Markers of systemic inflammation in psoriasis: a systematic review and meta-analysis.

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ABSTRACT

Background: Studies investigating systemic inflammation in psoriasis use different serum markers and report discrepant results.

Objectives: To determine whether systemic inflammation is elevated in psoriasis patients compared to healthy controls and to measure the extent of this elevation, by summarizing available data on serum inflammatory markers.

Methods: PubMed, Embase and Web of Science were searched from inception to March 2011. We included studies comparing the serum inflammatory markers Interleukin (IL)1-beta, IL-6, IL-10, C-reactive-protein (CRP), Intracellular adhesion molecule-1 (ICAM-1), E-selectin or Tumor necrosis factor-alpha (TNFα) in psoriasis with healthy controls. Difference in serum marker levels between patients and controls were pooled as standardized mean differences (SMD) (Cohen's d) using random-effects model.

Results: Seventy-eight studies were eligible. Of the 7852 individuals, 3085 had (severe plaque) psoriasis. The pooled SMDs were higher in psoriasis compared to healthy controls for IL-6 (d=1.32, 95%CI 0.83-1.81), CRP (d=1.83, 95%CI 0.76-2.90), TNFα (d=1.32, 95%CI 0.86-1.79), E-selectin (d=1.78, 95%CI 1.32-2.25) and ICAM-1 (d=1.77, 95%CI 1.15-2.39). The SMD between cases and controls for IL-1β and IL-10 was not significant. Age had a significant effect on the SMD for IL-6 and TNFα. For IL-6 the effect size was higher for plaque psoriasis studies (d=1.98). The effect size was not influenced by the PASI, measurement method or quality assessment.

Conclusions: The pooled analyses suggest modest, but significantly elevated levels of the pro-inflammatory cytokines in the serum of psoriasis patients with predominantly severe disease. To what extent this modest increment is clinically relevant could be investigated in a synthesis of all studies measuring inflammation before and after anti-psoriatic therapy.

INTRODUCTION

Psoriasis is a chronic, relapsing, inflammatory skin disease that affects 2% of the Caucasian population.[1] This skin condition is histologically characterized by abnormal proliferation of keratinocytes and infiltration of immune cells, predominantly T-cells and dendritic cells in psoriatic lesions.[2] The majority of inflammatory cells and cytokines remain in the tissue and a relatively small proportion can be measured in the peripheral blood, such as interleukins (ILs)[3] which have shown to be elevated in patients with cardiovascular disease, metabolic syndrome and diabetes.[4,5]

The search for markers in psoriasis was revived as these were not only found in the skin, but researchers also identified a spillover of inflammatory markers into the systemic circulation, using them to measure disease severity, to objectively monitor treatment response, find new targets for therapy and to explain comorbidities in psoriatic patients.[6,7]

Much attention has been drawn towards "upgrading" psoriasis from a skin condition to a systemic disease as serum biomarkers for inflammation are raised in psoriasis[8] and patients could therefore have a higher risk of developing systemic comorbidities.[6] Data on serum levels of pro- and anti- inflammatory cytokines in psoriasis patients compared to controls are controversial, with some authors not observing any difference, while others report elevated or decreased levels in psoriasis.[3] The studies to date have small sample sizes, investigate different markers and techniques to assess inflammation; moreover measurement of serum inflammation is often not their primary objective.

We conducted the first systematic review and meta-analysis to determine whether six well-known pro-inflammatory serum markers IL-1β, IL-6, C-reactive protein (CRP), Tumor necrosis factor-alpha (TNFα), Intracellular adhesion molecule-1 (ICAM-1), E-selectin are elevated and anti-inflammatory IL-10 decreased in treatment naïve psoriatic patients compared to controls.

MATERIAL AND METHODS

Background to literature search

We investigated whether certain markers of inflammation were elevated in psoriasis patients compared to controls and were interested the role of inflammatory markers in the development of comorbidities. We therefore conducted an open literature search listing inflammatory markers most commonly mentioned in psoriasis and cardiovascular disease (CVD) (Supplementary Figure 1). This is the case for IL-1β, IL-6 and TNFα which are produced in adipose tissue, are known to be pro-atherogenic but are also involved in skin inflammation in psoriasis as they are produced by the keratinocytes.[2,6] CRP is often used to measure suspected inflammatory state in psoriasis patients, whereas high sensitivity

CRP is used in the prediction of CVD.[9-11] The type of CRP measured depended on the objective of the study. We included all studies measuring CRP, regardless of the type. The adhesion molecules E-selectin and ICAM-1 expressed on endothelial cells are equally known as mediators of inflammation in the prediction of CVD.[12] (Figure 1, Table 1)

Other than the six above-mentioned pro-inflammatory markers, we chose IL-10 as anti- inflammatory cytokine to confirm the hypothesis that IL-10 is below detectable levels in psoriasis patients or at the same level as in healthy controls.[3,6]

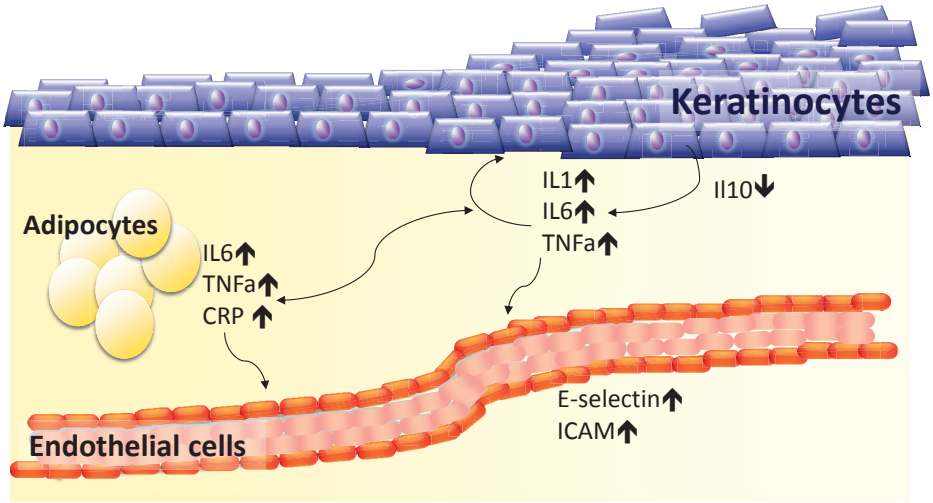

Figure 1. A simplified model, depicting the role of the inflammatory markers in this meta-analysis. Abbreviations: CRP, C-reactive protein; ICAM intracellular adhesion molecule; IL, interleukin; TNF, tumor necrosis factor.

Eligibility criteria

Inclusion and exclusion criteria were determined before the search was conducted. We included human studies comparing psoriasis patients with 'healthy' controls, in which one or more of the following inflammatory markers were measured in the serum: IL-1β, IL-6, IL-10, CRP, TNFα, E-selectin and ICAM-1. Studies were excluded if psoriatic arthritis (PsA) was the main exposure. Case reports and letters were excluded. If several studies reported results from the same study population, the most complete report was included.

Search strategy

The systematic search was performed by a medical librarian (L.V.) in PubMed, Embase and Web of Science from 1988 to March 2011. The search strategy is presented as supplementary material Table 1.

Table 1. Role of the selected inflammatory markers.

Il-1β	IL-1 is a pro-inflammatory cytokine which activates neutrophils, monocytes, eosinophils and basophils and triggers production of TNFα, IL-6 by macrophages. Keratinocytes are the main source of IL-1β in the skin.
Il-6	IL-6 is a pro-inflammatory cytokine and is involved in the growth and differentiation of dermal and epidermal cells and can directly stimulate T-cell migration to the epidermis. IL-1 and TNFα activate keratinocytes to produce IL-6.
Il-10	IL-10 acts as an anti-inflammatory cytokine and can be produced by different cell populations, including keratinocytes, T-cell subsets, macrophages and monocytes and is capable of inhibiting synthesis of pro-inflammatory cytokines.
TNFα	TNFα influences the proliferation, activation and differentiation of many cells and enhances the synthesis of IL-1, IL-6 and expression of adhesion molecules such as E-selectin and ICAM-1.
(hs)CRP	CRP is a pro-inflammatory acute phase protein produced by the liver and a sensitive marker of systemic inflammation. Traditional assays for CRP are insufficiently sensitive for measuring the lower serum values associated with atherosclerotic disease. These can be measured by the newer hsCRP assays.
E-selectin	E-selectin is a pro-inflammatory soluble cell adhesion molecule expressed on endothelial cells activated by cytokines. It is enhanced by TNFα and CRP through endothelial cells. During inflammation, E-selectin recruits leucocytes to the site of injury.
ICAM-1	The soluble intracellular adhesion molecule ICAM-1 is induced by TNFα and IL1 and CRP through endothelial cells. It is expressed by the vascular endothelium, macrophages and lymphocytes. It causes leucocytes to bind to endothelial cells and then to migrate into tissues.

Abbreviations: Il, Interleukin; TNF, Tumor Necrosis Factor; (hs)CRP, (high sensitivity) C-reactive protein; ICAM, Intracellular Adhesion Molecule.

Data extraction and quality assessment

Data was collected using a standard data extraction form (Table 2). Information from articles in a language other than English, Dutch, French or German was extracted if an English abstract and comprehensive tables were available.

The quality of the articles was assessed using a checklist based on the REMARK guidelines, also used in other meta-analyses.[13,14] The definition of each checklist item was discussed; two points were allocated to each positive item, one point to a partially fulfilled item and no points were given if the item criterion was not met. The sum of these points was divided by the maximum number of points an article could score.

Study selection

Two reviewers (E.A.D. and E.A.M.V.) independently screened all titles, abstracts and full texts of selected articles and conducted the data extraction and the quality assessment. Disagreements were resolved by consensus.

Table 2. Characteristics of included studies.

		Psoriasis					Healthy controls			Markers and measurement methods [1]							
Author, Year	**Country**	**N**	**Mean age**	**% Male**	**% Plaque psoriasis**	**PASI**	**N**	**Mean age**	**% Male**	**Il-1β**	**Il-6**	**Il-10**	**TNFα**	**(hs)CRP**	**E-selectin**	**ICAM-1**	**Quality score [2]**
Abdel-Hamid *et al*,[43] 2010	Egypt	60	40	48	83.3	11.8	21	43	48	·	·	·	1	·	·	·	27/52
Abe *et al*,[44] 2002	USA	13	44	77	100	18.9	40	-	-	1	·	·	·	·	·	·	23/56
Ameglio *et al*,[45] 1994	Italy	14	41	7	85.7	-	14	43	14	·	·	·	·	·	·	1	10/52
Anderson *et al*,[46] 2010	Sweden	14	47	29	100	8.5	14	47	29	5	5	5	5	·	·	·	32/56
Ardic *et al*,[47] 2010	Turkey	58	36	47	-	13.0	36	40	47	·	·	·	·	9	·	·	19/53
Arican *et al*,[48] 2005	Turkey	30	35	60	100	9.3	23	35	61	·	1	·	1	·	·	·	22/52
Asadullah *et al*,[49] 1999	Germany	29	-	-	-	-	28	-	-	·	·	·	1	·	·	·	24/52
Balci *et al*,[50] 2009	Turkey	51	40	47	100	6.6	32	42	47	·	·	·	·	4	·	·	17/56
Bevelacqua *et al*,[51] 2006 (mild pso)	Italy	18	36	56	100	-	25	40	56	1	1	·	1	4	·	·	23/52
Bevelacqua *et al*,[51] 2006 (severe pso)	Italy	26	46	62	100	-	25	40	56	1	1	·	1	4	·	·	23/52
Bonifati *et al*,[52] 1994	Italy	20	53	5	90	11.4	10	42	60	·	9	·	1	·	·	·	26/52
Bonifati *et al*,[53] 1995	Italy	19	53	32	100	-	22	57	36	·	·	·	·	·	1	·	22/52
Borghi *et al*,[54] 2008	Italy	65	54	80	100	21.2	114	54	80	·	·	5	·	·	·	·	28/56
Borska *et al*,[55] 2006	Czech	56	48	63	-	22.2	40	48	-	·	·	·	1	·	1	1	29/56
Borska *et al*,[56] 2008	Czech	55	38	64	-	21.7	47	31	57	·	·	1	·	·	·	·	26/56
Bubl *et al*,[57] 1994	Germany	41	-	-	100	-	31	-	-	·	·	·	·	·	·	1	15/55
Carducci *et al*,[58] 1994	Italy	25	51	24	92	11.4	50	48	40	·	·	·	·	·	·	5	15/52
Chandran *et al*,[59] 2010	Canada	26	45	46	100	4.9	26	43	46	·	·	·	·	1	·	·	26/53
Chodorowska,[60] 1998	Poland	27	35	100	-	25.8	20	35	100	·	·	·	1	·	·	·	28/56
Chodorowska *et al*,[61] 2004	Poland	175	38	100	-	29.0	30	40	100	·	·	·	·	1	·	·	22/56
Coimbra *et al*,[62] 2009	Portugal	56	44	55	100	19.3	37	47	57	·	·	·	·	3	·	·	23/56
Coimbra *et al*,[63] 2010a	Portugal	73	45	55	100	18.0	38	47	45	·	·	·	·	3	·	·	29/56
Coimbra *et al*,[64] 2010b	Portugal	66	43	53	100	18.8	37	50	57	·	1	·	1	3	·	·	32/56
Coimbra *et al*,[65] 2010c	Portugal	34	45	41	100	22.6	20	44	45	·	·	·	1	·	·	·	31/56
Coimbra *et al*,[66] 2010d	Portugal	34	43	47	100	14.8	37	47	57	·	·	·	·	3	·	·	34/56
Corbetta *et al*,[67] 2006	Italy	10	41	100	100	13.0	10	41	100	·	·	·	1	·	·	·	29/56
Ctirad *et al*,[68] 2008	Czech	49	38	53	100	20.9	48	30	-	·	·	·	·	3	·	·	28/56
Czech *et al*,[69] 1996	Germany	16	31	56	100	-	16	28	50	·	·	·	·	·	1	·	27/56
De Pita *et al*,[70] 1996	Italy	30	50	77	90	21.3	11	50	73	·	·	·	·	·	·	1	29/56
De Pita *et al*,[71] 1999	Italy	24	52	63	100	8.8	20	52	60	·	·	·	·	·	·	1	26/56

Table 2. Characteristics of included studies. (continued)

		Psoriasis					Healthy controls			Markers and measurement methods [1]						
Author, Year	**Country**	**N**	**Mean age**	**% Male**	**% Plaque psoriasis**	**PASI**	**N**	**Mean age**	**% Male**	**Il-1β**	**Il-6**	**Il-10**	**TNFα**	**(hs)CRP**	**E-selectin**	**ICAM-1**	**Quality score [2]**
Deeva *et al*,[72] 2010 (severe plaque pso)	Italy	10	33	50	100	44.2	10	37	50	·	9	9	·	·	·	·	23/52
Deeva *et al*,[72] 2010 (mild plaque pso)	Italy	35	50	57	100	8.7	10	37	50	·	9	9	·	·	·	·	23/52
Deeva *et al*,[72] 2010 (erythrodermic pso)	Italy	10	38	50	0 [3]	64.6	10	37	50	·	9	·	·	·	·	·	23/52
Fazio *et al*,[73] 1994	Italy	20	53	5	90	11.4	10	42	60	·	·	·	·	·	·	5	21/53
Galadari and Sheriff,[17] 2005 (mild pso)	Abu Dhabi	24	-	67	-	6.6	10	-	70	·	1	·	·	·	·	·	22/53
Galadari and Sheriff,[17] 2005 (moderate pso)	Abu Dhabi	9	-	78	-	22.5	10	-	70	·	1	·	·	·	·	·	22/53
Galadari and Sheriff,[17] 2005 (severe pso)	Abu Dhabi	5	-	40	-	44.4	10	-	70	·	1	·	·	·	·	·	22/53
Gangemi *et al*,[74] 2003	Italy	16	41	63	-	35.8	16	40	56	·	·	·	·	·	·	1	19/53
Gonul *et al*,[75] 2009	Turkey	54	39	65	-	8.9	50	38	66	1	1	·	1	·	·	.	14/56
Griffiths *et al*,[76] 1996	Germany	32	42	59	-	15.0	99	28	56	·	·	·	·	·	·	1	22/52
Groves *et al*,[18] 1995	UK	9	-	-	0 [3]	-	17	53	41	·	·	·	·	·	1	1	23/52
Jacob *et al*,[77] 2003	USA	12	48	58	75	-	5	35	20	5	5	5	5	·	·	·	15/52
Jadali *et al*,[78] 2007	Iran	40	38	55	52.5	6.3	40	39	55	·	·	1	·	·	·	·	23/52
Johnston *et al*,[37] 2008	Iceland	30	53	53	100	15.3	29	47	45	5	5	·	·	·	·	·	29/56
Kagami *et al*,[79] 2010	USA	21	42	-	-	22.2	17	34	0	·	·	·	1	·	·	·	22/56
Kanda *et al*,[80] 2010	Japan	61	52	74	100	8.1	31	46	65	1	1	1	1	·	·	·	24/56
Karabudak *et al*,[81] 2008	Turkey	20	23	100	-	13.0	20	21	100	·	·	·	·	4	·	·	20/52
Kaur *et al*,[82] 2008 (BMI<25)	Estonia	10	50	60	100	14.5	22	-	-	·	1	·	·	·	·	·	21/52
Kaur *et al*,[82] 2008 (BMI>30)	Estonia	12	47	58	100	12.4	22	-	-	·	1	·	·	·	·	·	17/52
Kaya *et al*,[83] 2010	Turkey	58	36	47	-	-	36	40	47	·	·	·	·	9	·	·	6/52
Kitamura *et al*,[84] 1999	Japan	30	49	50	0 [4]	-	20	47	50	·	·	·	1	·	1	1	19/56
Kowalzick *et al*,[85] 1993	Germany	10	46	100	100	18.6	17	33	53	·	·	·	·	·	·	1	24/56
Krasowska *et al*,[86] 1998a	Poland	59	-	41	100	23.8	10	-	40	·	1	·	·	·	·	·	13/52
Krasowska *et al*,[87] 1998b	Poland	23	-	-	-	-	20	-	-	·	·	·	·	·	·	9	8/56
Krasowska *et al*,[88] 2000	Poland	23	39	65	-	25.4	11	36	45	·	·	·	·	·	·	1	22/56
Laurent *et al*,[89] 1981	UK	15	-	-	-	-	21	-	-	·	·	·	·	5	·	·	20/52
Lecewicz-Torun *et al*,[90] 1997	Poland	19	35	47	78.9	-	14	38	50	·	·	·	·	·	·	1	18/52

Table 2. Characteristics of included studies. (continued)

		Psoriasis					Healthy controls			Markers and measurement methods [1]							
Author, Year	**Country**	**N**	**Mean age**	**% Male**	**% Plaque psoriasis**	**PASI**	**N**	**Mean age**	**% Male**	**Il-1β**	**Il-6**	**Il-10**	**TNFα**	**(hs)CRP**	**E-selectin**	**ICAM-1**	**Quality score [2]**
Long *et al*,[91] 2010	China	58	36	62	62.1	23.7	50	36	62	·	·	·	·	·	1	1	32/56
Love *et al*,[92] 2010	USA	71	42	46	-	-	2385	39	50	·	·	·	·	9	·	·	26/52
Martinez-Sales *et al*,[93] 2010	Spain	20	-	-	-	-	20	-	-	·	1	·	·	·	1	·	8/52
Martyn-Simmons *et al*,[94] 2011	UK	60	51	77	100	9.2	117	49	42	·	·	·	·	3	·	·	25/53
McLoone *et al*,[95] 2004	UK	5	43	100	-	-	15	43	100	·	·	1	1	·	·	·	21/56
Mizutani *et al*,[96] 1997	Japan	63	47	56	100	-	20	47	55	1	1	·	1	·	·	·	17/52
Mussi *et al*,[97] 1997	Italy	37	53	32	100	11.4	30	49	30	·	·	·	1	·	·	·	23/56
Ohtsuka,[98] 2008	Japan	52	54	62	100	12.8	147	54	62	·	·	·	·	4	·	·	15/52
Park and Kim,[99] 2004	Korea	15	-	-	-	-	15	-	-	·	·	·	·	·	1	·	12/52
Qiu *et al*,[100] 2005	China	33	32	55	-	12.9	30	32	57	·	1	·	1	·	·	·	29/56
Reddy *et al*,[19] 2010	Worldwide	105	45	70	100	17.0	30	-	-	·	·	1	1	·	·	1	31/56
Rocha-Pereira *et al*,[101] 2004	Portugal	60	47	57	100	-	40	47	55	·	·	·	·	4	·	.	20/52
Roussaki-Schulze *et al*,[102] 2005	Greece	45	-	69	100	-	45	-	-	·	1	1	1	·	·	.	23/56
Schopf *et al*,[103] 1993	Germany	17	42	-	94.1	-	17	42	-	·	·	·	·	·	·	1	23/52
Seishima *et al*,[104] 1998 (pso)	Japan	31	55	61	-	-	53	53	57	·	5	·	1	·	·	·	15/52
Seishima *et al*,[104] 1998 (active GPP)	Japan	9	23	56	0 [5]	-	53	53	57	·	5	·	1	·	·	·	15/52
Serwin *et al*,[105] 2006	Poland	37	31	62	100	12.7	20	37	-	·	·	·	·	4	·	·	36/56
Szegedi *et al*,[106] 2003	Hungary	18	47	78	100	20.1	10	34	60	·	·	1	·	·	·	·	18/52
Szepietowski *et al*,[107] 1999	Poland	33	38	64	100	20.7	10	38	60	·	·	·	·	·	1	·	24/56
Szepietowski *et al*,[108] 2000	Poland	40	47	70	100	26.0	18	43	67	·	1	·	·	·	·	·	26/56
Szepietowski *et al*,[109] 2002	Poland	20	25	55	100	23.7	20	25	55	·	·	·	·	·	1	·	19/52
Takahashi *et al*,[20] 2010	Japan	122	48	66	83.6	7.3	78	39	69	·	1	1	1	·	·	1	24/56
Toruniowa *et al*,[110] 1995	Poland	20	-	-	-	-	14	-	-	·	1	·	·	·	·	·	15/52
Vanizor Kural *et al*,[111] 2003a	Turkey	30	34	43	-	5.5	30	37	50	·	·	·	·	4	·	1	22/52
Vanizor Kural *et al*,[112] 2003b	Turkey	35	35	49	-	5.8	35	36	54	·	·	·	·	4	·	·	22/52
Yamamoto *et al*,[113] 1997 (plaque pso)	Japan	4	-	-	100	25.4	6	58	-	·	·	·	·	·	1	1	20/52
Yamamoto *et al*,[113] 1997 (GPP)	Japan	6	58	50	0 [5]	-	6	58	50	·	·	·	·	·	1	1	20/52

Table 2. Characteristics of included studies. (continued)

		Psoriasis					Healthy controls			Markers and measurement methods [1]							
Author, Year	**Country**	**N**	**Mean age**	**% Male**	**% Plaque psoriasis**	**PASI**	**N**	**Mean age**	**% Male**	**Il-1β**	**Il-6**	**Il-10**	**TNFα**	**(hs)CRP**	**E-selectin**	**ICAM-1**	**Quality score [2]**
Yiu *et al*,[114] 2010	China	52	44	73	100	14.7	50	43	76	·	·	·	·	9	·	·	31/52
Zalewska *et al*,[115] 2006	Poland	106	45	72	100	16.7	40	46	58	·	1	·	·	.	·	·	9/52
Total	·	**3085**	**43 ± 7.6**	**57%**	·	**17.7 ± 10.5**	**4913**	**42 ± 7.8**	**49%**	**9**	**29**	**13**	**26**	**22**	**1**	**22**	·

Abbreviations: PASI, Psoriasis Area and Severity Index; Il, Interleukin; TNF, Tumor Necrosis Factor; (hs)CRP, (high sensitivity) C-reactive protein; ICAM, Intracellular Adhesion Molecule; pso, psoriasis; GPP, Generalized Pustular Psoriasis. Areas marked with "-" indicate missing data and "·" indicates not applicable.

[1] The following measurement methods were used: 1=Enzyme Linked Immuno Sorbant Assay (ELISA), 2= Radio immunoassay, 3=Immunoturbidimetry, 4=Nephelometry, 5=other measurement method, 9=method not specified.

[2] Quality assessment score: study score / maximum possible score for the article.

[3] 100% erythrodermic psoriasis.

[4] 100% palmo-plantar psoriasis.

[5] 100% pustular psoriasis.

Data synthesis and analysis

The primary outcome was the difference in mean serum inflammatory marker levels between psoriasis patients and healthy controls for each study. The effect size representing this difference was calculated using the standardized mean difference (SMD), also referred to as Cohen's d and we reported its respective 95% confidence intervals (CI). In studies where the mean was not reported, the median was used. If the SD was not available, we assumed that the values lay within three SDs from the mean. SMDs were pooled using a random effects-model according to the method of DerSimonian and Laird, where within-study variance and between-study variance were taken into account. Heterogeneity between studies was quantified using I^2 statistics. In six studies the serum levels were given separately according to psoriasis type, severity or Body Mass Index (BMI), instead of reporting an overall mean. These were included as such in the meta-analysis; however, the control group remained the same for the studied outcome measures.

Publication bias was investigated graphically by funnel plots and was statistically assessed via Egger's regression. The trim and fill method provided an estimate of the number of missing studies and an estimate of the pooled effect size if these studies were to be included in the meta-analysis.

All statistical analyses were performed using Comprehensive Meta-Analysis Version 2.2 (Biostat, Englewood, NJ, U.S.A.).

Meta-regression and subgroup analyses

Sources of heterogeneity between studies were explored by performing meta-regression analyses for age, gender and psoriasis severity. Subgroup analyses were performed based on psoriasis type (only plaque psoriasis versus different or non-specified types), laboratory measurements (Enzyme Linked Immuno Sorbant Assay (ELISA) versus other techniques or when the measurement method was not specified, and for CRP: ELISA versus immunoturbidimetry versus nephelometry versus other or missing method). Subgroups were analyzed for quality assessment scores whereby studies above and below the upper quartile were compared to each other. For each subgroup the pooled SMD and 95%CI was presented.

We excluded all studies with PsA, however we did not exclude studies with a small number of PsA patients alongside other psoriasis patients. In order to ascertain that the impact of PsA was limited in the meta-analysis, we conducted subgroup analyses comparing studies where PsA patients were excluded to the rest of the studies, showing no significant difference in point estimates between these two categories. The interpretation of this analysis was limited due to the small number of studies explicitly mentioning that PsA patients were excluded. We therefore decided to refrain from further discussing this subgroup analysis in the manuscript.

The present study was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[15,16]

RESULTS

The search yielded 8447 articles (5385 after exclusion of duplicates), of which 78 were included in the meta-analysis. Figure 2 depicts the study selection process.

A total of 7852 individuals (3085 psoriasis patients) were included. Psoriasis patients and healthy controls were comparable as to age (Table 2). The psoriasis type was known in 69% of patients. Of these, 94% (n=1971) had plaque psoriasis and 3.4% (n=71) had erythrodermic psoriasis. A total of 70% of the studies reported a Psoriasis Area and Severity Index (PASI). Within this group, 75% of the patients were from studies reporting a mean PASI >10**,** indicating that the majority of the studies included patients with severe disease (overall mean PASI 17.7±10.5).

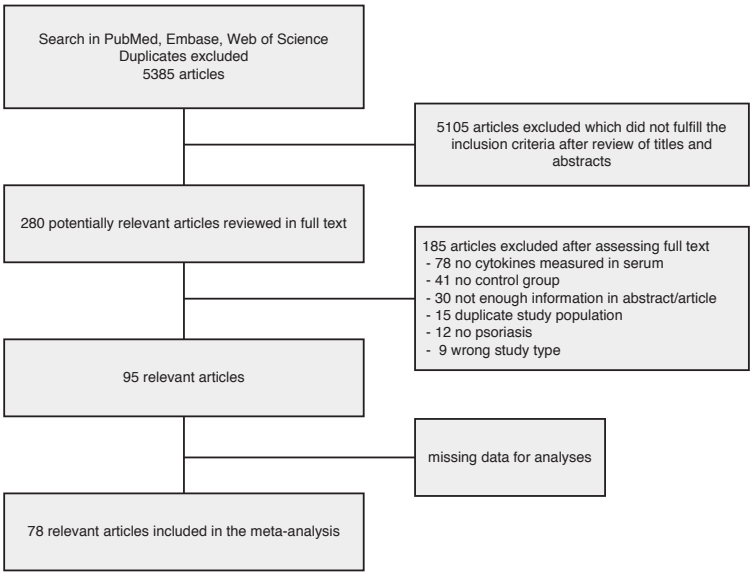

Figure 2. Flow diagram of study selection.

Interleukin-1β

The SMD for studies analyzing IL-1β was -0.32 (95% CI -1.05-0.41) indicating that there was no significant difference in serum IL-1β between psoriasis patients and controls (Figure 3a). Age and psoriasis severity did not explain the high degree of heterogeneity between the studies (I^2=93%). When adjusting for gender in the meta-regression, we noticed that the higher the percentage of women in the study, the larger the difference in IL-1β between psoriasis patients and controls in the study (p=0.001). Regarding the subgroup analyses, no significant differences were observed between studies including plaque psoriasis only and other studies (p=0.90) (Table 3).

Interleukin-6

Twenty two studies provided plasma IL-6 levels in 994 psoriasis patients and 594 controls (Table 2). Figure 3b shows a significantly higher level of IL-6 in psoriasis patients, with a pooled SMD of 1.32 (95%CI 0.83-1.81). In the forest plot, the study by Galadari et al showed high SMDs ranging from 25 to 36 for the three subgroups of psoriasis severity [17]. However, the point estimate remained significantly higher for psoriasis when excluding this study (d=1.07, 95%CI 0.65-1.49). Meta-regression for age indicates that the older the age of the patients in the study, the smaller the SMD between psoriasis patients and controls across studies (β=-0.08, p=0.04). Gender and PASI had no effect on the SMD in IL-6 (p=0.08 and p=0.66, respectively). The SMD for IL-6 was significantly lower in studies including only plaque psoriasis (n=13) compared to other studies (n=9) (Table 3),

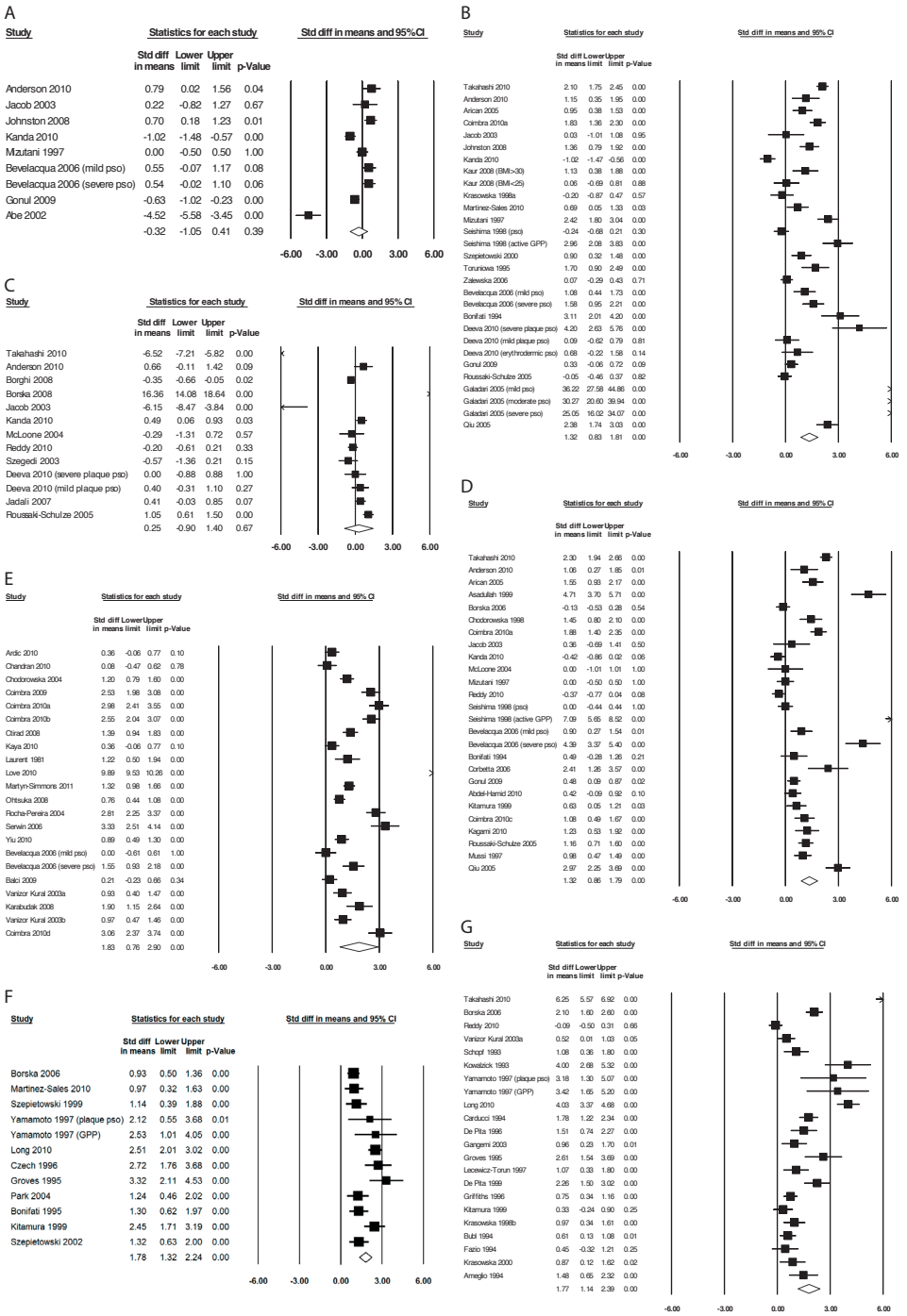

Figure 3 a to g.

Figure 3 a to g. Forest plots showing standardized mean difference and 95% CI of individual studies and pooled standardized mean difference and 95% CI in psoriasis patients and healthy controls using random effects model.
Abbreviations: Std diff in means, Standardized mean difference; CI, Confidence Interval; pso, psoriasis; BMI, Body Mass Index; GPP, Generalized Pustular Psoriasis.
a. Interleukin-1β
b. Interleukin-6
c. Interleukin-10
d. Tumor Necrosis Factor-alpha
e. C-Reactive Protein
f. E-Selectin
g. Intracellular Adhesion Molecule-1

indicating that the difference in IL-6 levels between psoriasis patients and controls was larger in studies not restricted to plaque psoriasis. These studies did not have a higher PASI score, nor did they include more erythrodermic patients (Table 2).

Interleukin-10

Pooling of IL-10 levels resulted in a small, positive but not statistically significant SMD between psoriasis patients and healthy controls (d=0.25; 95%CI -0.90-1.40) (Figure 3c), which could not be explained by age, gender or PASI in the meta-regression, or by psoriasis type in the subgroup analyses.

Tumor Necrosis Factor-alpha

The search yielded 24 studies showing an elevated SMD for TNFα of 1.32 (95%CI 0.86-1.79) (Figure 3d). Meta-regression showed that the older the age of patients within the studies, the smaller the difference in TNFα between psoriasis patients and controls (β=-0.13, p=0.002). Gender and PASI do not explain the difference in effect size between the studies.

C-Reactive Protein

The mean CRP across studies was significantly elevated in psoriasis compared to controls (d=1.83, 95%CI 0.76-2.90) (Figure 3e). The meta-regression for PASI showed a slope of 0.07 with a p=0.057, demonstrating a trend that an increase in PASI is associated with an increase in difference in mean CRP between psoriasis patients and controls. Regarding the subgroup analyses, no statistically significant differences were observed between subgroups for psoriasis type (Table 3).

E-selectin

The combined SMD for E-selectin was nearly twice as high in psoriasis compared to controls (d=1.78, 95%CI 1.32-2.25). Neither age, nor gender or psoriasis severity explained the high heterogeneity (I^2=78%) between the studies. The measurement method had no

Table 3. Summary of pooled standardized mean differences, meta-regression and subgroup analyses for all studied serum markers.

Markers (Number of Studies)	Pooled Effect Size SMD [1] (95% CI)	Meta-regression analyses [2] Regression coefficient (95% CI)			Subgroup analyses [1,3] SMD for each subgroup (95% CI)					
					Psoriasis type		Measurement method		Quality assessment	
		Age	Gender	PASI	Plaque psoriasis	Other [4]	ELISA	Other [5]	Lower quartile	Upper quartile
Il-1β (8)	-0.32 (-1.05–0.41)	0.02 (-0.21–0.25)	**0.04 (0.02–0.07)**	-0.26 (-0.56–0.05)	-0.36 (-1.27–0.55)	-0.23 (-1.96–1.49)	-0.75 (-1.59–0.10)	0.59 (-0.65–1.82)	-0.15 (-1.54–1.23)	-0.42 (-1.40–0.56)
Il-6 (22)	**1.32 (0.83–1.81)**	**-0.08 (-0.16– -0.003)**	-0.22 (-0.49–0.04)	0.06 (-0.20–0.33)	**0.92 (0.29–1.54)**	**1.98 (1.19–2.77)**	1.38 (0.76–2.01)	1.25 (0.43–2.08)	0.80 (0.05–1.55)	1.71 (1.06–2.35)
Il-10 (12)	0.25 (-0.90–1.40)	-0.36 (-0.87–0.16)	-0.01 (-0.18–0.17)	0.10 (-0.19–0.39)	0.19 (-1.29–1.66)	0.37 (-1.59–2.34)	0.98 (-0.63–2.59)	-0.89 (-2.94–1.16)	**-2.06 (-4.57–0.45)**	**0.89 (-0.43–2.22)**
(hs)CRP (20)	**1.83 (0.76–2.90)**	0.01 (-0.13–0.14)	0.01 (-0.05–0.07)	0.07 (-0.002–0.14)	1.67 (0.34–3.01)	2.11 (0.34–3.87)	0.64 (-3.00–4.27)	2.30 (0.20–4.40) [6] 1.38 (-0.34–3.10) [7] 2.55 (0.25–4.85) [8]	1.10 (-0.63–2.82)	2.25 (0.95–3.55)
TNFα (24)	**1.32 (0.86–1.79)**	**-0.13 (-0.23– -0.03)**	-0.01 (-0.04–0.03)	-0.01 (-0.09–0.07)	1.17 (0.47–1.87)	1.47 (0.82–2.12)	1.37 (0.88–1.86)	0.72 (-1.03–2.47)	1.06 (0.21–1.92)	1.44 (0.88–2.00)
E-selectin (11)	**1.78 (1.32–2.25)**	0.01 (-0.04–0.05)	-0.01 (-0.07–0.04)	0.31 (-0.05–0.66)	1.65 (0.89–2.41)	1.89 (1.26–2.52)	NA	NA	1.68 (0.97–2.39)	1.89 (1.22–2.56)
ICAM-1 (21)	**1.77 (1.15–2.39)**	0.04 (-0.06–0.14)	-0.04 (-0.09–0.004)	-0.02 (-0.13–0.09)	1.84 (0.50–3.18)	1.75 (1.04–2.46)	1.88 (1.19–2.57)	1.07 (-0.63–2.78)	1.28 (0.39–2.17)	2.24 (1.36–3.11)

Abbreviations: SMD, Standardized mean difference; CI, Confidence Interval; PASI, Psoriasis Area and Severity Index; ELISA, Enzyme Linked Immuno Sorbant Assay; Il, Interleukin; TNF, Tumor Necrosis Factor; (hs)CRP, (high sensitivity) C-reactive protein; ICAM, Intracellular Adhesion Molecule; NA not applicable.

Values in bold are significant ($p<0.05$).

[1] Random-effects model.

[2] Mixed effects regression. The regression coefficient represents the slope of the regression line.

[3] Comparison of two groups using random effects analysis, except for measurement method for CRP, where four groups are compared.

[4] Other psoriasis types, mix of types or type not specified.

[5] Measurement method other than ELISA or not specified. With the exception of CRP, where the subgroup of other measurements is split into immunoturbidimetry[6], nephelometry[7] and a fourth group with other or not specified measurement[8].

influence on the heterogeneity because all 11 studies used the ELISA technique. Analyzing the forest plot, the study by Groves et al including 9 patients with erythrodermic psoriasis appears to have the highest SMD, indicating that patients in this study with severe disease have higher levels of E-selectin than healthy controls[18] (Figure 3f).

Intracellular-Adhesion-Molecule-1

A total of 21 articles including 714 psoriasis patients and 601 controls yielded a significant positive association between psoriasis and ICAM-1 (d=1.77, 95%CI 1.15-2.39). Meta-regression and subgroup analyses did not show significant results. Interestingly the two largest studies including more than 100 therapy naïve psoriasis patients show SMDs varying from -0.09 (95%CI -0.50-0.31) to 6.25 (95%CI 5.57-6.92).[19,20] The remaining studies have SMDs which lie in between (Figure 3g).

Negative subgroups findings

The high level of heterogeneity between studies (all I^2>75%), could not be explained by the subgroup analyses. These showed that the measurement method did not have a significant impact on the SMD for any of the studied markers of inflammation. There was also no significant difference between studies with a higher and those with a lower quality assessment score, with the exception of IL-10, where nine studies with a higher score had a larger pooled effect size than the three studies with a lower score (Table 3).

Publication bias

The funnel plots for IL-1β, TNFα, CRP and ICAM-1 showed evidence of asymmetry (Supplementary Figure 2). The addition of the "missing" studies imputed using the trim and fill method shifted the effect size for IL-1β and IL-10 towards significance with adjusted point estimates of -0.84 (-1.60 to -0.08)) and 1.96 (0.50-3.43) respectively. For CRP, TNFα, E-selectin and ICAM-1, the addition of the "missing" studies only increased the magnitude of the pooled effect sizes, which remained significant.

The Egger's test confirmed the presence of publication bias for TNFα (6.09, 95%CI 1.42-10.76) and ICAM-1 (5.58, 95%CI 0.003-11.17), however there also appeared to be publication bias for IL-6 (p=0.002).

DISCUSSION

The current meta-analysis shows mild systemic inflammation in psoriasis patients compared to healthy controls with five of the six investigated pro-inflammatory serum markers being increased in psoriasis. The difference is nearly two points at the most

and is overall independent of age, gender, disease severity, psoriasis type, measurement methods and quality assessment for the different studies.

Contrary to expected, pooled anti-inflammatory IL-10 was not significantly decreased in psoriasis patients; of the 13 studies on IL-10, only 3 showed a significantly lower IL-10 in psoriasis. The literature on psoriasis suggests that IL-10 deficiency might play a role in its pathogenesis[21] and a study even showed that antipsoriatic treatment lead to normalization of IL-10 values.[20]

The cytokines IL-1β, IL-6 and TNFα produced by the keratinocytes are key in the activation of innate immunity through activation of dendritic and T-cells.[2] These pro-inflammatory cytokines are also produced in adipose tissue, hereby linking inflammation of the skin with obesity.[6] In this meta-analysis, pooled serum IL-1β was the only marker to not be significantly elevated in psoriasis patients compared to healthy controls. This was contrary to expected because IL-1 triggers the production of IL-6 and TNFα in the molecular cascade and should therefore also be elevated.[3] This result could be due to a limited number of studies on serum IL-1β. Age explained part of the heterogeneity between the studies for IL-6 and TNFα, indicating that the older the patients in the study, the smaller the SMD between the psoriasis patients and the controls. This could possibly be explained by decreasing immunity with increasing age.[22]

IL-1β and IL-6 act together to enhance CRP.[23] IL-6 was elevated in our analyses and can therefore explain the increased CRP obtained in psoriasis patients. In search of a novel biomarker to monitor disease progression and severity and improve cardiovascular risk prediction, CRP is also being used in other comorbidities.[9,24,25] In the past decade, numerous meta-analyses have investigated the use of CRP in the prediction of CVD, concluding that CRP is at the most a moderate predictor of CVD compared to major established risk factors.[9 10 11]

The soluble adhesion molecules E-selectin and ICAM-1, located at the end of the inflammatory cascade, are enhanced by TNFα and CRP through endothelial cells.[26,27] Of the inflammatory markers studied in this meta-analysis, the SMD between psoriasis and controls was the highest for E-selectin and ICAM-1. These adhesion molecules have been available for several decades; however their clinical relevance is yet unclear. They can be involved in various conditions, from infections, vasculitis, cancer to atherosclerosis and CVD.[27,28] However, the evidence on adhesion molecules is contradictory, even within the same condition such as CVD.[12,29]

In other inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis, there seems to be a general consensus that inflammatory markers are elevated in patients compared to healthy controls.[30-32] This consensus is based on convenient individual studies rather than on meta-analysis. The concept that the elevation of inflammatory markers leads to systemic inflammation and comorbidities such as CVD seems to be logical, however there is a large gap between measuring systemic inflammation in the blood and the registration of events, and it is a further challenge to determine whether these events have a causal relationship to the exposure.[26] This gap should be filled with hard evidence in order to prove a possible relationship between exposure and outcome. The present study confirms the elevation of markers in psoriasis, however does not investigate the link between this modest elevation and eventual metabolic diseases or cardiovascular events.

As to the clinical relevance of these markers of inflammation based on the results of this meta-analysis, we believe that they cannot be considered as markers of disease severity because they were only modestly increased in psoriasis patients compared to controls and the increase was independent of the PASI. However this does not exclude the fact that markers of inflammation could be important targets for therapy, such as is the case with TNFα and recently Interleukin-17.[33]

Strengths and limitations

This is the first and largest meta-analysis on markers of inflammation in psoriasis combining 78 studies with a psoriasis and comparative group of healthy subjects to pool information on seven different serum markers. We performed an extensive systematic search using three databases to retrieve articles. We limited selection bias of the articles by not restricting the language of the search and included foreign articles if the abstract and full text provided sufficient data. We included a considerably large number of studies, which were mainly observational in nature and consisted of small numbers of psoriasis patients. We not only investigated pro-inflammatory markers but also anti-inflammatory IL-10.

We analyzed baseline values of markers in naïve psoriatic patients and therefore could not draw conclusions on the use of serum markers in measuring disease progression. Approximately two studies per outcome did not report the mean marker values completely and therefore could not be included in the meta-analysis, however we do not expect this to have influenced our the effect size because these studies showed varying results.[34-42]

We assume that most patients had moderate to severe disease (75% of studies had a PASI>10), possibly limiting the generalizability of our findings. On the other hand, the

analyses showed that that the effect size for the serum markers was independent of disease severity.

In order to explain the high degree of heterogeneity between the studies, we conducted several meta-regression and subgroup analyses. The results should be interpreted cautiously because they were based on covariates at the level of the study in contrast to covariates from individual patient data, possibly leading to aggregation bias.

We used three different methods to assess publication bias and depending on the method used there seemed to be publication bias. This bias however did not change the direction of the association for any of the markers when using the trim and fill method.

The quality assessment scores were not high due to incomplete data on several items, the latter also influencing our selection of subgroup analyses. We acknowledge that REMARK is more a reporting device; nevertheless we did not expect the study quality to influence the studied outcomes because we compared objective measurements (serum marker levels) which are not dependent on factors such as blinding or allocation concealment. This was confirmed in the subgroup analysis showing no difference in pooled estimate between studies with a high and those with a low quality assessment score.

CONCLUSION

Psoriasis patients show at the most mild systemic inflammation compared to controls. The elevation of the inflammatory markers is independent of psoriasis type and severity, questioning their use as biomarkers. In order to investigate the clinical relevance of this modest increase in inflammation, it would be interesting to conduct a review summarizing the evidence on the effect of antipsoriatic therapy on markers of inflammation.

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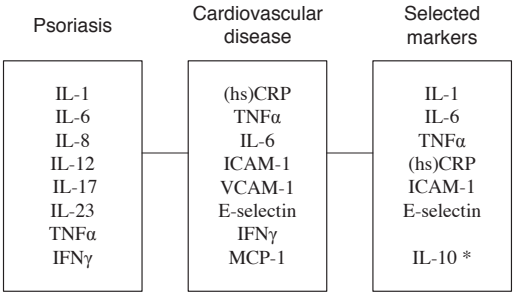
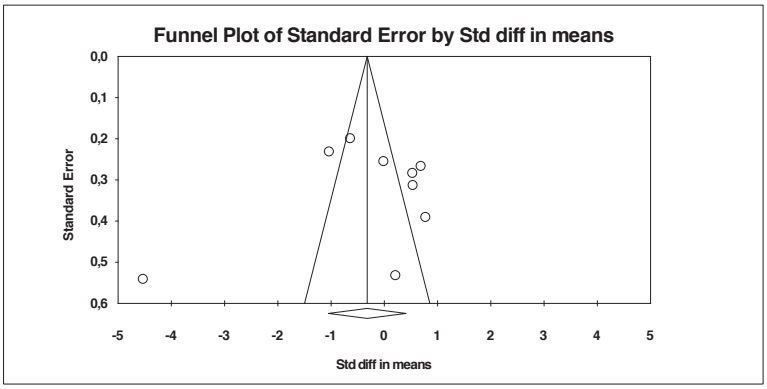
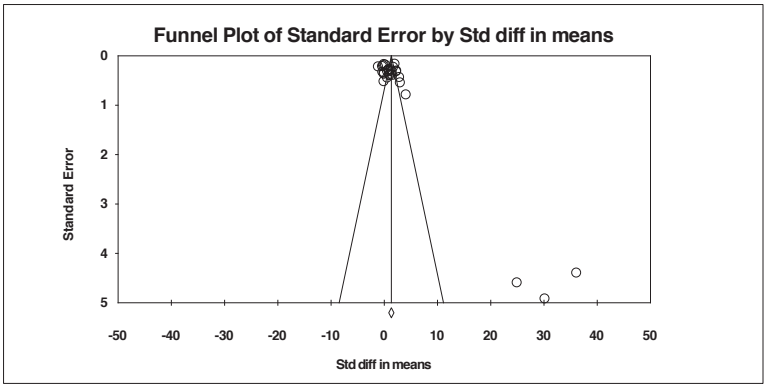
SUPPLEMENTARY MATERIAL



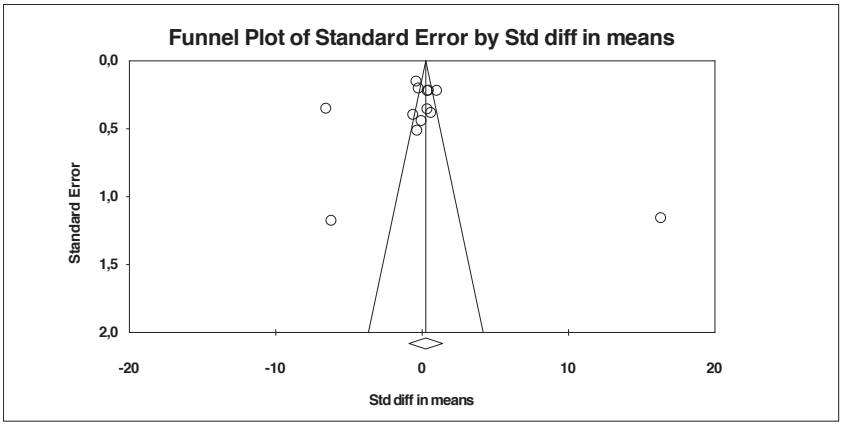
Supplementary Figure 1. Selected inflammatory serum markers based on a selection of markers analyzed in psoriasis and cardiovascular disease.
Abbreviations: Il, Interleukin; hsCRP, high sensitivity C-Reactive Protein; TNFα, Tumor Necrosis Factor alpha; ICAM-1, Intracellular Adhesion Molecule 1; IFNγ, Interferon gamma; MCP-1, Monocyte Chemoattractant Protein-1
* Il-10 was deliberately chosen as an anti-inflammatory serum marker.



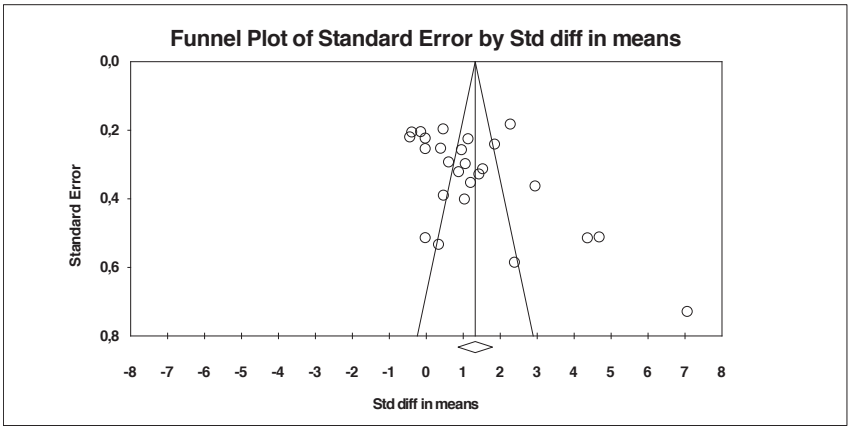
Supplementary Figures 2a



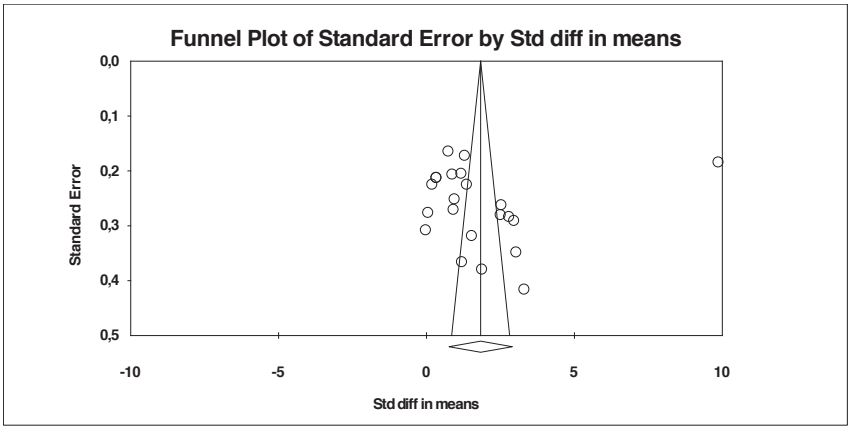
Supplementary Figures 2b



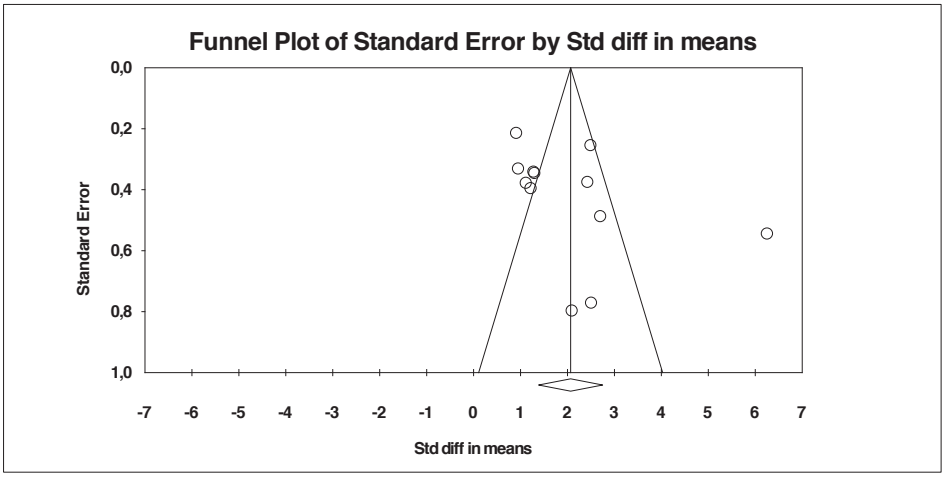
Supplementary Figures 2c



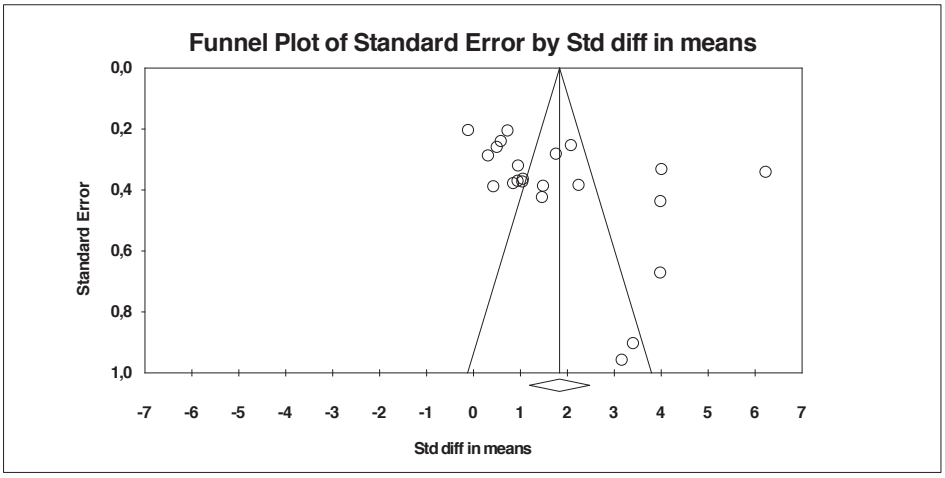
Supplementary Figures 2d



Supplementary Figures 2e



Supplementary Figures 2f



Supplementary Figures 2g

Supplementary Figures 2 a to g. Funnel plots identifying publication bias for all studied outcomes.
a. Interleukin-1β
b. Interleukin-6
c. Interleukin-10
d. Tumor Necrosis Factor-alpha
e. C-Reactive Protein
f. E-Selectin
g. Intracellular Adhesion Molecule-1

Table 1. Search strategy

Database	Search string
PubMed	psoriasis[tw] AND (interleukin-1[tw] OR il-1[tw] OR interleukin-10[tw] OR il-10[tw] OR interleukin-6[tw] OR il-6[tw] OR tumor necrosis factor*[tw] OR tnf[tw] OR c-reactive protein*[tw] OR crp[tw] OR icam[tw] OR sicam[tw] OR intercellular adhesion molecule*[tw] OR e-selectin*[tw] OR se-selectin*[tw] OR endothelial leukocyte adhesion molecule*[tw] OR elam[tw] OR selam[tw]) NOT (animals[mesh] NOT humans[mesh]) NOT (case reports[pt] OR letter[pt])
EMbase	(psoriasis/syn AND (((interleukin OR il) NEAR/1 (1 OR 6 OR 10 OR 1a* OR 1α OR 1b* OR 1β)):ti,ab,de OR ('tumor necrosis' NEAR/1 factor*):ti,ab,de OR tnf:ti,ab,de OR ('c-reactive' NEAR/1 protein*):ti,ab,de OR crp:ti,ab,de OR icam:ti,ab,de OR sicam:ti,ab,de OR ('intercellular adhesion' NEAR/1 molecule*):ti,ab,de OR ((e OR se) NEAR/1 selectin*):ti,ab,de OR ('endothelial leukocyte adhesion' NEAR/1 molecule*):ti,ab,de OR elam:ti,ab,de OR selam:ti,ab,de) NOT ([animals]/lim NOT [humans]/lim)) NOT ('case reports' OR 'case report'):ti,ab,de NOT [letter]/lim
Web of Science	psoriasis AND (((interleukin OR il) SAME (1 OR 6 OR 10 OR 1a OR 1alpha OR 1alfa OR 1b OR 1beta)) OR "tumor necrosis factor" OR tnf OR "c reactive protein" OR crp OR icam OR sicam OR "intercellular adhesion molecule*" OR "e selectin*" OR "se selectin*" OR "endothelial leukocyte adhesion molecule*" OR elam OR selam) NOT (animal* NOT human*) NOT "case report" NOT "case reports"