia pneumonia*, CRP: C-reactive protein, CT: *Chlamydia trachomatis*, GAS: Group A streptococci, GBS: Group B streptococci, HBDs: Healthy blood donors, HD: Healthy donors, HLT: Healthy controls, IBD: Inflammatory bowel disease, NAP: Non-arthritis psoriasis, OA: *Osteoarthritis*, PBL: Peripheral blood lymphocytes, PBMC: Peripheral blood mononuclear cells, PG: Peptidoglycan, PG-PS: Peptidoglycan-polysaccharide, PsA: Psoriatic arthritis, PS: Psoriasis, PV: Psoriasis vulgaris, RA: Rheumatoid arthritis, RR: Relative risk, RS: Reiter's syndrome, SCW: Streptococcal cell wall preparation, SEA: Staphylococcal enterotoxin A, SEB: Staphylococcal enterotoxin B, SEC1: Staphylococcal enterotoxin C1, SF: Synovial fluid, SFL: Synovial fluid lymphocytes, SNSA: Seronegative spondyloarthropathy arthritis, YEC: *Yersinia enterocolitica* and YPT: *Yersinia pseudotuberculosis*.

Table 2: Main characteristics of the 7 Included studies presenting data on virus infections, by publication year.

Reference, Country	Study Design, Groups, Exposure	Adjusted Covariates	N(PsA)/ Controls	Results
Louthrenoo (1997) [35]; <i>Thailand</i> .	Cross-sectional study, 100 consecutive HIV patients with musculoskeletal symptoms, detection of HIV antibodies.	None.	9	9 PsA patients.
Njobvu and colleagues (1998) [37]; <i>Africa – Zambia</i> .	Cross-sectional study, 595 new consecutive attendees in arthritis clinic in a 30-month period, presence of antibodies to HIV.	None.	13	Positive test: PsA 92%.
Taglione and colleagues (1999) [39]; <i>Italy</i> .	Case-control study, PsA vs. PS, RA and general Italian population, detection of anti-HCV antibodies in sera.	None.	50/76	Positive test: PsA 12% (95% CI 4.73-25.25) (reference). General Italian population 3.2% p=0.015.
Njobvu and McGill (2000) [36]; <i>Zambia</i> .	Cross-sectional study, 702 new inflammatory arthritis patients attending arthritis clinic in 40-month period, presence of antibodies to HIV.	None.	28	Positive test: PsA 96.4%.
Mehraein and colleagues (2003) [42]; <i>Germany – Homburg</i> .	Cross-sectional study, PsA, RA, ReA/S vs. normal, detection of B19 capsid protein in synovial specimens.	None.	6/2	Positive test, PsA vs. controls: 66% vs. 50%, p=1.000.
Mehraein and colleagues (2004) [41]; <i>Germany</i> .	Cross-sectional study, PsA, RA, ReA/S vs. normal, CMV-DNA and EBV positive cells in synovial specimens.	None.	6/2	Positive test, PsA vs. controls: CMV-DNA 50% vs. 0%, p=0.46. CMV-EA 33.3% vs. 0%, p=1.000. EBV 50% vs. 0%, p=0.46. EBV latent 16.7% vs. 0%, p=1.000. B19 33.3% vs. 50 %, p=1.000. SVI 66.7% vs. 50%, p=1.000. DVI 66.7% vs. 0%, p=0.43.
Palazzi and colleagues (2005) [38]; <i>Italy</i> .	Cross-sectional study, consecutive PsA vs. consecutive OA or sciatica patients, detection of anti-HCV antibodies.	None.	100/100	Positive test, PsA vs. controls: HCV 1% vs. 4%, p=0.68.

Abbreviations: B19: *Parvovirus B19*, CMV: *Cytomegalovirus*, CMV-EA: *Cytomegalovirus* early antigen, DVI: Double virus infection, EBV: *Epstein-Barr virus*, HCV: *Hepatitis C virus*, HIV: *Human immunodeficiency virus*, OA: *Peripheral osteoarthritis*, PsA: *Psoriatic arthritis*, PS: *Psoriasis*, RA: *Rheumatoid arthritis*, ReA/S: *Reactive arthritis/synovitis and* SVI: *Single virus infection*.

Table 3: Main characteristics of the 4 included studies presenting data on infections in general, by publication year.

Reference, Country	Study Design, Groups, Exposure	Adjusted Covariates	N(PsA)/ Controls	Results
Pattison and colleagues (2008) [12]; <i>United Kingdom – Manchester.</i>	Case-control study, PsA vs. PS, self-completion questionnaire.	Age and gender.	98/163	PsA vs. controls: Infectious diarrhea 2.3% vs. 8.7%, p=0.035 (OR 0.23 95% CI 0.05-1.06). Conjunctivitis 11% vs. 5.3%, p=0.15 (OR 2.1 95% CI 0.78-5.74). Recurrent oral ulceration 25.3% vs. 8.9%, p=0.0006 (OR 4.20 95% CI 1.96-9.0).
Eder and colleagues (2011) [15]; <i>Canada – Toronto.</i>	Case-control study, PsA vs. PS, standardized questionnaire.	Age, sex, education level, duration and severity of PS.	159/159	PsA vs. controls: Infective diarrhea 12.7% vs. 7%, p=0.68 (OR 1.7 95% CI 0.76-3.79). Infections requiring antibiotics 34.4% vs. 23.7%, p=0.05 (OR 1.7 95% CI 1.00-2.77). Infections that required hospitalization 7.2% vs. 0%, p<0.001.
Brzewski and colleagues (2013) [43]; <i>Poland – Krakow.</i>	Cross-sectional study, PsA, PS and patients with chronic urticaria, results from consultation and CRP value.	None.	16/85	PsA vs. PS: Laryngological foci of infection 43.75% vs. 17.65%, p=0.028. Gynecological foci of infection 14.29% (1/7 women) vs. 14.81% (4/27 women), p=1.000.
Eder and colleagues (2016) [34]; <i>Canada - Toronto.</i>	Cohort study of 464 PS patients followed up for 8 years, information collected from patients.	Analyses controlled for age at onset and stratified by sex.	51	Recent infection (within 1 year): RR 0.96 (CI 0.52 – 1.77, p=0.89).

Abbreviations: CRP: C-reactive protein, PsA: Psoriatic arthritis, PS: Psoriasis and RR: Relative risk.

Figures

Figure 1: PRISMA flow diagram of the literature search and study selection.