Untaaveesup et al. World Allergy Organization Journal (2025) 18:101035
http://doi.org/10.1016/j.waojou.2025.101035

WORLD ALLERGY ORGANIZATION JOURNAL

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Cardiovascular and metabolic outcomes associated with moderate-to-severe atopic dermatitis: A systematic review and meta-analysis

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ABSTRACT

Background: Chronic systemic inflammation in individuals with moderate-to-severe atopic dermatitis (AD) potentially predisposes them to metabolic and cardiovascular diseases. Nevertheless, evidence with regard to such association is limited.

Objective: To assess the association between metabolic and cardiovascular outcomes and moderate-to-severe AD.

Methods: A systematic search was performed through PubMed, Scopus, EMBASE, and Cochrane for population-based studies that addressed the effects of moderate-to-severe AD on metabolic and cardiovascular outcomes compared with the general population from inception to August 31, 2023. Meta-analysis was performed using the random effects model. The pooled odds ratio (OR) and certainty of evidence for each outcome were reported.

Results: We included 11 studies, 4 retrospective cohorts, 1 prospective cohort, 4 cross-sectional, and 2 case-control studies involving 405,170 moderate-to-severe AD patients compared to 4,591,478 unaffected controls. Moderate-to-severe AD was associated with a higher risk of myocardial infarction with an OR (95% CI) of 1.33 (1.07, 1.65), angina 1.33 (1.06, 1.66), heart failure 1.56 (1.28, 1.90), stroke 1.45 (1.21, 1.74), hypertension 1.38 (1.18, 1.63), dyslipidemia 1.27 (1.15, 1.41), and metabolic syndrome 1.24 (1.05, 1.42) with very low certainty of evidence. No significantly increased risk of cardiovascular death with an odds ratio (95% CI) of 1.81 (0.96, 3.44) and diabetes of 1.24 (0.91, 1.68) was observed. High heterogeneity was observed in most studies for all of the outcomes.

Conclusion: Our meta-analysis demonstrated a modest but significant association between moderate-to-severe AD and increased susceptibility to metabolic and cardiovascular diseases.

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http://doi.org/10.1016/j.waojou.2025.101035
Received 22 July 2024; Received in revised from 10 January 2025; Accepted 10 February 2025
Online publication date xxx

Initial assessment of cardiovascular and metabolic risk for patients with moderate-to-severe AD should be considered to enable early management strategies.

Keywords: Atopic dermatitis, Atopic eczema, Cardiovascular outcomes, Meta-analysis, Metabolic outcomes

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disorder characterized by persistent cycles of flares and remission, affecting over 200 million individuals worldwide.[1] Recent international surveys demonstrated the prevalence of moderate-to-severe adult AD, with a wide range of 2.4%–41.6%, depending on measures used to assess the severity.[2] The greater AD severity was associated with a higher disease burden, sleep disturbances, impaired mental health, and reduced quality of life.[3,4]

Moderate-to-severe AD had widespread chronic inflammation involving both lesional and non-lesional skin suggesting the existence of systemic inflammation.[5,6] Chronic systemic inflammation in psoriasis and other immune-mediated diseases, such as rheumatoid arthritis, was associated with an increased risk of accelerated atherosclerosis and cardiovascular diseases.[7,8] A previous meta-analysis revealed that the severity of psoriasis correlated with the likelihood of increased adverse cardiovascular events.[9] Both severe psoriasis and severe AD were associated with an increased prevalence of coronary artery diseases based on computed tomography coronary angiography.[10] In contrast to moderate-to-severe AD, mild AD showed fewer inflammatory cell activations, primarily localized to the lesional skin, and no evidence of systemic inflammation in the peripheral blood.[11] This finding may elucidate the inconsistent findings regarding the correlation between AD and cardiovascular diseases observed in prior systematic reviews and meta-analyses, which encompassed studies involving AD patients across all severity levels.[12,13]

Notably, systemic inflammation not only contributes to cardiovascular outcomes but is also closely associated with metabolic dysregulation, including the development of diabetes, hypertension, dyslipidemia, and metabolic syndrome, which are established key risk factors for cardiovascular diseases.[14,15] Investigating these metabolic outcomes alongside cardiovascular outcomes should provide a more comprehensive understanding of the broader impact of moderate-to-severe AD on cardiovascular health. Accordingly, we conducted a systematic review and meta-analysis to assess the association between moderate-to-severe AD and cardiovascular outcomes, including cardiovascular death, myocardial infarction, angina, heart failure, stroke, and metabolic outcomes, including diabetes, hypertension, dyslipidemia, and metabolic syndrome.

METHODS

This systematic review and meta-analysis were conducted following the Cochrane Handbook for Systematic Reviews of Intervention and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The review protocol was registered on PROSPERO (CRD42023454573).

Data sources and search strategies

Two investigators (SU, TA) independently searched the potentially eligible studies from 4 databases, including PubMed, EMBASE, Scopus, and Cochrane, from inception to August 2023. Table E1-E4 provide a search strategy for each database. The investigators manually searched the references in each included study to ensure comprehensiveness.

Study selection and outcomes

The inclusion criteria were: 1) Eligible studies were case-control, cross-sectional, or cohort studies. 2) Participants were adults (≥18 years old) diagnosed

with moderate-to-severe AD. The control group consisted of individuals from the general population without AD. 3) Moderate-to-severe AD was identified based on 3.1) The following scoring systems: Patient-Oriented Scoring of Atopic Dermatitis (PO-SCORAD) index,[16] Patient-Oriented Eczema Measure (POEM),[17] Dermatology Life Quality Index (DLQI),[18] or self-reported global AD severity,[19] 3.2) Treatment with 1 of the following: second potent topical corticosteroids within 1 year, or topical calcineurin inhibitors, or oral corticosteroids, or systemic immunosuppressants, or phototherapy.[20-22] 3.3) Evidence of healthcare utilization, defined as the number of physician visits or at least 1 hospitalization due to AD exacerbations or required specialist referral for AD management.[23-25] 4) The outcomes of interest were cardiovascular diseases, encompassing cardiovascular death, myocardial infarction, angina, heart failure, stroke, and traditional metabolic diseases, including diabetes, hypertension, dyslipidemia, and metabolic syndrome. The exclusion criteria were: 1) Studies published in non-English language or studies with no available full-texts, or 2) Studies involving patients with other types of dermatitis, such as seborrheic or contact dermatitis.

The primary outcomes of interest were the association of moderate-to-severe AD and cardiovascular death, myocardial infarction, angina, heart failure, stroke, diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome.

Screening

The 2 rounds of screening full-text papers were conducted through Covidence (SaaS enterprise, Melbourne, Australia), an online tool for data management. The first round, screening titles and abstracts, was independently conducted by 2 authors (SU and TA). The second round, screening full-text papers, was independently conducted by 6 authors (SU, TA, AB, TrT, PS, and CY). Any disagreements were discussed with the corresponding author until consensus was achieved.

Data extraction

Two investigators (SU and TA) independently extracted data from the included studies regarding the authors' names, year of published studies, study design, gender, age, body mass index, smoking habit, disease severity, criteria for diagnosis, ascertainment of the outcomes of cardiovascular and metabolic diseases, and factors adjusted for quantitative analyses. Any discrepancies were resolved by discussion with the clinical epidemiologists (NJ and PP) and the corresponding author.

For the primary outcomes, we aimed to extract the reported odds ratio (ORs) and 95% confidence intervals (CI) comparing moderate-to-severe AD patients and unaffected controls. However, for studies that did not report ORs, we extracted the number of events and non-events within each outcome to perform manual ORs calculated.

Risk of bias assessment

Two authors (SU and TA) independently assessed the risk of bias in each included study using the "Quality In Prognosis Studies" (QUIPS) tool to evaluate prognostic factors.[26] Any discrepancies were resolved by discussion with the clinical epidemiologists (NJ and PP) and the corresponding author.

Data synthesis and analysis

In the qualitative analysis, the outcomes of interest were evaluated based on their relevance to the predefined criteria. For the quantitative analysis, a meta-analysis was conducted only for outcomes reported in at least 2 studies to ensure adequate data for meaningful synthesis. All analyses were conducted using Stata 17 (StataCorp, Texas, USA). For studies that did not provide the data on ORs, we calculated the unadjusted ORs and 95% CI from the extracted raw data. The reported and calculated ORs of each outcome were pooled using a random-effects model via the *metagen* package in the R program.[27] Heterogeneity among the included studies was assessed using Cochrane's Q test and the I-squared statistics (I^2). The statistical significance level was set at $p < 0.05$. Sensitivity analysis was conducted to assess the robustness of the pooled results by excluding unadjusted ORs. A leave-one-out analysis was conducted on outcomes from studies with the same population and overlapping study periods. Publication bias was evaluated using a funnel plot and Eggar's

regression test if the number of studies exceeded 10 for each predictor.

Certainty of evidence

Two authors (SU and TA) independently graded the certainty evidence for each outcome using the Grading of Recommended Assessment, Development, and Evaluation (GRADE) approach.[28] Any discrepancies were resolved through the discussion with NJ and PP. The degree of confidence was categorized into 4 levels: high, moderate, low, or very low. We determined the initial certainty of evidence at low. Quality may be downgraded due to the risk of bias, imprecision, inconsistency, indirectness, or publication bias, as appropriate.

RESULTS

Search results

A total of 9344 records were identified from databases. Of these, 3659 duplicates were detected and subsequently removed. After screening titles and abstracts, 98 full-text articles were assessed for eligibility. Eighty-seven studies were excluded: 42 due to inappropriate study design, 4 for being non-English language studies, 22 for lacking the relevant population, and 19 for not reporting the outcomes of interest. Eleven studies met our inclusion criteria and were included in this systematic review. The study by Su et al[29] was excluded at this point due to the absence of reported ORs and raw categorical data (Table E5). Therefore, only 10 studies were included in the meta-analysis. The PRISMA 2020 flow diagram is shown in Fig. 1.

Characteristics of included studies

This systematic review included a total of 11 studies, 4 retrospective cohorts,[29-32] 1 prospective cohort,[33] 4 cross-sectional,[34-37] and 2 case-control studies,[38,39] involving 405,170 patients with moderate-to-severe AD and 4,591,478 controls with no AD. The summary of baseline characteristics and main results of each study are presented in Table 1. All studies enrolled participants with moderate-to-severe AD, 18 years of age or older, assessing either cardiovascular or metabolic outcomes or both compared with the general population with no AD. Two retrospective cohort studies, Egeberg et al[31] and Andersen et al,[30] were conducted in the same population during overlapping study periods. The most common outcomes of focus encompassed were myocardial infarction, stroke, hypertension, and diabetes, with 7 studies evaluating each of these endpoints. Details on the definition of moderate-to-severe AD, ascertainment of AD diagnosis and associated outcomes, and confounders of each study are shown in Table E6. In most included studies, patients diagnosed with AD were identified through the International Classification of Diseases (ICD)[40] criteria and stratified according to disease severity based on their systemic therapy.

Risk of bias of included studies

According to QUIPS, Fig. 2 illustrates the details of the risk of bias assessment on the rating of each domain. Six studies[29,30,32,33,35,39] were classified as having a low risk, 2 studies[31,37] as having a moderate risk, and 3 studies[34,36,38] as having a high risk of bias. The summarized proportions for each domain of QUIPS of all included studies are shown in Figure E1. Details of the risk-of-bias assessment of included studies are shown in Table E7.

Grading certainty of evidence

Table 2 shows the overall quality rating according to GRADE. All cardiovascular and metabolic outcomes were rated as very low certainty of evidence.

Outcomes associated with moderate-to-severe atopic dermatitis

Cardiovascular death

Three studies assessed cardiovascular death outcomes in patients with moderate-to-severe AD versus those without AD (Figure E2).[30,33,39] Andersen et al[30] and Silverwood et al[33] found a positive association between moderate to severe AD and cardiovascular death with the OR (95% CI) of 3.30 (2.37, 4.59) and 1.81 (1.76, 1.86), respectively. In contrast, Ivert et al[39] found no such association with the OR (95% CI) of 1.04 (0 88, 1.23). In the quantitative analysis, moderate-to-severe AD was not significantly associated with an increased risk of cardiovascular death with OR

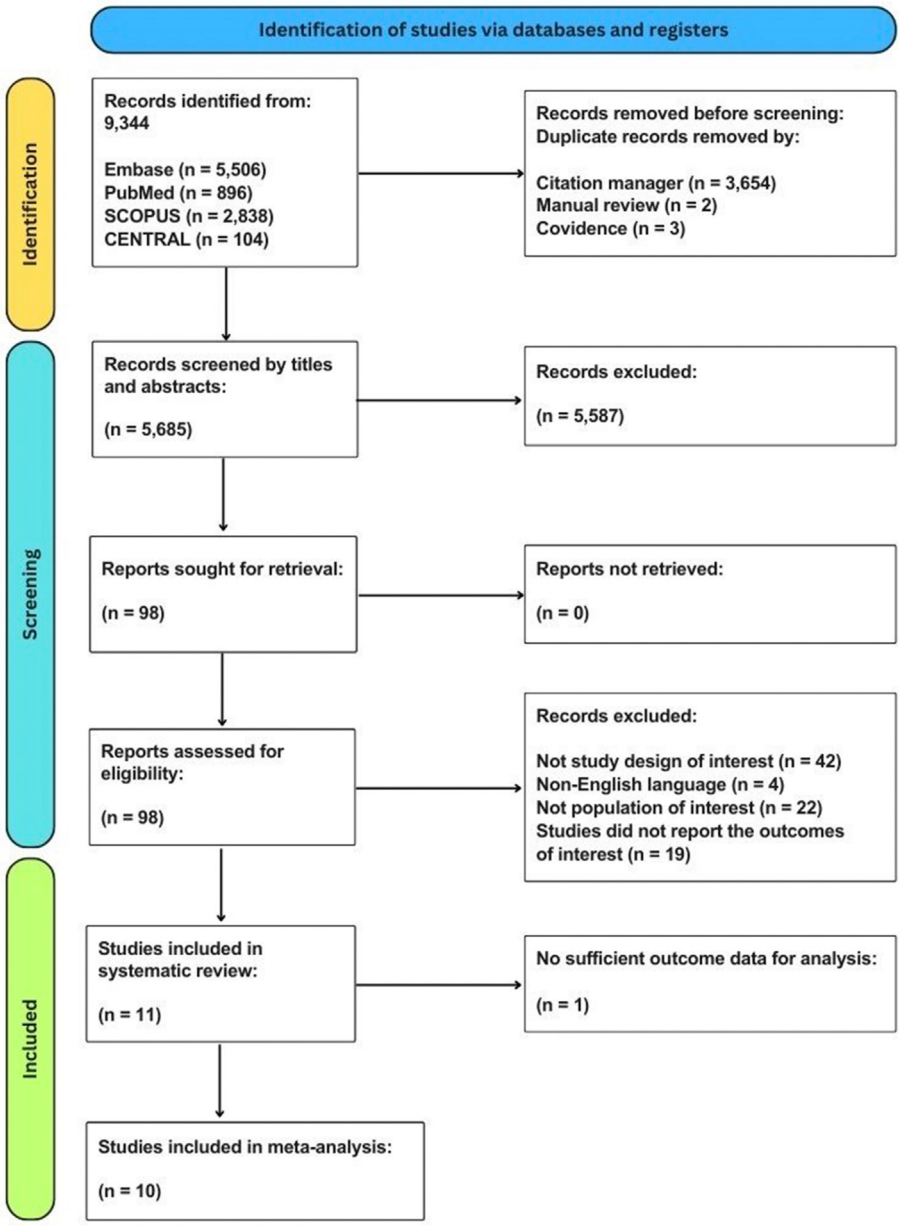

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of included and excluded studies

(95% CI) of 1.81 (0.96, 3.44), compared to the general population (Fig. 3 and E2).

Myocardial infarction

Myocardial infarction outcome was evaluated by 7 studies,[30–33,35,38,39] involving 400,536 patients with moderate to severe AD compared with 4,543,403 individuals without AD (Fig. 4A). Wan et al,[32] Silverwood et al,[33] and Andersen et al[30] found a higher risk of myocardial infarction in patients with moderate to severe AD compared to the population with no AD with OR (95% CI) of 1.31 (1.27, 1.34), 1.52 (1.46, 1.59), and 2.65 (1.74, 4.04), respectively. The remaining 4 studies also supported a higher myocardial infarction risk in moderate-to-severe AD but did not reach statistical significance.[31,35,38,39] The Meta-analysis combining the results of 7 studies observed that patients with moderate-to-severe AD had a significantly increased risk of myocardial infarction compared to those without AD, with OR (95% CI) of 1.33 (1.07, 1.65), as shown in Figs. 3 and 4A. The results of the leave-one-out sensitivity analysis by excluding either Egeberg et al[31] or Andersen

Studies	Study design, Country	Study period	Age, y[a]	No. of controls	No. of moderate/ severe AD patients	Reported outcome parameters[c]								
						Cardiovascular death	MI	Angina	HF	Stroke	DM	HT	DLP	Metabolic syndrome
Wan 2023[32]	RC, UK	1994-2015	47[b]	2,678,888	Moderate AD 196,101 Severe AD 18,115	NA	HR 1.01 (0.97, 1.04) HR 1.27 (1.15, 1.39)	NA	NR	HR 1.03 (1.01, 1.06) HR 1.21 (1.13, 1.30)	HR 1.08 (1.06, 1.10) HR 1.15 (1.09, 1.22)	HR 0.99 (0.98, 1.01) HR 1.05 (1.01, 1.10)	HR 1.02 (1.00, 1.04) HR 1.11 (1.06, 1.17)	NA
Luger 2022[34]	CS, EU-5 (France, Germany, Italy, Spain, UK)	2017	45.6	1014	Moderate-to-severe AD 1014	NA	NA	NR	NR	NR	NR	NR	NR	NA
Smirnova 2020[37]	CS, Sweden	2017	62[b]	25, 955	Severe AD 419	NA	NA	NA	NA	NA	1.96 (1.37, 2.79)	1.76 (1.36, 2.29)	NA	NA
Ivert 2019[39]	CC, Sweden	1968-2016	42.41	93,013	Severe AD 9558	1.04 (0.88, 1.23)	1.03 (0.92, 1.15)	1.11 (1.00, 1.24)	NA	1.19 (1.07, 1.33)	NA	NA	NA	NA
Shalom 2019[35]	CS, Israel	1998-2016	>18	45,157	Moderate-to-severe AD 1909	NA	1.05 (0.86, 1.27)	NA	1.26 (0.91, 1.73)	1.14 (0.89, 1.46)	1.19 (1.02, 1.37)	1.27 (1.10, 1.46)	1.45 (1.28, 1.64)	1.24 (1.05, 1.42)
Silverberg 2018[36]	CS, USA	NR	52 (16.3)	783	Moderate AD 172 Severe AD 34	NA	NA	NA	NA	NA	RR 1.58 (1.03, 2.13) RR 2.49 (1.16, 3.82)	RR 1.12 (0.95, 1.29) RR 1.29 (1.04, 1.62)	NA	NA
Silverwood 2018[33]	PC, UK	1998-2015	43[b]	1,528,477	Moderate AD 145,583 Severe AD 19,700	HR 1.01 99% CI (0.93, 1.10) HR 1.30 99% CI (1.10, 1.53)	HR 1.07 99% CI (0.97, 1.18) HR 1.37 99% CI (1.12, 1.68)	HR 1.11 99% CI (0.96, 1.29) HR 1.41 99% CI (1.02, 1.95)	HR 1.20 99% CI (1.09, 1.33) HR 1.67 99% CI (1.36, 2.05)	HR 1.09 99% CI (1.00, 1.20) HR 1.20 99% CI (0.99, 1.46)	NA	NA	NA	NA
Egeberg 2017[31]	RC, Denmark	1995-2012	34.3 (14.1)	46,200	Severe AD 4620	NA	1.23 (0.98, 1.54)	NA	NA	1.45 (1.19, 1.77)	0.80 (0.69, 0.93)	1.28 (1.16, 1.42)	1.22 (1.11, 1.34)	NA
Andersen 2016[30]	RC, Denmark	1997-2011	24.54	145,372	Severe AD 2527	IRR 1.06 (0.77, 1.46)	IRR 1.06 (0.72, 1.56)	NA	NA	IRR 1.19 (0.85, 1.65)	NA	NA	NA	NA
Su 2014[29]	RC, Taiwan	2005-2009	40[b]	20,323	Moderate AD 2256 Severe AD 739	NA	NA	NA	NA	HR 1.64 (1.23, 2.19) HR 1.71 (1.15, 2.56)	NA	NA	NA	NA
Schmitt 2008[38]	CC, Germany	2003-2004	29 (26)	6296	Moderate-to-severe AD 2423	NA	1.25 (0.27, 6.30)	0.90 (0.45, 1.79)	NA	NA	0.71 (0.47, 1.05)	0.97 (0.76, 1.24)	1.21 (0.77, 1.93)	NA

Table 1. Characteristics and reported outcome parameters of included studies in patients with moderate-to-severe atopic dermatitis. *Abbreviations: AD, Atopic dermatitis; CC, Case-control study; CI, Confidence interval; CS, Cross-sectional study; DLP, Dyslipidemia; DM, Diabetes mellitus; HF, Heart failure; HR, Hazard ratio; HT, Hypertension; IRR, Incidence rate ratio; MI, Myocardial infarction; NA, Not applicable; NR, Not reported; PC, Prospective cohort study; RC, Retrospective cohort study; RR, Relative risk, y, year(s).* [a]*The numbers are mean with or without standard deviation unless stated otherwise.* [b]*Median.* [c]*The numbers are odds ratio (95% confidence interval) unless stated otherwise*

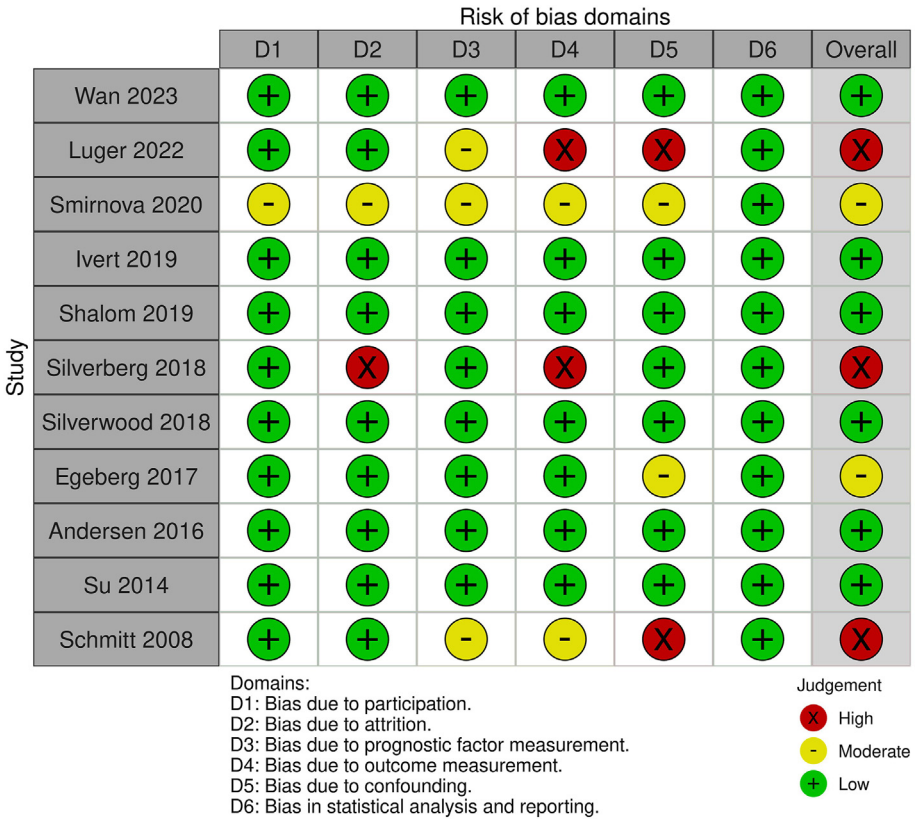

Fig. 2 Risk-of-Bias assessment of the included studies

et al[30] studies were consistent with the main finding (Figure E3).

Angina

Four studies assessed the risk of angina among individuals with moderate-to-severe AD and those without AD (Figure E4).[33,34,38,39] Silverwood et al[33] and Luger et al[34] reported a significant correlation between moderate-to-severe AD and angina with OR (95% CI) of 1.50 (1.41, 1.59) and 1.66 (1.22, 2.24), respectively. Ivert et al.[39] exhibited a trend toward a higher angina risk with OR (95% CI) of 1.11 (1.00, 1.24), while Schmitt et al[38] found no such correlation. The meta-analysis revealed a significantly increased risk of angina among moderate-to-severe AD patients compared to those without AD, with OR (95% CI) of 1.33 (1.06, 1.66), as shown in Fig. 3 and E4.

Heart failure

The association between heart failure and moderate-to-severe AD was reported in 4 studies (Figure E5).[32-35] Wan et al[32] and Silverwood et al[33] demonstrated a significantly increased risk of heart failure in moderate-to-severe AD patients compared to the control group, with OR (95% CI) of 1.44 (1.40, 1.48) and 1.85 (1.78, 1.92), respectively. The remaining 2 studies revealed a similar trend, but no statistical significance.[34,35] Upon the quantitative analysis, patients with moderate-to-severe AD had a significantly increased risk of heart failure compared to those without AD, with OR (95% CI) of 1.56 (1.28, 1.90), as shown in Fig. 3 and E5.

Stroke

Seven studies investigated the stroke outcomes, involving 399,093 patients with moderate-to-severe AD compared to 4,538,121 controls without AD (Fig. 4B).[30-35,39] All studies but Shalom et al[35] identified a significantly increased risk of stroke for patients with moderate-to-severe AD compared to the control group with OR ranging from 1.19 to 8.63. Based on quantitative analysis, moderate-to-severe AD had a significantly higher risk of stroke compared to the general population without AD with OR (95% CI) of 1.45 (1.21, 1.74), as

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Certainty assessment							Certainty	Importance
Outcomes	No. of studies (Total N)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias		
CV death	3 (3,217,980)	Not serious	serious[b]	Not serious	serious[c]	Unlikely[d]	⨁◯◯◯ Very low	Critical
Myocardial infarction	7 (6,712,164)	Not serious	serious[b]	Not serious	Not serious	Unlikely[d]	⨁◯◯◯ Very low	Important
Angina	4 (3,064,191)	Not serious	serious[b]	Not serious	Not serious	Unlikely[d]	⨁◯◯◯ Very low	Important
Heart failure	4 (5,318,617)	Not serious	serious[b]	Not serious	serious[c]	Unlikely[d]	⨁◯◯◯ Very low	Important
Stroke	7 (6,707,988)	Not serious	serious[b]	Not serious	serious[c]	Unlikely[d]	⨁◯◯◯ Very low	Important
Diabetes mellitus	7 (3,539,050)	serious[a]	serious[b]	Not serious	serious[c]	Unlikely[d]	⨁◯◯◯ Very low	Important
Hypertension	7 (3,539,050)	serious[a]	Not serious	Not serious	Not serious	Unlikely[d]	⨁◯◯◯ Very low	Important
Dyslipidemia	5 (3,502,600)	serious[a]	Not serious	Not serious	Not serious	Unlikely[d]	⨁◯◯◯ Very low	Important

Table 2. GRADE (Grading of Recommended Assessment, Development, and Evaluation) quality rating of the pooled evidence of included studies in patients with moderate-to-severe atopic dermatitis. *[a]Serious limitation (High risk of bias) downgrade one level of the quality of evidence. [b]Serious inconsistency downgrades one level of the quality of evidence due to unexplained significant heterogeneity test. [c]Imprecision downgrades one level of the quality of evidence due to non-clinical significance effect size. [d]Publication bias is unlikely because we used a search strategy and included fewer than 10 relevant studies*

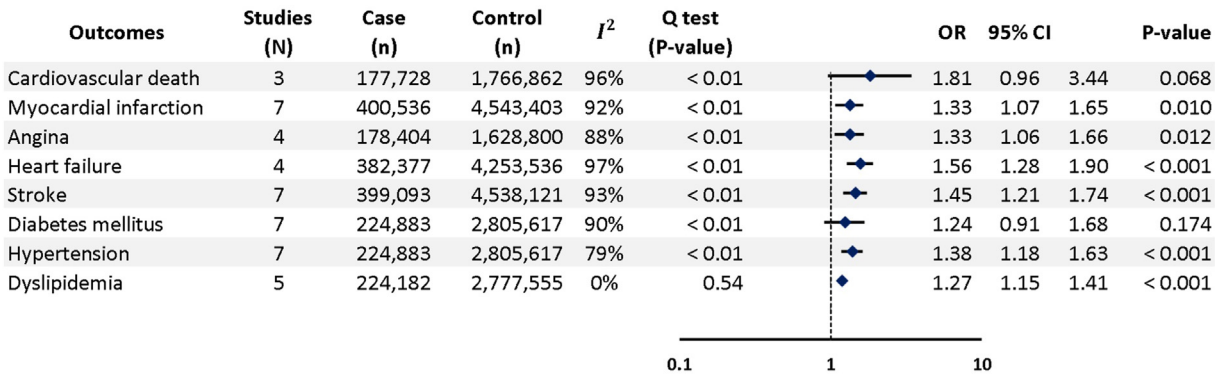

Fig. 3 Forest plots estimating the association between moderate-to-severe atopic dermatitis and cardiovascular and metabolic diseases

shown in Figs. 3 and 4B. The results of the leave-one-out sensitivity analysis by excluding either Egeberg et al[31] or Andersen et al[30] studies were consistent with the main finding (Figure E6). Of interest, stroke was the only outcome that showed the robustness of pooled results in the sensitivity analysis excluding unadjusted ORs (Table E8).

Diabetes mellitus

Seven studies involving 224,883 patients with moderate-to-severe AD and 2,805,617 individuals without AD assessed the prevalence of diabetes mellitus (Fig. 4C).[31,32,34-38] Silverberg et al,[36] Shalom et al,[35] Smirnova et al,[37] and Wan et al[32] supported the association between moderate-to-severe AD and increased risk of diabetes mellitus with OR (95% CI) of 2.33 (1.69, 3.21), 1.19 (1.03, 1.38), 1.96 (1.37, 2.80), and 1.19 (1.17, 1.22), respectively. In contrast, the remaining 3 studies found no such association.[31,34,38] In the quantitative analysis, moderate-to-severe AD was not significantly associated with an increased risk of diabetes mellitus, with OR (95% CI) of 1.24 (0.91, 1.68), as shown in Figs. 3 and 4C.

Hypertension

The association between moderate-to-severe AD and hypertension was investigated across 7 studies, comprising 224,883 patients with moderate-to-severe AD and 2,805,617 those without AD (Fig. 4D).[31,32,34-38] All studies but Schmitt et al[38] study revealed a significant link between moderate-to-severe AD and hypertension with OR (95% CI) ranging from 1.23 to 1.84. The meta-analysis indicated a significantly increased risk of hypertension in moderate-to-severe AD patients compared to the general population without AD, with OR (95% CI) of 1.38 (1.18, 1.63), as shown in Figs. 3 and 4D.

Dyslipidemia

The outcome of dyslipidemia was evaluated in 5 studies (Figure E7).[31,32,34,35,38] Compared with individuals without AD, patients with moderate-to-severe AD had a significantly increased risk of dyslipidemia with OR (95% CI) ranging from 1.17 to 1.45.[31,32,34,35] The remaining 1 studies revealed a consistent trend indicating a higher risk of dyslipidemia in patients with moderate-to-severe AD, albeit with no statistical significance.[38] The quantitative analysis confirmed such association with OR (95% CI) of 1.27 (1.15, 1.41), as shown in Fig. 3 and E7.

Metabolic syndrome

Of the 11 included studies, only the Shalom et al[35] study investigated the correlation between metabolic syndrome and moderate-to-severe AD compared to the controls. Moderate to severe AD was associated with a higher risk of metabolic syndrome with OR (95% CI) of 1.24 (1.05, 1.42).

DISCUSSION

This systematic review and meta-analysis included 11 studies, 4 retrospective cohorts, 1 prospective cohort, 4 cross-sectional, and 2 case-control studies assessing cardiovascular and metabolic outcomes in moderate-to-severe AD patients compared to normal controls without AD. Patients with moderate-to-severe AD exhibited an increased risk of myocardial infarction, angina,

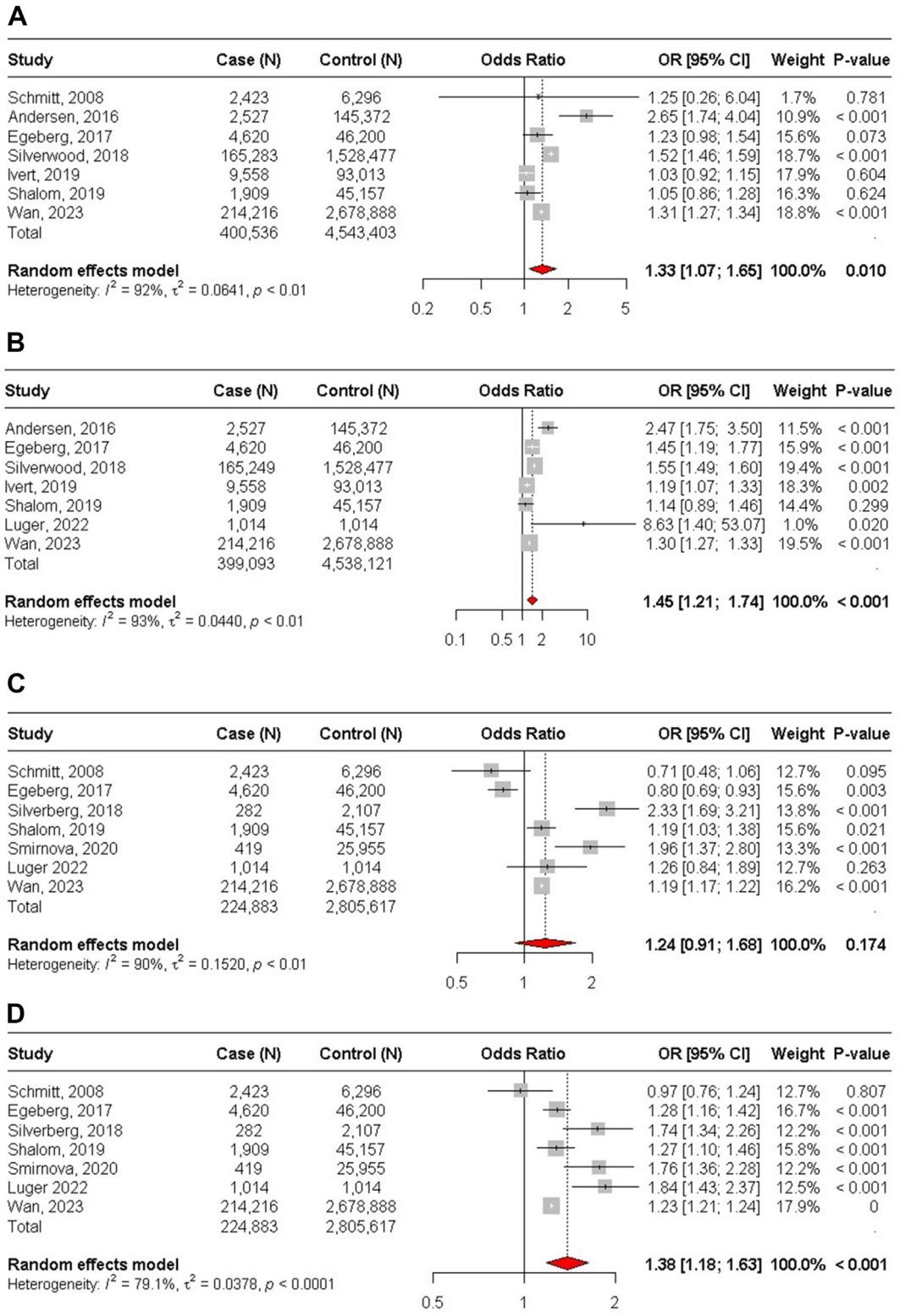

Fig. 4 Forest plots estimating the association between moderate-to-severe atopic dermatitis and **A)** Myocardial infarction, **B)** Stroke, **C)** Diabetes, and **D)** Hypertension

heart failure, stroke, hypertension, dyslipidemia, and metabolic syndrome with very low certainty of evidence. No significantly increased risk of cardiovascular death and diabetes mellitus was observed.

Multiple pathophysiological mechanisms may contribute to the elevated cardiovascular and metabolic risks observed in patients with AD. First, altered blood components in AD patients, including fibrin clot properties, have been linked to inefficient clot lysis, potentially facilitating atherosclerotic plaque formation.[41] Second, increased platelet activation, which correlates with the severity of skin inflammation in AD, adds to the pro-thrombotic environment.[42] Third, proteomic studies have demonstrated higher levels of inflammatory and cardiovascular risk proteins, such as E-selectin, platelet growth factor, vascular endothelial growth factor A, matrix metalloproteinase, and myeloperoxidase, in the serum of individuals with AD, which may accelerate both atherosclerosis and angiogenesis.[43,44] Fourth, oxidative stress associated with skin inflammation in AD also promotes the progression of atherosclerosis.[45,46] Fifth, vascular inflammation and injuries due to chronic inflammation in AD further enhance atherosclerosis risks.[47] Moreover, Evidence suggests that more severe AD is associated with increased skin inflammation, which intensifies the development of these pro-atherosclerotic factors.[43,44,47] Our findings reinforce those of a prior meta-analysis that demonstrated a significant association between AD severity and cardiovascular outcomes.[13]

Our analysis further explored the relationship between moderate-to-severe AD and metabolic disorders, which are established risk factors for cardiovascular diseases and mortality.[14,15] The findings demonstrated a significant association between moderate-to-severe AD and both hypertension and dyslipidemia, suggesting that chronic inflammation may contribute to increased cardiovascular risk either directly or through these metabolic disorders. Additionally, systemic corticosteroid use, a criterion to define severe AD, was closely associated with an increased risk of diabetes and cardiovascular diseases.[48,49]

As chronic skin inflammation in moderate-to-severe AD is attributed to increased cardiovascular and metabolic risks, effective management to control inflammation is crucial to mitigate these risks. Evaluations for cardiovascular and metabolic disorders should be incorporated into the care of patients with moderate-to-severe AD to guide risk stratification and personalized prevention strategies. Medications that may exacerbate these risks should be minimized, and safer alternatives should be considered. Additionally, lifestyle modifications, such as achieving a healthy body weight and smoking cessation, should be actively promoted as part of a comprehensive risk reduction strategy.

This study's strength lies in its focus on moderate-to-severe AD, which minimizes the heterogeneity among included studies and increases the accuracy of association analysis. Our methodology followed the PRISMA guidelines to ensure the quality and validity of results. However, the study has several limitations, including the fact that the relevant studies might be missed despite extensive search, inherent heterogeneity among trials, and the observational nature of cohort studies, which may influence causal inference. Due to the limited number of studies, estimates of heterogeneity and associated statistics may lack precision, as reflected in GRADE assessments indicating very low certainty evidence. Our inclusion and exclusion criteria for study selection may have allowed for the inclusion of studies with overlapping populations. Nonetheless, the results of leave-one-out sensitivity analyses remained consistent with the main findings. Lastly, the reported pooled ORs in this meta-analysis were based on both the extracted adjusted ORs and calculated unadjusted ORs. This approach potentially introduces bias, as the effects of extraneous variables were not taken into account. Sensitivity analysis results were also not robust for most outcomes except for stroke. Further prospective cohort studies of moderate-to-severe AD, defined by validated severity scoring systems, are needed. The studies should include sufficiently long follow-

up periods and adjustments for relevant confounders to confirm the association between AD and cardiovascular and metabolic diseases and to evaluate whether optimized treatment strategies can reduce the incidence of these comorbidities.

In conclusion, our systematic review and meta-analysis yield supporting evidence that individuals with moderate-to-severe AD are at heightened risk of developing various cardiometabolic conditions, including myocardial infarction, angina, heart failure, stroke, hypertension, dyslipidemia, and metabolic syndrome. Clinicians should consider incorporating an assessment of cardiovascular and metabolic risk into the care regimen for patients with moderate-to-severe AD.

Abbreviations
AD, Atopic dermatitis; CI, Confidence interval; OR, Odds ratio.

Acknowledgments
The graphical abstract was created with Canva Pro/ Anchaya Boonsom. The Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand, and the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, partially supported this study.

Funding sources
No funding has been received for this manuscript.

Availability of data and materials
The data used in this study are available from the corresponding author, on special request.

Author contributions
SU, TA, NJ, PP, WL, and T. Thongngarm conceived and designed the project and drafted the study protocol. SU, TA, AB, T. Treemethawee, PS, and CY screened all retrieved records from database searching to determine the eligible studies. SU and TA extracted data from the included studies. SU, TA, and NJ assessed the risk of bias and certainty of evidence for each study. PP and T. Thongngarm supervised the data extraction and the assessment of risk-of-bias and certainty of evidence. NJ and PP performed the statistical analyses. SU, TA, NJ, PP, WL, and T. Thongngarm critically analyzed and interpreted data. SU, TA, NJ, PP, WL, and T. Thongngarm drafted the manuscript. AB and TA created the graphical abstract. All authors provided significant intellectual contributions to the manuscript, reviewed and revised its content, and approved the final version.

Ethics approval
This systematic review and meta-analysis followed the Cochrane Handbook for Systematic Reviews of Intervention and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The review protocol was registered on PROSPERO (CRD42023454573). The study protocol complies with a "Research with Exemption" by the Institutional Review Board and Ethics Committee.

Authors' consent for publication
All the Authors approved the final version of the manuscript and consented to the publication.

Declaration of competing interest
The authors declare the following financial interests/ relationships which may be considered as a potential conflict of interest:
S. Untaaveesup, T. Amnartpanich, A. Boonsom, T. Treemethawee, P. Srichana, C. Yimkijboriharn, N. Jirattikanwong, and P. Phinyo declare no conflict of interests;
W. Laisuan has received honoraria for scientific lectures from A. Menarini, Astra-Zeneca, GSK, Novartis, Sanofi, Takeda, and Viatris.
T. Thongngarm has received honoraria for scientific lectures from A. Menarini, Astra-Zeneca, GSK, Novartis, Sanofi, Takeda, and Viatris; research supports from Abbott and Sanofi; has served on the advisory board for Sanofi and Viatris.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2025.101035.

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