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Risk Factors for Psoriasis: An Umbrella Review of 12 Published Meta-analyses

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Aim

- To summarise and critically appraise the evidence of associations between biomarkers, lifestyle factors and medications and the risk of psoriasis.

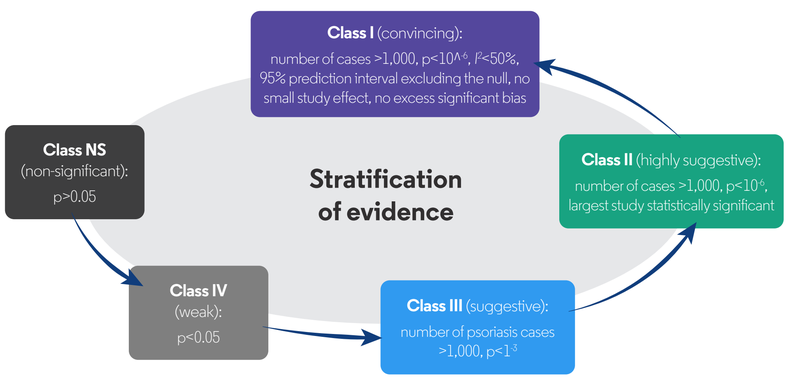
Background

- Psoriasis affects 125 million people globally, making it crucial for healthcare professionals and patients to identify modifiable risk factors that can guide prevention and treatment strategies.
- The vast amount of information on psoriasis risk factors is difficult to navigate and potentially hinders actionable steps in disease management.
- An umbrella review was performed to systematically consolidate and evaluate existing evidence, streamlining information from multiple reviews while assessing the epidemiological credibility of studies.
- This review provides a clear and concise resource that enables more efficient and informed healthcare decisions without overwhelming patients or professionals.

Methods

- Electronic databases (EMBASE, MEDLINE, and the COCHRANE library) were searched in May 2024, using a search strategy that included MeSH terms and keywords.
- Two independent reviewers screened abstracts and then full-text articles, according to the predefined inclusion and exclusion criteria which covered study designs, relevant risk factors (biomarkers, lifestyle factors, medications), control group comparison and sufficient data.
- Key measures (relative effects, study designs and the number of participants across the exposure and outcome strata) were extracted from eligible reviews and primary articles where relevant.
- All meta-analyses underwent quality assessment and were graded as high, moderate, low or critically low quality, according to the 16 step 'A Measurement Tool to Assess Systematic Reviews 2' (AMSTAR2) index (1).
- Measures of effect size and 95% confidence interval (CI) were re-calculated using fixed and random effect models, using odds ratios (ORs) for binary factors and Hedge's g for continuous factors (the latter considered the 'corrected mean difference' since the measure is weighted by the pooled standard deviations).
- To allow straightforward comparisons between summary effects of binary and continuous factors, Hedge's g was converted into the equivalent OR (eOR). Findings are presented in forest plots.
- Between-study heterogeneity was calculated using the I^2 statistic. When I^2>50%, there was a high level of heterogeneity and therefore the random effects model was presented.
- Egger's test and the Ioannidis and Trikalinos test for excess significance were used to assess small-study effects and publication bias. A p<0.1 was considered statistically significant for all statistical tests of heterogeneity and bias.
- The strength of evidence for each risk factor was stratified according to the criteria described by Fusar-Poli & Radua (2018) (2). The classification ranged from I to NS (convincing to non-significant) and was defined as shown in Figure 1.
- Study-level sensitivity analyses were conducted on risk factors classified Class I to III, restricting analyses to exclusively prospective studies to establish the temporality of events, thereby mitigating the influence of reverse causation which impacts case-control and cross-sectional studies.
- All analyses were performed using R, version 4.4.1, with packages including 'metafor' and 'metaumbrella'.

Figure 1: Criteria used to stratify the level of evidence for the association of risk factors and psoriasis



Abbreviations: p, p-value; PI, prediction interval.

Results

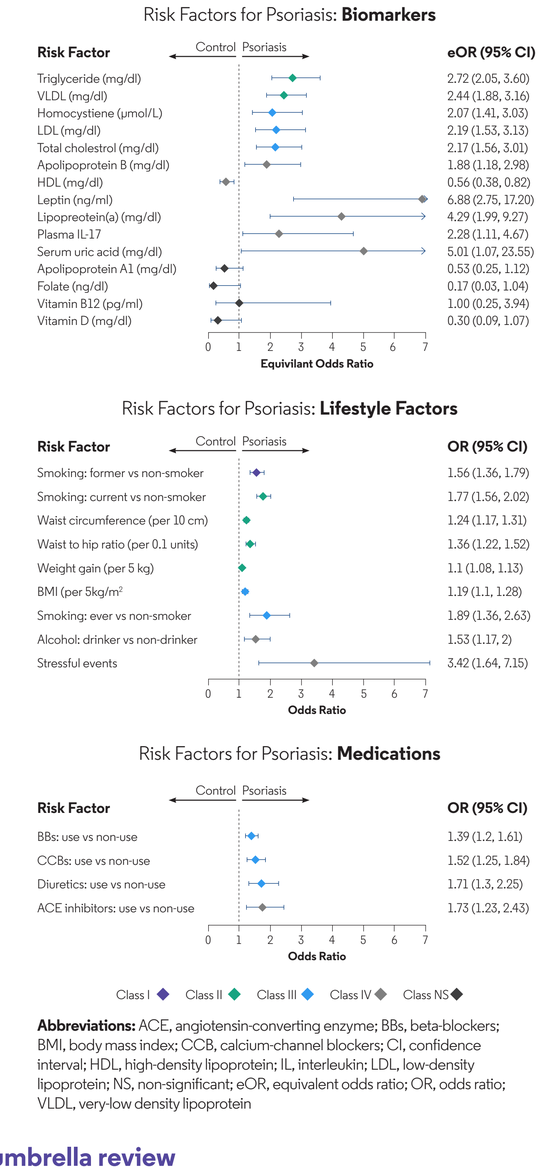
- Twelve meta-analyses (Table 1) were included in this review and yielded evidence on 28 risk factors (15 biomarkers, 9 lifestyle factors and 4 medications) for psoriasis.

Table 2: Level of evidence for the association of risk factors for psoriasis

Risk Factor	Components used for classification of evidence strength										Class
	No. psoriasis cases	Effect size			Heterogeneity, I^2		95% Prediction interval	Egger's test	Excess significant bias test	Largest study p<0.05	
		Measure	Effect (95% CI)	p-value	I^2 (%)	p-value					
Apolipoprotein A1 (mg/dL)	641	Hedge's g	-0.35 (-0.76, 0.06)	p≥0.05	89.20	p<0.001	(-1.84, 1.14)	p=0.67	NP	Yes	NS
Apolipoprotein B (mg/dL)	569	Hedge's g	0.35 (0.09, 0.60)	0.00001≤ p<0.01	71.58	p<0.001	(-0.49, 1.18)	p=0.18	p=0.05	No	IV
Folate (ng/dL)	847	Hedge's g	-0.98 (-1.98, 0.02)	p≥0.05	93.72	p<0.001	(-5.22, 3.26)	p=0.25	NP	Yes	NS
HDL (mg/dL)	2,735	Hedge's g	-0.32 (-0.54, -0.11)	0.00001≤ p<0.01	87.96	p<0.001	(-1.73, 1.09)	p=0.25	p<0.001	No	IV
Homocysteine (µmol/L)	1,124	Hedge's g	0.4 (0.19, 0.61)	0.00001≤ p<0.01	75.29	p<0.001	(-0.47, 1.27)	p=0.77	NP	Yes	III
LDL (mg/dL)	2,205	Hedge's g	0.43 (0.24, 0.63)	0.00001≤ p<0.01	88.26	p<0.001	(-0.78, 1.65)	p=0.04	p=0.25	Yes	III
Leptin (ng/mL)	789	Hedge's g	1.06 (0.56, 1.57)	0.00001≤ p<0.01	93.52	p<0.001	(-0.89, 3.01)	p=0.59	p=0.69	Yes	IV
Lipoprotein(a) (mg/dL)	446	Hedge's g	0.8 (0.38, 1.23)	0.00001≤ p<0.01	87.78	p<0.001	(-0.67, 2.28)	p=0.03	p<0.001	No	IV
Plasma IL-17	345	Hedge's g	0.45 (0.06, 0.85)	0.01≤ p<0.05	77.24	p<0.001	(-0.86, 1.77)	p=0.02	p=0.45	Yes	IV
Serum uric acid (mg/dL)	1,644	Hedge's g	0.89 (0.04, 1.74)	0.01≤ p<0.05	97.91	p<0.001	(-2.66, 4.43)	p=0.41	p<0.001	No	IV
cholesterol (mg/dL)	2,621	Hedge's g	0.43 (0.25, 0.61)	p<0.00001	88.68	p<0.001	(-0.73, 1.58)	p=0.54	NP	Yes	III
Triglyceride (mg/dL)	2,853	Hedge's g	0.55 (0.4, 0.71)	p<0.00001	83.69	p<0.001	(-0.45, 1.56)	p=0.13	NP	Yes	II
Vitamin B12 (pg/mL)	594	Hedge's g	0 (-0.76, 0.76)	p≥0.05	88.12	p<0.001	(-2.93, 2.93)	p=0.71	NP	No	NS
Vitamin D (mg/dL)	693	Hedge's g	-0.66 (-1.35, 0.04)	p≥0.05	96.20	p<0.001	(-3.32, 2.00)	p=0.11	p=0.15	Yes	NS
VLDL (mg/dL)	2,880	Hedge's g	0.49 (0.35, 0.63)	p<0.00001	83.20	p<0.001	(-0.43, 1.42)	p=0.28	NP	Yes	II
Alcohol: drinker vs non-drinker	7,681	OR	1.53 (1.17, 2.00)	0.00001≤ p<0.01	92.10	p<0.001	(0.53, 4.4)	p=0.12	p<0.001	No	IV
BMI (per 5 kg/m²)	17,634	OR	1.19 (1.1, 1.28)	p<0.00001	82.30	p<0.001	(0.93, 1.51)	p=0.13	p<0.001	Yes	III
Smoking: current vs non-smoker	146,934	OR	1.77 (1.56, 2.02)	p<0.00001	91.00	p<0.001	(0.97, 3.23)	p<0.001	p<0.001	Yes	II
Smoking: ever vs non-smoker	177,484	OR	1.89 (1.36, 2.63)	0.00001≤ p<0.01	99.50	p<0.001	(0.45, 7.89)	p=0.29	p=0.17	Yes	III
Smoking: former vs non-smoker	3,320	OR	1.56 (1.36, 1.79)	p<0.00001	43.20	p=0.1	(1.31, 1.87)	p=0.26	p=0.56	Yes	I
Stressful events	4,713	OR	3.42 (1.64, 7.15)	0.00001≤ p<0.01	86.50	p<0.001	(0.23, 50.60)	p=0.53	p=0.03	No	IV
Waist circumference (per 10 cm)	1,378	OR	1.24 (1.17, 1.31)	p<0.00001	0	p=0.73	(0.87, 1.77)	p=0.5	p=0.38	Yes	II
Waist to hip ratio (per 0.1 units)	1,376	OR	1.36 (1.22, 1.52)	p<0.00001	0	p=0.93	(0.67, 2.79)	p=0.88	p=0.54	Yes	II
Weight gain (per 5 kg)	1,827	OR	1.1 (1.08, 1.13)	p<0.00001	43.00	p=0.17	(0.97, 1.26)	p=0.15	p=0.05	Yes	II
ACE inhibitors: use vs non-use	122,445	OR	1.73 (1.23, 2.43)	0.00001≤ p<0.01	95.70	p<0.001	(0.51, 5.84)	p=0.06	NP	Yes	IV
BBs: use vs non-use	207,906	OR	1.39 (1.2, 1.61)	p<0.00001	96.60	p<0.001	(0.82, 2.37)	p=0.66	NP	Yes	III
CCBs: use vs non-use	121,744	OR	1.52 (1.25, 1.84)	0.00001≤ p<0.01	96.10	p<0.001	(0.83, 2.78)	p=0.43	p=0.25	Yes	III
Diuretics: use vs non-use	121,385	OR	1.71 (1.3, 2.25)	0.00001≤ p<0.01	98.20	p<0.001	(0.66, 4.45)	p=0.1	p=0.17	Yes	III

Abbreviations: ACE, angiotensin-converting enzyme; BBs, beta-blockers; BMI, body mass index; CCB, calcium-channel blockers; CI, confidence interval; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; NP, not pertinent (fewer significant effects observed than expected); NS, non-significant; OR, odds ratio; VLDL, very-low density lipoprotein.

Figure 2: Association between biomarkers, lifestyle factors, medications and psoriasis risk



Abbreviations: ACE, angiotensin-converting enzyme; BBs, beta-blockers; BMI, body mass index; CCB, calcium-channel blockers; CI, confidence interval; HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; NS, non-significant; eOR, equivalent odds ratio; OR, odds ratio; VLDL, very-low density lipoprotein

- At a threshold of p<0.05, 24 of the 28 identified associations were nominally significant and 15 associations yielded convincing (n=1), highly suggestive (n=6) or suggestive (n=8) evidence of an association with psoriasis risk (Table 2).
- There was Class I evidence that, relative to non-smokers, former smokers had a higher risk of psoriasis; low between-study heterogeneity was observed, and there was no significant evidence of small study effects or publication bias.
- There was Class II evidence that lifestyle factors, including current smoking and an increase in measures of adiposity (waist circumference, waist to hip ratio and weight gain), elevated the risk of psoriasis. An increase in two biomarkers, triglycerides and very low- density lipoprotein (VLDL), also demonstrated highly suggestive evidence of an association with psoriasis risk.
- When the effect measures for the continuous factors were transformed to the eOR scale, the average effect size of several biomarkers was considerably larger than the effect size of most lifestyle factors and all medications, although uncertainty increased (Figure 2).
- Eight risk factors included evidence from <1,000 cases of psoriasis (Table 2), of which four risk factors were graded Class IV even in the presence of nominally significant evidence.
- Sensitivity analysis was only feasible on 7 of the 15 associations graded Class I to III, since there were no prospective trials contributing to the other 8 associations. The Aune 2018 review on adiposity included exclusively prospective studies. Therefore, each measure of adiposity retained its original evidence level and findings are robust to reverse causation. One prospective study contributed to the association between BBs, CCBs, diuretics and psoriasis risk. Under the sensitivity analysis, each factor was downgraded from Class III to Class IV for BBs and diuretics, and there was no longer significant association between CCBs and psoriasis risk.

Limitations

- Umbrella reviews are subject to the limitations of the primary studies. Importantly, association is not necessarily causation. In the absence of temporal events, reverse causation is a pertinent concern when aiming to demonstrate that one variable is a risk factor of another. In this review, we specifically targeted the issues surrounding reverse causation using sensitivity analyses. The ability to extensively investigate the temporality of events is restricted by the few meta-analyses that included prospective trials; more large-scale prospective studies are required to verify results.
- Any grading criterion that applies cut-offs to a continuous scale can be highly sensitive. For example, a study with 1,001 cases could be graded up to Class I, but a study with 1,000 cases at most to Class IV. This impacts factors investigated by only a few studies, regardless of the effect size. This issue is poignant for several biomarkers, where the effect size is substantial in magnitude, but small sample size limits the certainty and impacts evidence stratification.

Table 1: Characteristics of the eligible meta-analyses included in the umbrella review

Meta-analysis	Risk Factor	Risk Factor Category	No. of studies	AMSTAR2 index
Armstrong, 2014(3)	Lifestyle	Smoking: current vs non-smoker, former vs non-smoker	25, 7	L
Aune, 2018(4)	Lifestyle	BMI per 5 kg/m², waist circumference per 10 cm, waist to hip ratio per 0.1 units, weight gain per 5 kg	7, 3, 3, 3	L
Gazel, 2020(5)	Lifestyle	Smoking: ever vs non-smoker	16	M
Li, 2016(6)	Biomarker	Serum uric acid	13	L
Pitukweerakul, 2019(7)	Biomarker	Vitamin D	10	L
Ramezani, 2019(8)	Biomarker	Apolipoprotein A1, Apolipoprotein B, HDL, LDL, Lipoprotein(a), Total cholesterol, Triglycerides, VLDL	9, 9, 45, 40, 8, 44, 47, 48	L
Snast, 2018(9)	Lifestyle	Stressful events	5	M
Song, 2022(10)	Medication	ACE inhibitors use vs non-use, BBs use vs non-use, CCBs use vs non-use, Diuretics use vs non-use	9, 12, 10, 9	L
Tsai, 2019(11)	Biomarker	Folate, Homocysteine, Vitamin B12	14, 18, 11	M
Zhou, 2017(12)	Biomarker	Plasma IL-17	8	CL
Zhu, 2012(13)	Lifestyle	Alcohol: drinking vs non-drinking	15	CL
Zhu, 2013(14)	Biomarker	Leptin	11	CL

Abbreviations: ACE, angiotensin-converting enzyme; AMSTAR2, A Measurement Tool to Assess Systematic Reviews; BBs, beta-blockers; BMI, body mass index; CCB, calcium-channel blockers; CL, critically low; HDL, high-density lipoprotein; IL, interleukin; L, low; LDL, low-density lipoprotein; M, medium; VLDL, very low-density lipoprotein.

Conclusion

- The output of this review is a high-level comprehensive and critical summary of existing evidence on biomarkers, lifestyle factors and medications, and the risk of psoriasis.
- Evidence stratification formally quantified the robustness of evidence, which allowed minor associations, heavily influenced by biases, to be extricated from the truly convincing risk factors.
- We identified several biomarkers, lifestyle factors and medications that demonstrate Class I, II and III evidence to increase psoriasis risk.

Presented at ISPOR Europe 2024, Barcelona, Spain | November 17-20 2024

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Acknowledgments and Disclosures:
LR, PG, SJ, SD, AN, and SN are all employees of Clarivate.
The study has been funded by Clarivate.