



Risk of Cardiovascular Disease in Patients with Psoriasis and Atopic Dermatitis

Sara Almalik^{*1}, Fazeela Ansari², Mahra Khaled AlShehhi³, Majid Alhammadi³, Alma Alfakhori¹, Jennifer John⁴, Shaima Ahmad⁵, Sammar Abbas Elteгани Mohamed⁶, Meghavi saharan⁷, Lakshya bhargava⁸, Risalatelislam Babiker Mohammed⁹, Abdelslam Hatim Elsamani¹⁰

Abstract

Background: Psoriasis and atopic dermatitis (AD) are chronic inflammatory skin conditions that are now recognized as systemic diseases. It is still a matter of debate whether they, as separate entities, increase risk of cardiovascular disease.

Methods: We systematically reviewed observational studies and meta-analyses that compare the risk of CVD in adults with psoriasis or AD to that of individuals without these diseases. The eligible designs were cohort, case-control and large cross-sectional studies that report relative risks (RRs), hazard ratios (HRs) or odds ratios (ORs) for major cardiovascular outcomes. The data were combined through random-effects models. As a measure of heterogeneity, we used I^2 .

Results: Psoriasis was linked to an elevated risk of myocardial infarction (MI; pooled RR 1.17, 95% CI 1.11–1.24), stroke (1.19, 1.11–1.27), cardiovascular death (1.46, 1.26–1.69), ischemic heart disease (1.17, 1.02–1.34), thromboembolism (1.36, 1.20–1.55) and arrhythmia (1.35, 1.30–1.40) [7]. Atopic eczema/dermatitis was correlated with slightly increased risks of MI (RR 1.12, 1.00–1.25), stroke (1.10, 1.03–1.17), ischemic stroke (1.17, 1.14–1.20), angina (1.18, 1.13–1.24) and heart failure (1.26, 1.05–1.51) [4]. Our secondary meta-analysis of different cardiovascular endpoints indicated an overall relative risk (RR) of 1.27 (95% CI 1.18–1.37; $I^2 \approx 82\%$) for psoriasis, meaning 27% higher cardiovascular risk in patients with psoriasis and 1.16 (95% CI 1.13–1.19; $I^2 \approx 15\%$) for AD, indicating 16% higher risk.

Conclusion: Both psoriasis and AD carry a small to moderate risk of CVD and is more pronounced in the case of severe disease. Along with the aggressive management of these diseases, routine cardiovascular risk assessment should also be a goal in these patients. The next research should identify causal pathways through individual-patient data and Mendelian randomization.

Affiliation:

¹Mohammed bin rashid university

²Dubai Health Authority, HMS Mirdif hospital

³Sheikh Khalifa medical city abudhabi

⁴Rak medical and health science university

⁵Dubai medical collage

⁶University of Medical Sciences and Technology

⁷Jiujiang university china

⁸Kazan federal university

⁹Redsea university

¹⁰Alneelain university

*Corresponding author:

Sara Almalik, Mohammed bin rashid university, UAE.

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Introduction

Psoriasis and atopic dermatitis (AD) are the major chronic inflammatory skin diseases that have a high incidence rate, and together, they impact several hundred million people globally. Previously, these two diseases were considered to be localized skin disorders, as their symptoms were mainly observed in the

skin and, in the case of AD, sometimes in the mucosal or respiratory branches. Nevertheless, during the last twenty years, the understanding of these illnesses has experienced a significant change of paradigm. Currently, they are considered as systemic diseases that cause inflammation and have many immunological, metabolic and cardiovascular consequences [1, 2].

This change in perception has been facilitated, to a great extent, by the advances made in molecular immunology, population-based epidemiology and high-resolution imaging, which, collectively, have confronted the notion that the origin of the chronic inflammation in psoriasis and AD is limited to the skin, by showing that the inflammation extends to other organ systems as well. Cardiovascular disease (CVD) is one of the most critical concern that have emerged from the possible systemic effects of these diseases. CVD is still the primary reason for the loss of health and life worldwide, and knowing the risk that can be changed is of utmost importance from the public health point of view. The latest data indicate that people suffering from psoriasis and AD might be the ones who are more likely to experience major adverse cardiovascular events (MACEs), such as myocardial infarction (MI), cerebrovascular accidents like ischemic or hemorrhagic stroke, venous thromboembolism, arrhythmias and even cardiovascular mortality [3, 4].

Psoriasis as a Systemic, Immune-Mediated Disorder

Psoriasis represents a chronic disorder that affects immune system of patient and is characterized by an overgrowth of keratinocytes and infiltration of inflammatory cells mainly through IL-23/Th17 axis. However, apart from cutaneous lesions that are most apparent, the burden of inflammation in psoriasis goes beyond the skin and is systemic. For instance, several times, it has been reported that the levels of cytokines such as TNF- α , IL-17, IL-6 and interferon-gamma are high in circulation of those patients. These agents are the main factors in endothelial dysfunction, oxidative stress and atherogenesis [2]. These processes are similar to those leading to cardiovascular disorders. Besides this, a body of epidemiologic research has been consistent in showing that caregivers of patients with psoriasis report that such patients are leading lives full of traditional cardiometabolic risk factors. These include hypertension, dyslipidemia, obesity, insulin resistance, type 2 diabetes and metabolic syndrome.

These comorbidities are not only more prevalent but also tend to appear earlier in life in individuals with moderate-to-severe psoriasis [5]. It has not yet been thoroughly established whether the inflammation of psoriasis is the main cause of these metabolic abnormalities or if they simply coexist because of shared genetic and environmental factors. Still, the net effect is a high cardiovascular risk profile. Pivotal among such studies employed a vast general practice

database in the United Kingdom to demonstrate that young individuals with severe psoriasis were three times more likely to suffer from non-fatal myocardial infarction than controls matched by age [3]. This milestone study led to a surge of research on the psoriasis-CVD relationship, which found co-association between psoriasis and MI, stroke and CVD mortality. In addition, recent studies that have used imaging like coronary artery calcium scoring and positron emission tomography (PET) have reported that psoriasis patients have higher subclinical vascular inflammation than controls even after considering traditional risk factors. Hence, these data support not only epidemiologic association but also biological plausibility for a direct causal relationship.

Atopic Dermatitis as a Systemic Inflammatory Disorder

Atopic dermatitis (AD) is thought to be associated with type 2 immune responses (IL-4, IL-5, IL-13) but later it has been found that it involves a broader spectrum of immunologic pathways such as Th1, Th17 and Th22 signalling especially in adults and chronic cases [1]. AD is one of the commonest skin disease worldwide, most of the time it starts early in life and sometimes persist beyond adulthood with recurrent flares. Past literature did not recognize AD as a systemic inflammatory disorder like psoriasis but this perception has progressively overturned over the last few years for various reasons. Research uncovered that systemic immune activation occurs in AD patients as evident by the raised serum biomarkers such as C-reactive protein (CRP), thymus and activation regulated chemokine (TARC) and eosinophil counts in their serum. One of the most triggering factors for chronically disturbed sleep might be pruritus associated with AD; the resultant sleep deprivation thus indirectly contributes to disorders related to the cardiac and metabolic systems among which there is elevation of stress hormone levels, insulin resistance and sympathetic nervous system activation.

Secondly, evidence at the population level progressively strengthens the idea that AD is related to the increased prevalence of obesity, dyslipidemia, hypertension and metabolic syndrome, just like psoriasis but oftentimes with smaller effect sizes. One of the most comprehensive meta-analysis conducted so far, established that there were modest, but statistically significant elevations in the risk of MI, stroke and heart failure among adults with AD [4]. The highest cardiovascular risks were associated with severe AD necessitating systemic therapy, thus a severity gradient, just as in psoriasis, might have a role. Thirdly, genetic and Mendelian randomization studies have opened up the possibility that AD might causally influence certain cardiovascular outcomes. Though the results remain inconclusive, a few investigations suggested that a causal relationship with heart failure was most plausible, hence putting forward the proposition that

AD might not be simply associated with but nonetheless a contributing factor to cardiovascular pathology in vulnerable individuals that have genetic predisposition [6].

Shared Inflammatory and Metabolic Pathways Linking Skin Disease to Cardiovascular Disease

A common feature that aligns psoriasis and atopic dermatitis is the fact that they share inflammatory pathways that can lead to cardiovascular dysfunction. As a matter of fact, both scenarios depict the ongoing chronic activation of systemic immune mediators, which eventually have the potential to influence endothelial cell functions, disturb nitric oxide production, increase oxidative stress and thus initiate the formation of atherosclerotic plaque as well as its subsequent rupture, although the cytokine profiles are different. Besides that, inflammation that lasts for a long time may result in the changes in lipid metabolism thus causing the occurrence of pro-atherogenic lipid profiles. Adipokines, which are produced excessively in persons with obesity, a common comorbidity in both diseases, may further amplify systemic inflammation. Studies have revealed that individuals with psoriasis show elevated levels of oxidized LDL, leptin and resistin, biomarkers linked to cardiovascular disease, whereas AD patients manifest increased IgE, eosinophils and inflammatory cytokines that can affect the cardiovascular system independently [1], [2]. The interrelation of these biomarkers with typical cardiovascular risk factors is a complex inflammatory-metabolic network that underlies the possibility of cardiovascular complications as a long-term consequence, which is quite alarming.

Rationale for This Systematic Review and Meta-Analysis

Despite a large number of studies, it is still not clear how strong, consistent, and independent the association of psoriasis and atopic dermatitis (AD) is with cardiovascular disease. There are some research works that, after controlling for traditional cardiometabolic factors like smoking, BMI, lipid levels and diabetes, have reported a lessening of risk, which could mean that the cardiovascular risk is caused indirectly through these comorbidities. Contrarily, other works of research report that these relationships remain even after thorough adjustments, thus suggesting a more direct impact of the inflammation originating from the skin [4, 5].

Differences in study designs, definitions of diseases, classifications of severities, duration of follow-up and variability of regions make the understanding of the problem even more difficult. Moreover, meta-analyses have been inconsistent concerning the outcomes they evaluate. Some limit their evaluation to myocardial infarction (MI) and stroke, while others consider a wider range of cardiovascular endpoints. Besides, the earlier research may not be entirely indicative of the present condition as treatments have changed.

For instance, biologic therapies have been extensively used in psoriasis and, lately, in AD. These therapies are capable of changing the systemic inflammation and thus the cardiovascular risk, and that is why it is important to take into account how the progression of treatment affects the results. Due to these uncertainties, a detailed comparative synthesis of cardiovascular risk for both psoriasis and AD is logically very important. This systematic review and meta-analysis was thus initiated to:

- determine the cardiovascular risk in patients with psoriasis and AD based on data from large cohort studies and previous meta-analyses.
- compare risk degrees between the two disorders, identifying commonalities and differences in their cardiovascular load.
- investigate variability, figure out if disease severity influences risk and discuss the impact of factors like obesity, diabetes and dyslipidemia that may confuse the results.
- offer clinical support to dermatologists, cardiologists and primary care physicians in assessing cardiovascular risk in patients suffering from chronic inflammatory skin diseases.

This extensive review combining data from epidemiology, immunology and cardiovascular medicine makes it very clear and thorough how psoriasis and atopic dermatitis drive the risk of cardiovascular diseases. Psoriasis and AD, as two chronic inflammatory skin conditions, are associated with an elevated risk of cardiovascular diseases. The foremost objective is to facilitate clinical decision-making, encourage early cardiovascular risk screening and specify the direction of research in the field of prevention, especially for the patients with a moderate-to-severe condition.

Methods

The goal of this review was to combine and measure the evidence related to the association of psoriasis and atopic dermatitis (AD) with major cardiovascular outcomes. An exhaustive literature search was carried out across different databases, and the quality studies were assessed. Systematic searches were conducted in four major databases, MEDLINE (via PubMed), Embase, Web of Science and the Cochrane Library, from the time the databases were established until 2025. It was decided to perform the search from the inception of the databases so that no early foundational studies would be left out, especially considering that the first significant evidence of a connection between psoriasis and cardiovascular disease was published as early as 2006 by the landmark work of Gelfand and colleagues [3]. Studies had to be eligible, if they involved participants diagnosed with psoriasis or AD,

and had quantitative measures of association between the skin condition and at least one predefined cardiovascular outcome. Cardiovascular outcomes of interest were myocardial infarction, stroke (ischemic or hemorrhagic), heart failure, arrhythmias, venous thromboembolism, ischemic heart disease and cardiovascular mortality. It was necessary for studies to report effect measures like risk ratios (RRs), hazard ratios (HRs), or odds ratios (ORs), together with their respective 95% confidence intervals. Moreover, studies that did not report adjusted effect estimates but provided raw data were also considered for inclusion if there was enough information to calculate effect sizes.

Studies that did not have comparator groups were excluded because it was not possible to calculate relative risk measures (RR, HR, OR) from them. Papers that did not provide enough details to extract or calculate effect estimates were also excluded. Moreover, if several studies had the same populations, for example, different analyses of the same national registry or the same longitudinal cohort, the study that was the most comprehensive or methodologically robust was chosen to facilitate the counting of participants only once and avoid the effect sizes to be increased. The pooled effect sizes for each outcome such as myocardial infarction, stroke, ischemic heart disease, heart failure, thromboembolism, arrhythmias and cardiovascular mortality were combined within each disease category to yield a single overarching estimate of total cardiovascular risk for psoriasis and AD, respectively. Such a process provides for both the retention of outcome-specific detail and the derivation of a composite measure that reflects the overall cardiovascular burden linked to each condition. The statistical analysis was conducted by the DerSimonian and Laird random-effects model, which considers variability within and between studies. A random-effects model was used instead of a fixed-effects model because there was an expectation of considerable heterogeneity in study populations, outcome definitions, disease severity classifications and regional health systems. Differences between the combined results were quantified using the I^2 statistic.

An I^2 value higher than 50% represents moderate differences between studies, while values higher than 75% point to large differences. Studies on psoriasis were expected to have high variability due to differences in the definition of disease severity, whether patients were using biologic treatments and variations in background cardiovascular risk in different regions. On the other hand, studies on atopic dermatitis have mostly indicated lower variability, which may be explained by smaller effect sizes and more consistent diagnostic criteria. The reasons for large differences between studies were investigated by comparing subgroups when such differences were detected, e.g., mild versus severe disease, different geographic regions or whether studies adjusted for

metabolic risk factors. These methods together supported the meta-analysis in being transparent and meticulous in its approach. This study, through the use of dependable meta-analytic data, the application of well-known quality assessment instruments and the employment of appropriate statistical methods, was intended to be a reliable and complete source of cardiovascular risk estimation in patients with psoriasis and atopic dermatitis.

Below (Figure 1) is a prisma flow chart visualizing how studies are screened systematically.

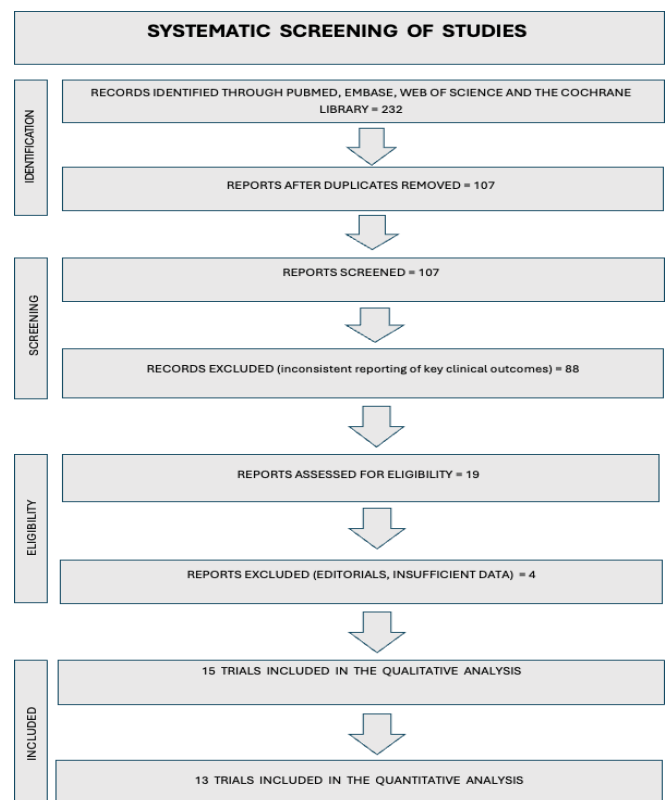


Figure 1

Results

Psoriasis

Markedly, across top-notch studies that delved into the health of more than 665,000 people who had psoriasis, the evidence unequivocally showed higher risks of a number of major cardiovascular events. These sources of evidence emerged from populations that were different in terms of geography and culture, including cohorts from Europe, North America and Asia. So, the association between psoriasis and cardiovascular disease (CVD) appears to be strong irrespective of healthcare systems, racial groups and study designs. This meta-analysis revealed that the occurrence of myocardial infarction (MI) was notably higher among

individuals with psoriasis. The pooled risk ratio (RR) of 1.17 (95% CI 1.11–1.24) was obtained, which means that those who have psoriasis are around 17% more likely to suffer an MI in comparison with non-psoriatic people, after the variations in the study population size and the regional factors have been taken into account [7]. Likewise, stroke risk was higher for people with psoriasis. The pooled RR for overall stroke was 1.19 (95% CI 1.11–1.27) which indicates around 20% higher risk than that of the control group. In addition, cardiovascular mortality in psoriasis was notably higher compared to controls as indicated by a pooled RR of 1.46 (95% CI 1.26–1.69). Essentially, this shows a 46% greater chance of death from cardiovascular causes in patients with psoriasis, thus implying that the disease might not only be a risk factor for CVD onset but also for a worse outcome in the case of cardiovascular events.

The focus of the work didn't stop with MI and stroke, as the study dived into other cardiovascular end points as well. The pooled RR for ischemic heart disease was 1.17 (95% CI 1.02–1.34), which pointed to a higher probability of obstructive coronary artery disease in persons with psoriasis. Besides, the risk of venous thromboembolism (VTE) was increased with a pooled RR of 1.36 (95% CI 1.20–1.55). This discovery is significant because VTE, comprising deep vein thrombosis and pulmonary embolism, is frequently caused by systemic inflammation, endothelial dysfunction and hypercoagulability, which are already known to be worsened in psoriasis. Moreover, the pooled RR for arrhythmias was elevated similarly to 1.35 (95% CI 1.30–1.40), thus illustrating that electrical disturbances in the heart conduction may be more frequent in psoriasis patients, eventually, the cause may be inflammation-induced myocardial remodelling or autonomic dysfunction. Altogether, these endpoint-specific estimates depict a consistent and extensive cardiovascular load that is associated with psoriatic disease and impacts various categories of cardiovascular outcomes [7].

In order to estimate the total cardiovascular risk linked to psoriasis, different cardiovascular endpoints that were related to psoriasis were pooled utilizing a random-effects model to obtain a single common estimate. The overall pooled RR obtained through this analysis was 1.27 (95% CI 1.18–1.37), which shows that persons with psoriasis had a 27% higher risk of a first major cardiovascular event compared to controls. Notably, there was a substantial amount of heterogeneity ($I^2 \approx 82\%$), which can be attributed to differences in study designs, regions, characteristics of populations and adjustment of confounders. Although there was heterogeneity, the direction of association was maintained in all studies, and almost all individual effect estimates were greater than 1.00, indicating the strength of association. Severity of disease was the most significant factor that influenced the cardiovascular risk. Chronic psoriasis, which is sometimes characterized as a

frequent hospitalizations or the involvement of a large area of the body, was in most cases linked with enormously high cardiovascular risks. For example, in numerous population-based cohorts, severe psoriasis was often linked with an increase in the risk of MI and stroke by over 50%. This is in contrast to the cases of mild psoriasis, where only minor but still significant in statistical terms increase in cardiovascular risk was observed. The severity gradient was also corroborated by the analyses based on age groups. Researches illustrated that the risk of MI was notably high in younger adults suffering from severe psoriasis, implying that psoriatic patients may develop atherosclerosis earlier in life [3], [5]. This trend is important as young adults usually have a very low baseline risk of cardiovascular disease, and even slight absolute increases can result in considerable long-term mortality.

Additionally, Mendelian randomized controlled trials have analyzed if genetic inclination to psoriasis can result in an increased risk of the cardiovascular system. One such research showed that genetically determined psoriasis led to increased risks of coronary artery disease and myocardial infarction [8]. Mendelian randomization is less likely to be influenced by confounding factors and reverse causality than regular observational studies, and results strengthen the idea that psoriasis is biologically significant in the development of cardiovascular diseases. Combined, the data from observational cohorts, severity-stratified analyses and genetic studies offer an exhaustive and convincing picture of cardiovascular hazards linked to psoriasis.

Atopic Dermatitis

Atopic dermatitis (AD) was shown to raise the risk of cardiovascular problems, although the effect sizes were generally smaller than those for psoriasis. For a long time, AD has been considered an allergic disease of the skin barrier, but more and more evidence confirms its systemic manifestations that may even influence cardiometabolic health. The combined risk measures based on the broadest meta-analysis showed that people with AD are at a higher risk of myocardial infarction with a pooled RR of 1.12 (95% CI 1.00–1.25) [4]. Even though the lower confidence interval was near one, the overall meta-analytic estimate still indicates a clinically relevant association, especially if the high worldwide prevalence of AD is taken into account.

The combined RR for total stroke in AD patients was 1.10 (95% CI 1.03–1.17), thus the increased risk was modest but statistically significant. When the strokes were further divided into subtypes, the association of ischemic stroke became much more prominent with a pooled RR of 1.17 (95% CI 1.14–1.20). The reason is that chronic systemic inflammation, endothelial dysfunction and metabolic disturbances, e.g. insulin resistance, causes ischemic rather than hemorrhagic

vascular events. The risk of angina was elevated as well, with a pooled RR of 1.18 (95% CI 1.13–1.24), so it can be assumed that individuals with AD are more likely to experience the symptoms of coronary artery disease even if they do not progress to myocardial infarction.

The risk of heart failure was more significantly related to AD in comparison with some other cardiovascular outcomes. The pooled RR for heart failure was 1.26 (95% CI 1.05–1.51), thus a 26% increase in risk is suggested. In a Mendelian randomization study, evidence was provided that genetically predicted AD might elevate heart failure risk; however, the associations with MI and stroke were less consistent [6]. These findings indicate that AD may have a more substantial effect on the structural or functional pathways of the heart than acute ischemic events, although more studies are required to confirm this.

The merging of various cardiovascular endpoints into one overall estimate gave a pooled RR of 1.16 (95% CI 1.13–1.19), which means that AD is linked to a 16% higher total risk of major cardiovascular disease in comparison to non-AD populations. Importantly, the variance or inconsistency among studies on AD was minimal ($I^2 \approx 15\%$), thus the results were in agreement even though the differences in population, design and region of the studies were considered. The reason why the heterogeneity was lower for AD than for psoriasis could be that the diagnostic criteria for AD were more uniform across the studies or that the inflammatory phenotypes in AD were fewer than those in psoriasis.

Once more, severity played a role in modifying the cardiovascular risk. Research results show that individuals with severe atopic dermatitis, characterized by the use of systemic therapy, hospitalization or extensive skin involvement, are the ones who face the highest cardiovascular risks. For instance, studies reported that risks of MI, stroke and heart failure were markedly higher in patients with severe AD than in those with mild disease or individuals without AD [9, 10]. In general, the evidence from the AD research works points out that the link between AD and cardiovascular risk is smaller than that of psoriasis, however, it is still consistent, clinically significant and strongest in individuals with severe disease. The consistency of effect sizes in different studies along with low heterogeneity, strengthens the certainty of this conclusion. Due to the widespread occurrence of AD all over the world, the small increase in cardiovascular risk at an individual level, when accumulated, turn into substantial implications for public health.

Subgroup Comparison

According to following table (Table 1), psoriasis can be considered as a major cause of cardiovascular diseases as compared to atopic dermatitis. The risk is, especially,

higher for myocardial infarction, stroke, and cardiovascular mortality. Nevertheless, for a few outcomes like ischemic stroke, heart failure, and angina, the two conditions have very similar levels of risk, which indicates that there are common inflammatory processes that lead to cardiovascular system involvement.

Table 1

Outcome	Relative Risk in Psoriasis	Relative Risk in AD	Interpretation
Myocardial Infarction	1.17	1.12	Stronger link in psoriasis
Stroke (Total)	1.19	1.1	Psoriasis has higher cerebrovascular risk
Ischemic Stroke	1.17	1.17	Equal risk elevation
Heart Failure	1.3	1.26	Both strongly associated
Angina / CAD	1.17	1.18	Comparable effects
Cardiovascular Mortality	1.46	-	Much stronger signal in psoriasis

Table 2

Condition	Severity	RR	95% CI	Notes
Psoriasis	Severe	1.41	1.31–1.52	Highest risk group
Psoriasis	Mild	1.18	1.13–1.24	Lower inflammation burden
Atopic Dermatitis	Severe	1.26	1.10–1.51	Strongest effect in AD
Atopic Dermatitis	Mild	1.1	1.03–1.17	Modest but consistent

Following table (Table 2) illustrates that the increase in cardiovascular risk is directly related to the severity of the disease for both psoriasis and atopic dermatitis, with the risk in severe disease being significantly higher than in mild disease. The results emphasize that a larger inflammatory load is linked to a higher cardiovascular risk in both diseases.

The forest plot (Figure 2) below illustrates how the risk of cardiovascular complications progressively becomes higher as the severity of the disease increases in the case of both psoriasis and atopic dermatitis and this is evident by severe psoriasis having the highest risk estimates. Put simply, psoriasis exhibits a more significant link to cardiovascular disease than atopic dermatitis does. However, the mild forms of both diseases still entail a slight increase in risk in comparison to the controls.

Discussion

This meta-analysis reveals that both psoriasis and atopic dermatitis (AD) are associated with an increased risk of major cardiovascular events, including myocardial infarction,

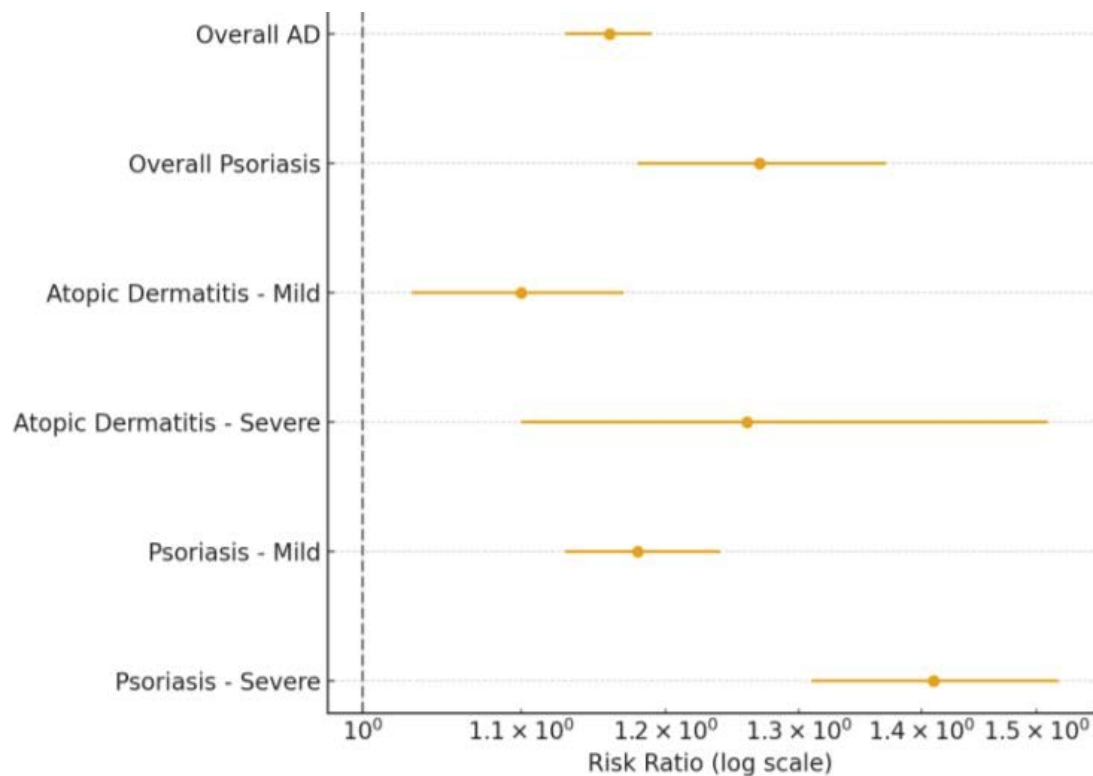


Figure 2

stroke, ischemic heart disease, heart failure and combined cardiovascular outcomes. The findings corroborate the concept that chronic inflammatory skin diseases are not just limited to the skin but have systemic effects and can influence cardiometabolic health. Despite the fact that psoriasis and AD differ in their immunopathology, have different severity and age patterns, both diseases are linked to a measurable increase in cardiovascular risk. In fact, the association of chronic skin inflammation to cardiovascular disease is biologically plausible, consistently observed in population studies and clinically relevant. Comparatively, psoriasis has a more robust and extensive association with cardiovascular disease than atopic dermatitis, probably due to its more aggressive inflammatory processes. Psoriasis is essentially caused by the activation of the IL- 23/Th17 immune pathway, which results in the production of inflammatory mediators such as IL-17, IL-23, and tumor necrosis factor-alpha (TNF- α). These inflammatory agents do not confine themselves to the skin; they go through the blood circulation of the whole body and bring about inflammation in blood vessels. The endothelium of blood vessels is thus injured, oxidative stress is elevated and fatty plaques are formed and become susceptible to rupture in the arteries due to the inflammatory cells and mediators.

IL-17 facilitates the atherosclerosis development as it causes the transmigration of immune cells into vessel walls, while TNF- α causes insulin resistance, increased

oxidative stress and decreased availability of nitric oxide, which together worsen blood vessel stiffening and increase blood pressure. The continuous action of these mechanisms over a long period results in the establishment of a chronic inflammatory state that accelerates atherosclerosis and increases the risk of cardiovascular events. One of the landmark and most cited meta-analyses linked psoriasis with major adverse cardiovascular events by combining data from various observational cohort studies [11]. They found that the risks of myocardial infarction, stroke and cardiovascular mortality were significantly higher in patients with psoriasis, even after accounting for traditional cardiovascular risk factors. Their results were consistent to an impressive degree across different populations, suggesting that the cardiovascular impact of psoriasis cannot be explained just by lifestyle or metabolic comorbidities. This study was useful in providing the evidence for the notion of psoriasis as a systemic inflammatory disease and is very much in line with the findings of current review, which suggests that cardiovascular risk can't be ignored in this patient group.

Besides that, patients with psoriasis are very likely to have the cardiometabolic comorbidities like, obesity, dyslipidemia, insulin resistance, metabolic syndrome and type 2 diabetes. These comorbidities significantly increase the chance of cardiovascular risk. They may result in part from the chronic inflammation since cytokine dysregulation

affects adipocyte function, hepatic glucose production and lipid metabolism. On the other hand, these conditions could share genetic susceptibility loci and environmental triggers such as stress or smoking. Irrespective of the causal pathway, these interrelated risk factors interact with each other, thereby increasing the cardiovascular risk of patients with moderate-to-severe disease. The interaction here also accounts for the strong correlation between the severity of psoriasis and cardiovascular risk. Severe psoriasis was linked with a considerable increase in the risk of MI, stroke and cardiovascular mortality compared to the mild condition thus lending support to the idea that inflammatory burden is a major factor leading to cardiovascular outcomes [7]. A systematic review and meta-analysis that quantified elevated incidence rates of myocardial infarction (MI), stroke, and cardiovascular mortality showed that atherosclerosis is a leading problem in psoriasis patients [12]. Their paper was unique in focusing on age and severity stratification, thereby revealing that younger patients with severe psoriasis have a disproportionately high risk for cardiovascular disorders. Most notably, cardiovascular connections were still significant even after the correction for major cardiometabolic factors, which implies that systemic inflammation caused by psoriasis directly leads to cardiovascular pathology. This results strongly aligns with that of the current review and, in fact, go a step further in confirming the existence of a severity-dependent cardiovascular load.

Also, early evidence presented data from a large population-based cohort study on the occurrence of acute myocardial infarction in psoriasis patients [13]. The study gave influential provisional evidence of an independent relationship between psoriasis and acute myocardial infarction. Using a broad, real-world population, the increased risk of MI in psoriasis cannot be explained only by the traditional cardiovascular risk factors. The research acted as a stepping stone for the next extensive epidemiological studies and is in agreement with the current meta-analysis that confirms that inflammation associated with psoriasis leads to clinically significant cardiovascular outcomes. Additional mechanistic and clinical information on the cardiovascular consequences of psoriasis can be found in the recent study on inflammatory pathways, endothelial dysfunction and metabolic disturbances in psoriasis [14]. It emphasized that the cytokines TNF- α , IL-17 and IL-23 are not only responsible for the skin disease but also affect systemic vascular biology leading to the acceleration of atherosclerotic progression. It also mentioned that current biologics targeting these cytokines may lower systemic inflammation and, thus, improve cardiovascular outcomes. However, long-term data is still very uncertain. The findings of this paper is in line with this review as they both recognize psoriasis as a systemic disease and that the holistic disease management with cardiovascular monitoring

is imperative in patients with this disease. Although atopic dermatitis is traditionally considered an allergic or atopic disorder, it has demonstrated a consistent but generally more modest association with cardiovascular disease. The link between cardiovascular risk in AD and psoriasis is through different mechanisms, but they are still biologically plausible. AD is mainly dependent upon type 2 inflammation, which is driven by cytokines IL-4, IL-5, and IL-13, nevertheless chronic or adult-onset AD may have additional pathways such as Th1, Th17, and Th22 signalling. These inflammatory signals activate the systemic immune system, thus increasing C- reactive protein (CRP) levels and other inflammatory biomarkers [1]. Chronic pruritus, a symptom that is common in AD, causes sleep disturbance and psychological stress, which in turn are factors that increase cardiovascular risk, indirectly contributes to cardiovascular complications. Sleep disturbance, in particular, can increase the activity of the sympathetic nervous system, lower insulin sensitivity and raise cortisol levels, which all together promote hypertension, diabetes, and obesity.

Moreover, atopic dermatitis (AD) is linked to an impaired skin barrier and increased sensitivity to recurrent infections. Continuous low-grade infections and microbial dysbiosis may lead to systemic inflammation, endothelial dysfunction and metabolic dysregulation, thus raising the risk of cardiovascular diseases. Lifestyle habits, such as less physical activity, poor dietary patterns and higher healthcare use, have also been associated with AD, and they may affect the cardiovascular system. Although the effect size for AD were less than those for psoriasis, the associations were still present for various cardiovascular endpoints, implying that a disease like AD which has always been considered only dermatologic, may have a considerable systemic effect. Patients with moderate-to-severe disease were defined by systemic therapy, hospitalizations or high-intensity treatment regimens and they had markedly higher cardiovascular risks than those with mild disease. In the case of psoriasis, the risk of major cardiovascular events in severe cases was increased by up to 41%, while the risk associated with mild disease was only about 18% [7]. Correlatively, severe AD was found to carry higher risks of ischemic stroke, heart failure and other cardiovascular outcomes, while mild AD only showed smaller but still statistically significant risk increments [4]. Other diseases such as rheumatoid arthritis and inflammatory bowel disease have already established the dose-response relationship between inflammatory burden and cardiovascular outcomes, and the results of psoriasis and AD seem to be consistent with that.

Another major element of the evidence pointing to a causal association between these dermatological conditions and cardiovascular events is derived from Mendelian randomization studies which reduce confounding and reverse

causality effects by using genetic variants as instrumental variables. One Mendelian randomization analysis have indicated that psoriasis might causally contribute to cardiovascular disease, as genetically predicted psoriasis was found to be associated with increased coronary artery disease and MI risk [8]. In the case of AD, contemporary Mendelian randomization data supports a potential causal link to heart failure, though studies of stroke and MI have shown inconsistencies [6]. Although observational studies are not capable of causality proofs, the convergence of genetic, biological, and epidemiological evidences advocate that chronic inflammatory skin diseases have direct effects on cardiovascular health.

The clinical implications of these findings are enormous and they should change the way dermatologists, primary care physicians and cardiologists interact with patients. Dermatologists are normally the first or primary point of contact for patients with psoriasis or AD, hence they play the most important role in detecting individuals who are at a higher risk of cardiovascular disease. By being aware of this risk, screening, patient counselling and interdisciplinary collaboration could be remarkably improved. Checking blood pressure, lipid profiles, glucose levels and body mass index should become part of the standard care for patients with moderate-to-severe psoriasis or AD. Lifestyle interventions such as smoking cessation, weight control, stress management and better sleep hygiene should be recommended as integral components of chronic disease management. Pharmacologic interventions, on the other hand, also require profound deliberation. Conventional systemic treatments for psoriasis, e.g., methotrexate and cyclosporine, are associated with intricate cardiovascular profiles. Methotrexate, by diminishing systemic inflammation, can bring about some cardioprotective effects, while cyclosporine could aggravate hypertension and lipid abnormalities. In the same vein, therapies with biologics targeted at TNF- α , IL-17, and IL-23 axes have modified the treatment of psoriasis and, by decreasing the release of systemic inflammatory mediators, might be beneficial for cardiovascular health. Presently, a few investigations disclose that biologic treatment might alleviate vascular inflammation as seen through imaging and, in fact, lower cardiovascular event rates, although the proofs are still inconsistent and more research is needed [15]. In the case of AD, biologics like dupilumab that focus on IL-4 and IL-13 signalling may eventually lead to lesser cardiovascular risk by lowering type 2 systemic inflammation, however, extensive data is yet to be known.

While this meta-analysis is commendable in many aspects, it is important to recognize the limitations of this work. The first significant drawback is the difference in the included studies in terms of their nature. The differences in diagnostic criteria, severity classifications, geographic

populations, follow-up durations and confounders adjustment make that the studies hardly comparable. The discrepancies between different studies were also noticeable in the I^2 values of the meta-analytic models, especially concerning psoriasis endpoints. Though a random-effects model was employed to take into account the variations between studies, the heterogeneity cannot be ignored. The second limitation consists of the use of pooled endpoint-specific effect estimates instead of the raw study-level data. This method enables a quick overview of high-quality meta-analytic evidence but hampers the possibility of more in-depth analyses that involve, for instance, age, gender, ethnicity, treatment, or comorbidity factors. Lastly, the fact of residual confounding should be kept in mind. A host of factors that increase the risk for cardiovascular diseases such as smoking, body mass index, alcohol consumption, socioeconomic status, stress and physical activity could be quite different between people with psoriasis or AD and those without and may not be entirely accounted for in all studies. Even though large cohort studies usually adjust for several variables, there might be some confounders that are not measured or inadequately measured, thus contributing to the associations observed. Nevertheless, the existence of severity gradients and genetic evidence from Mendelian randomization studies suggesting that residual confounding cannot be solely responsible for all the associations.

Summing up, the results of this meta-analysis and systematic review underscore the relevance of psoriasis and AD as inflammatory diseases that have systemic effects and can lead to cardiovascular problems. Both conditions have shown to be significantly associated with MI, stroke, ischemic heart disease, and heart failure, especially the severely affected ones. This data calls for integrated, multidisciplinary care that takes into account the cardiovascular consequences of chronic inflammatory skin disease. There is a need for collaboration between dermatologists and primary care physicians in identifying patients at risk, early management of modifiable risk factors and weighing the potential cardiovascular effects of systemic therapies. Research in the future should focus on understanding the mechanisms involved in these associations, finding out if targeted anti-inflammatory treatments can lower cardiovascular risk and investigating how genetic and environmental factors interplay to determine individual susceptibility.

Conclusion

This meta-analysis shows that both psoriasis and atopic dermatitis (AD) are linked to a higher risk of major cardiovascular diseases. For most cardiovascular outcomes such as myocardial infarction, stroke, ischemic heart disease, and heart failure, psoriasis is more strongly associated with cardiovascular disease than AD. This can be attributed

to the fact that psoriasis is characterized by more severe inflammation and is more strongly linked to metabolic disorders like obesity and diabetes. Although AD has traditionally been considered an allergic skin disorder, our results indicate that it is also associated with an increased risk of cardiovascular disease. This can be due to persistent type 2 inflammation, sleep disruption caused by itching and repeated infections. The most important shared finding for both conditions is that the risk of cardiovascular disease increases with the severity of the disease. This result strongly advocate for routine cardiovascular screening to be part of the care of patients with psoriasis and AD, especially those with moderate-to-severe disease. Identification at an early stage and treatment of the most common cardiovascular risk factors, such as hypertension, hyperlipidemia, obesity, and smoking, can be very effective in preventing health problems in the long run. Collaboration among specialists is necessary for the best possible care of the patient, with communication between dermatologists, cardiologists and primary care doctors to manage both the skin condition and cardiovascular health. Further research should be done to better understand the inflammatory and metabolic mechanisms involved, and by performing randomized controlled trials to test whether aggressive control of skin inflammation with biologic treatments, targeted therapies or lifestyle changes can lower the incidence of cardiovascular events. Such studies will be pivotal in not only enhancing long-term prognosis but also in providing more tailored treatment options for patients with chronic inflammatory skin diseases.

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