Dermatology Practical & Conceptual

Atopic Dermatitis and Autoimmune Connective Tissue Diseases: Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: The association between atopic dermatitis (AD) and autoimmune connective tissue diseases (ACTD) is not well investigated.

Objective: We aimed to conduct a systematic review and meta-analysis to assess the association between AD and ACTD.

Methods: A comprehensive literature search was performed on PubMed, Embase, Cochrane Library, and Web of Science to identify relevant studies, which included those providing original data on the prevalence, incidence, or risk of ACTD in people with AD. Pooled point prevalence and odds ratio (OR) with 95% confidence intervals (CI) were estimated using a random effect inverse variance method.

Results: Twenty-one studies were included in the systematic review, of which 18 were included in the meta-analysis. The pooled ORs were statistically significant overall for ACTD, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome (SS), and polymyositis (PM)/dermatomyositis (DM), but not for ankylosing spondylitis (AS) or systemic scleroderma (SSc): any ACTD 1.76 (95% CI: 1.57–1.97, I^2 =94%, P<0.01), RA 1.40 (95% CI: 1.23–1.58, I^2 = 97%, P<0.01), SLE 1.92 (95% CI: 1.66–2.23, I^2 = 86%, P<0.01), SS 2.08 (95% CI: 1.48–2.94, I^2 = 92%, P<0.01), AS 1.75 (95% CI: 1.32–2.33, I^2 = 47%, P=0.13), PM/DM 2.37 (95% CI: 1.54–3.67, I^2 = 73%, P<0.01), and SSc 2.75 (95% CI: 1.44–5.27, I^2 = 60%, P=0.06).

Conclusion: AD is associated with a significantly increased risk of ACTD, particularly RA, SLE, SS, and PM/DM, while no significant association was observed with AS or SSc.

Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by dry skin, recurrent eczematous lesions, and intense itching. AD typically manifests during early childhood [1], affecting up to 20% of children and up to 10% of adults [2]. With over 230 million people affected worldwide, AD is a significant global health concern [3]. The burden of AD extends beyond its cutaneous manifestations; it negatively impacts quality of life by imposing lifestyle limitations, reducing social interactions, and affecting daily activities [4].

The etiology of AD stems from a complex and multifactorial interaction between genetic predisposition, skin barrier abnormalities, immune dysregulation, and environmental and lifestyle factors [1]. The co-occurrence of AD and autoimmune disorders has been widely investigated, and there is growing evidence suggesting that AD is a systemic disease [5-6]. While the coexistence of AD and other atopic disorders, e.g., asthma and allergic rhinoconjunctivitis, is a well-established phenomenon [7], the potential association between AD and ACTD represents a novel and quite unexpected finding.

Objectives

The aim of this study was to systematically investigate the existing literature to elucidate whether individuals with AD have an increased risk of autoimmune diseases affecting connective tissue, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome (SS), ankylosing spondylitis (AS), polymyositis/dermatomyositis (PM/DM), systemic scleroderma (SSc), and mixed connective tissue disease (MCTD).

Methods

The protocol for this systematic review and meta-analysis was registered in PROSPERO (CRD42024519053). This study was conducted in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [8] (Figure 1).

Literature Search

PubMed, Embase, Cochrane Library, and Web of Science were searched to identify the existing literature related to the association between AD and ACTD from March to June 2024. The search strategy consisted of terms related to AD and ACTD (Table S1). No language or date restriction was applied to the database searches. All references were imported into Covidence, an online software tool that streamlines the production of systematic and other literature reviews [9]. Covidence was utilized to remove duplicates and assess the references while blinding the reviewers.

Screening and Study Selection

Two reviewers (SN and MNG) independently screened all titles identifying studies meeting the inclusion criteria. Full text articles were retrieved and screened to confirm eligibility. Any discrepancy in eligibility between the two reviewers was resolved through discussion. Studies were excluded if they were non-English, non-original papers, reviews, or study population with fewer than 100 AD patients.

Data Extraction

Data from the studies were extracted manually by SN and The Newcastle-Ottawa Scale (NOS) [10], a validated tool, was used to evaluate the quality of included studies. NOS assesses the quality of cohort and case-control studies based on eight items in three domains: selection (four items), comparability (one item), and outcome/exposure (three items). Each item can be graded with one point, except comparability, which can be graded with two points, with the highest possible score being nine points. Cross-sectional studies were assessed through an adapted version of NOS, with the highest possible score of ten points. Studies receiving an NOS score of ≥7 were considered as high quality.

Statistical Analysis

The association between AD and ACTD was analyzed using random effects models with the inverse variance method. Separate analyses were conducted for each ACTD, reporting an estimated pooled point prevalence and odds ratio (OR) with 95% confidence interval (CI). If point prevalence or OR was not reported, but the necessary data were available, we calculated the crude estimators with 95% CI. Study heterogeneity was assessed using Sidik-Jonkman, as an estimator for τ^2, and the I^2 statistics, where heterogeneity levels were categorized as low >25%, moderate >50%, or high >75%. Funnel plots were used to visually assess publication bias. All statistical analyses were performed using R version 4.3.2.

Results

The database search identified 8013 studies (PubMed: 1361, Embase: 4733, Cochrane Library: 224, Web of Science: 1695). Additionally, one study was identified through review of references. Covidence removed 1939 duplicates, resulting in 6075 for title and abstract screening. A total of 58 studies were retrieved for full text screening. Ultimately, 21 studies met the inclusion criteria and were included in the review. Eighteen studies provided quantitative results and were included in the meta-analyses (Figure 1).

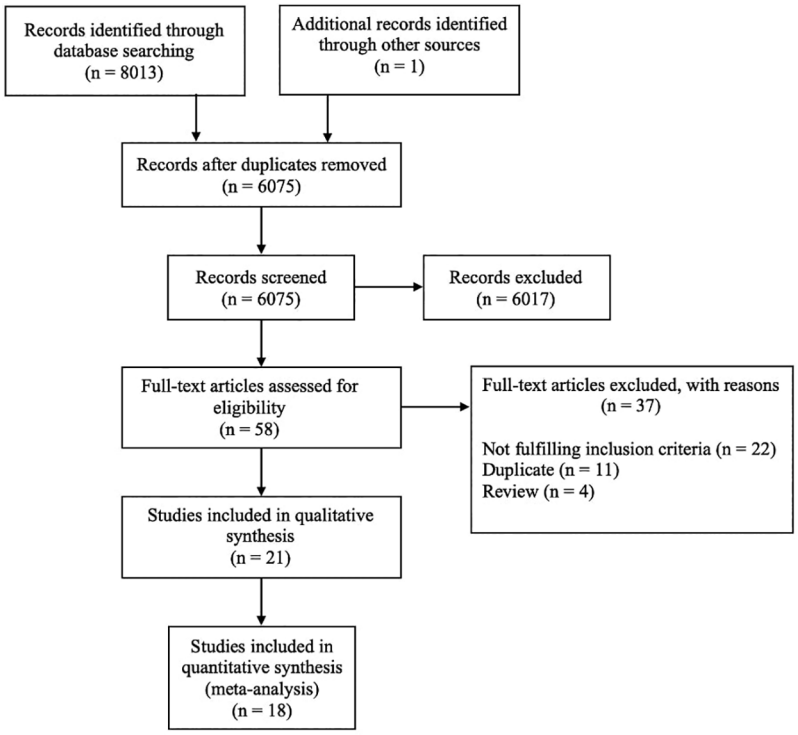


Figure 1. PRISMA flow diagram of the search strategy.

Characteristics of Included Studies

The details of the included studies are listed in Table 1. The publication year ranged from 2014 to 2024, and the majority of the studies were from Europe and North America. The predominant study designs were cohort studies [11-22] and cross-sectional studies [23-28]. The population sizes varied across studies, with the smallest population being 48,672 [23] and the largest population being 87,053,155 [26]. The age distribution of study populations is summarized in Table 1. The studies primarily assessed AD and ACTD through ICD-9 or 10 coding [11,14-15,17-19,22-23,26-31], but medical records [13,16,21], physician diagnosis, clinical laboratory testing, and self-reported questionnaires [24,32] were also used. However, six studies did not specify their source of information for AD and/or ACTD [12,14-15,20,25,33]. Thirteen studies reported the point prevalence of ACTD in AD [12-13,16,18-19,21-23,26-27,29-31] and nine studies reported ORs [15,23-29,31], while nine studies provided the necessary data to calculate ORs manually [12-13,16-19,21-22,30]. Quality assessment using the Newcastle-Ottawa Scale was conducted on a total of 13 studies [11,13,15-17,19,22-23,26-29,31], which reported the association between AD and ACTD as primary outcome. The remaining studies were either not primary articles or not observational studies, or they reported the association between AD and ACTD as cohort baseline characteristics. All assessed studies were considered of high quality, with a NOS score ≥7 (Table S2).

Despite the comprehensive search, no study investigating the association between AD and MCTD was identified.

Association Between Atopic Dermatitis and Any Autoimmune Connective Tissue Disease

To estimate the prevalence of any ACTD, we combined 36 reported point prevalence estimates from 13 distinct studies [12-13,16,18-19,21-23,26-27,29-31]. The prevalence of any ACTD was estimated to be 0.17% (Figure 2A). Forty-five ORs, extracted from 18 individual studies [12-13,15-19,21-31], were pooled to estimate an overall estimate. The combined odds of any ACTD in patients with AD were estimated to be 1.76 (95% CI: 1.57–1.97, I^2 = 94%, P <0.01) (Figure 3A).

Association Between Atopic Dermatitis and Rheumatoid Arthritis

Eighteen studies investigated the association between AD and RA [12-13,15-21,23-27,29,31-33]. Eleven studies reported the point prevalence of RA in AD [12-13,16,18-19,21,23,26-27,29,31], and the pooled point prevalence was estimated to 0.43% (Figure 2B). The OR was reported in 15 studies [12-13,15-19,21,23-27,29,31]; 13 studies identified a statistically significant association [12-13,15-18,21,23-27,29], while two did not [19,31]. The meta-analysis estimated the pooled OR to be 1.40 (95% CI: 1.23–1.58, I^2 = 97%, P <0.01) (Figure 3B). Narla et al. [26] detected a significant association in adults (OR 1.37, 95%

Table 1. Characteristics of Included Studies.

Author (year)	Country	Design	STUDY POPULATION		ATOPIC DERMATITIS		ASSOCIATION					Conclusion	NOS
			Recruitment site	Age	Definition	Total, n	ACTD	n (%)	OR (95% CI)	Definition	Primary outcome		
Alexander et al. (2019)	United Kingdom	Cohort	Royal College of General Practitioners Research and Surveillance Centre database	N/A	N/A	470 240	RA	2821 (0.6)	1.50 (1.44 – 1.57)	N/A	Yes	AD is associated with an increased risk of subsequent RA	N/A
Andersen et al. (2016)	Denmark	CS	The Danish National Patient Registry	≥ 18 years	ICD-10 code: L20	8112	AS RA SSc SS SLE	27 (0.33) 126 (1.55) 16 (0.20) 41 (0.51) 29 (0.36)	2.33 (1.42-3.83) 1.61 (1.29-2.01) 2.42 (1.26-4.64) 3.74 (2.41-5.82) 2.65 (1.63-4.31)	ICD-10 codes	Yes	AD was significantly associated with AS, RA, SSc, SS and SLE	8
Schmitt et al. (2015)	Germany	Cohort	Allgemeine Ortskrankenkasse Saxony database	≤ 40 years	≥ 2 ICD-10 code: L20	49 847	RA	21 (0.04)	0.87 (0.56-1.36)	ICD-10 code	Yes	AD patients are at a significantly increased risk to develop RA than patients without AD (significant RR), while OR was not found to be significant.	9
de Lusignan et al. (2022)	United Kingdom	Cohort	Oxford-Royal College of General Practitioners Research and Surveillance Centre primary care database	All ages	2 AD records (either diagnoses or treatments) appearing within any 1-year period	173 709	AS RA SS SLE	32 (0.02%) 342 (0.20%) 67 (0.04%) 37 (0.02%)	1.58 (1.05-2.38) 1.72 (1.51-1.95) 2.39 (1.77-3.24) 1.85 (1.25-2.73)	Clinical codes using or previously validated definitions	Yes	AD is associated with increased odds for AS, RA, SS and SLE AD is associated with increased risk for RA, SS, but not AS and SLE	9
Deng et al. (2022)	International	Cohort	TriNetX, international healthcare network with medical records	≥ 18 years	≥ 2 ICD-10 code: L28	92 459	SLE	N/A	N/A	N/A	Yes	Patients with AD had an elevated risk of SLE	N/A
Hou et al. (2021)	USA	CS	2012 National Health Interview Survey	N/A	Self-reported	N/A	RA SLE	N/A	1.76 (1.36–2.29) 3.02 (1.54–5.93)	Self-reported	Yes	Increased risk of RA and SLE in AD indviduals	N/A

Ivert et al. (2021)	Sweden	CC	Swedish national healthcare registers	≥ 15 years	ICD-10 code: L20.0–L20.9 or ICD-9 code: 691 or ICD-8 code: 691.00	104 832	AS DM PM RA SSc SLE	278 (0.3) 34 (0.03) 21 (0.02) 896 (0.9) 64 (0.1) 214 (0.2)	1.46 (1.29–1.66) 2.80 (1.91–4.10) 1.35 (0.86–2.14) 1.44 (1.34–1.54) 1.87 (1.43–2.44) 1.65 (1.42–1.90)	ICD-8 or ICD-9 or ICD-10 codes	Yes	AD was significantly associated with AS, DM, RA, SSc and SLE but not PM	8
Krishna et al. (2019)	United Kingdom	Cohort	The Health Improvement Network	All ages	Read Codes (current and past)	1 393 570	RA SS SLE	6933 (0.50) 693 (0.05) 1445 (0.10)	1.05 (1.02-1.08) 1.33 (1.20-1.47) 1.40 (1.30-1.50)	Read Codes (current and past)	Yes	The long-term risks of autoimmune disorders are significantly higher in patients with allergic diseases	9
Kuo et al. (2016)	Taiwan	CC	The National Health Insurance Research Database of Taiwan	≤ 20 years	ICD-9 code: 691, 691.8	31 237	SLE	49 (0.2)	2.00 (1.42-2.82)	Comorbidity	No	The results showed that SLE was associated AD	N/A
Lai et al. (2015)	Taiwan	Cohort	The National Health Insurance Research Database of Taiwan	≥ 20 years	≥ 3 ICD-9 code: 691, 691.8	18 907	RA	N/A	1.64 (1.12-2.39)	ICD-9 code	Yes	Risk of developing RA marginal among patients with AD	9
Narla et al. (2018)	USA	CS	USA Nationwide Inpatient Sample	N/A	ICD-9 code	Weighted frequency: Adults: 44 605 Children: 48 496	Adults AS PM RA SSc SS SLE Children RA SSc SLE	 47 (0.1) 29 (0.1) 688 (1.5) 82 (0.2) 63 (0.1) 370 (0.8) 24 (0.05) 19 (0.04) 44 (0.09)	 2.63 (1.31-5.27) 2.04 (0.72-5.73) 1.37 (1.11-1.69) 2.32 (1.35-3.98) 1.63 (0.85-3.13) 1.80 (1.38-2.34) 1.09 (0.35-3.40) 9.35 (2.97-29.44) 1.27 (0.58-2.80)	ICD-9 codes	Yes	Significant associations with AS, RA, SSc and SLE and no significant associations with PM and SS in adults Significant associations with SSc and no significant associations with RA or SLE in children	8

Table 1 (*continued*)

Table 1. Characteristics of Included Studies. *(continued)*

Author (year)	Country	Design	STUDY POPULATION		ATOPIC DERMATITIS		ASSOCIATION					Conclusion	NOS
			Recruitment site	Age	Definition	Total, n	ACTD	n (%)	OR (95% CI)	Definition	Primary outcome		
Roh et al. (2021)	USA	CS	MarketScan Commercial Claims database	18–64 years	≥ 2 ICD-10 code: L20	39 779	PM/DM SS SLE	N/A	3.54 (2.47–5.08) 2.17 (1.86-2.53) 2.46 (2.17-2.78)	ICD-10 codes	Yes	AD patients had a higher likelihood of PM/DM, SS and SLE	8
Syed et al. (2021)	United Kingdom	Cohort	The Health Improvement Network	All ages	N/A	Adults: 625 083 Children: 409 431	RA	N/A	N/A	N/A	Yes	Overall increased risk of RA in patients with AD	N/A
Wei et al. (2014)	Taiwan	Cohort	The National Health Insurance Research Database of Taiwan	< 18 years	≥ 3 ICD-9 code: 691	192 357	SLE	32 (0.02)	2.91 (1.85-4.59)	ICD-9 code and confirmation by Registry for Catastrophic Illness Patient Database	Yes	Significantly increased incidence rate of JSLE in children with AD	9
Wu et al. (2014)	Taiwan	CC	The National Health Insurance Research Database of Taiwan	All ages	≥ 2 ICD-9 code: 691.8	41 950	RA SLE	200 (0.48%) 97 (0.23%)	0.89 (0.74–1.06) 1.94 (1.48–2.54)	ICD-9 codes	Yes	Patients with AD have a higher risk of SLE, and no relationship with RA	8
Fuxench et al. (2023)	USA	Cohort	Optum Clinformatics Data Mart database	N/A	ICD codes	601 783	RA	N/A	1.70 (1.60-1.81)	N/A	Yes	Individuals with AD have an increased risk of RA	8
Radtke et al. (2017)	Germany	CS	German nationwide statutory health insurance Gmuender Ersatzkasse	≥ 18 years	ICD-10 code: L20	48 140	RA	164 (0.34)	1.20 (1.04–1.41)	ICD-10 code	Yes	Increased prevalence of RA among AD patients compared to those without AD	7

Meyers et al. (2021)	USA	Cohort	IBM Watson MarketScan Commercial Claims and Encounters, Medicare Supplemental, and Medicaid databases	≥ 18 years	ICD-9 code: 691.8 or ICD-10 code: L20.0, L20.8x, L20.9	198 685	RA SLE	2062 (1.0) 450 (0.2)	1.44 (1.38-1.50) 1.72 (1.56-1.89)	Comorbidity	No	Cohort characteristics	N/A
Warren et al. (2023)	United Kingdom, Wales and Scotland	Cohort	Optimum Patient Care Research Database	≥ 18 years	Read and SNOMED CT codes and two or more AD treatments prescribed on different dates	150 975	RA	1219 (0.8)	1.16 (1.09-1.24)	Comorbidity	No	Cohort characteristics	N/A
Joo et al. (2017)	Korea	CS	Korean National Health and Nutrition Examination Survey	N/A	N/A	N/A	RA	N/A	2.22 (1.81-2.73)	N/A	Yes	AD was positively associated with RA	N/A
Ahn et al. (2024)	Korea	Cohort	The National Health Insurance Service	< 18 years	≥ 5 ICD-10 code L20.9 and ≥ 2 prescriptions of AD treatment	39 832	AS SLE SS PM/DM	N/A	N/A	ICD-10 codes	Yes	AD was significantly associated with an increased risk of AS, SLE, SS, and PM/DM.	9

Abbreviations: ACTD, autoimmune connective tissue diseases; AD, atopic dermatitis; AS, ankylosing spondylitis; CC, case–control; CI, confidence interval; CS, cross-sectional; PM, polymyositis; DM, dermatomyositis; OR, odds ratio; SS, Sjögren's syndrome; SLE, systemic lupus erythematosus; SSc, systemic scleroderma; RA, rheumatoid arthritis; NOS, Newcastle-Ottawa Scale; N/A, not available.

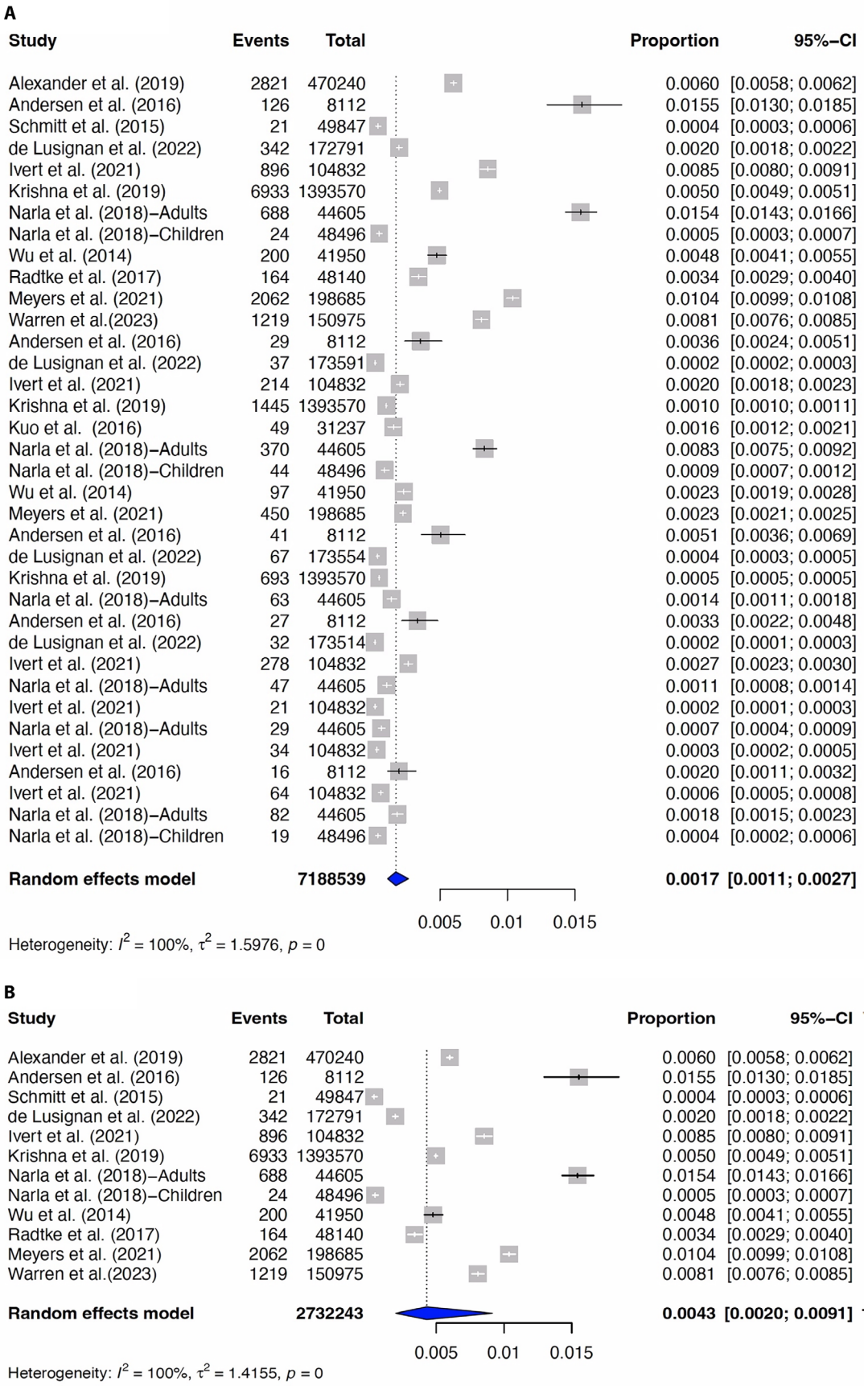
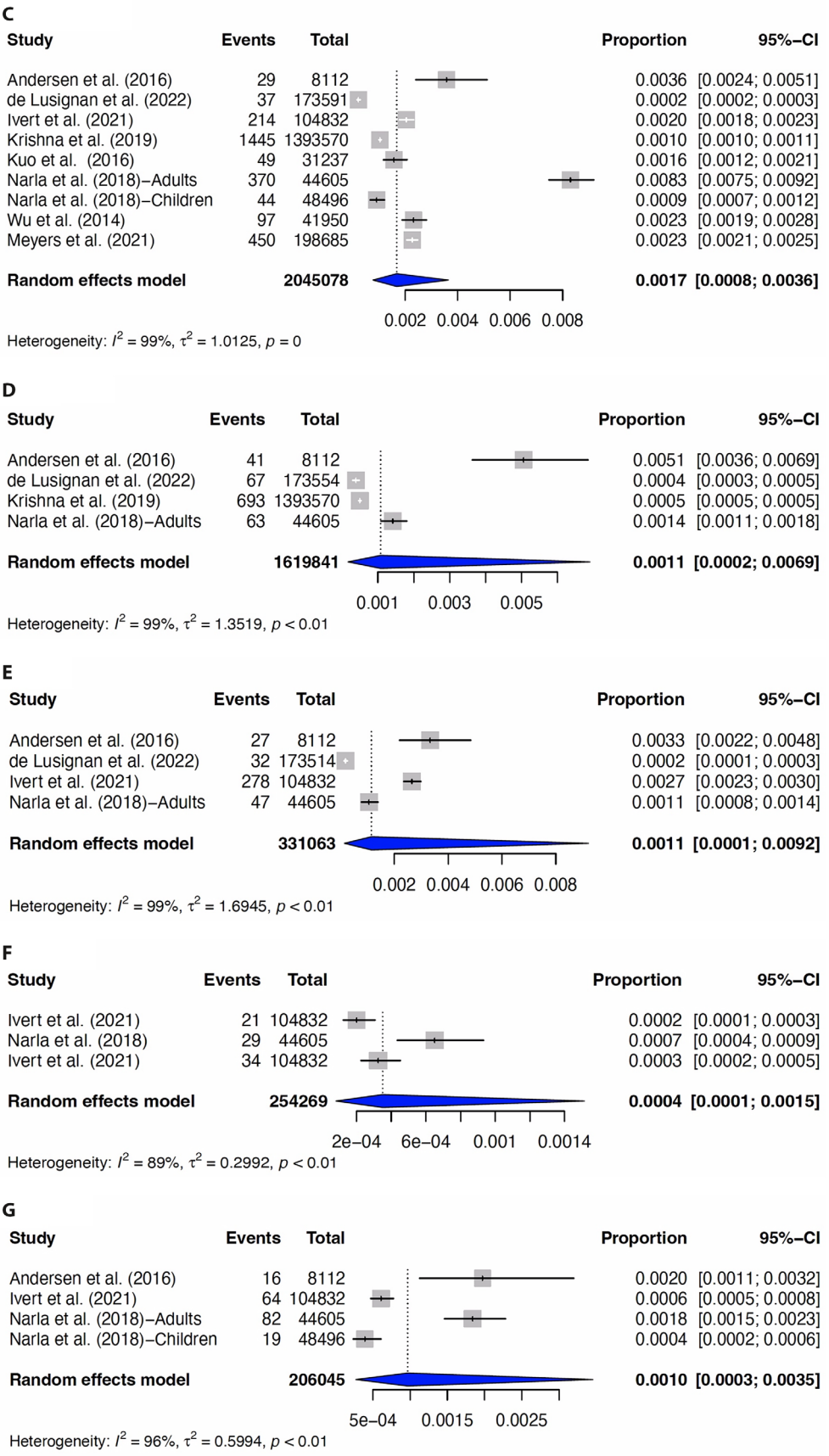


Figure 2. Forest plot for the meta-analysis of the pooled point prevalence of ACTD in AD. (A) Any autoimmune connective tissue diseases. (B) Rheumatoid arthritis. (C) Systemic lupus erythematosus. (D) Sjögren syndrome. (E) Ankylosing spondylitis. (F) Polymyositis/dermatomyositis. (G) Systemic scleroderma. (AD, atopic dermatitis; ACTD, autoimmune connective tissue diseases; CI, confidence interval.)



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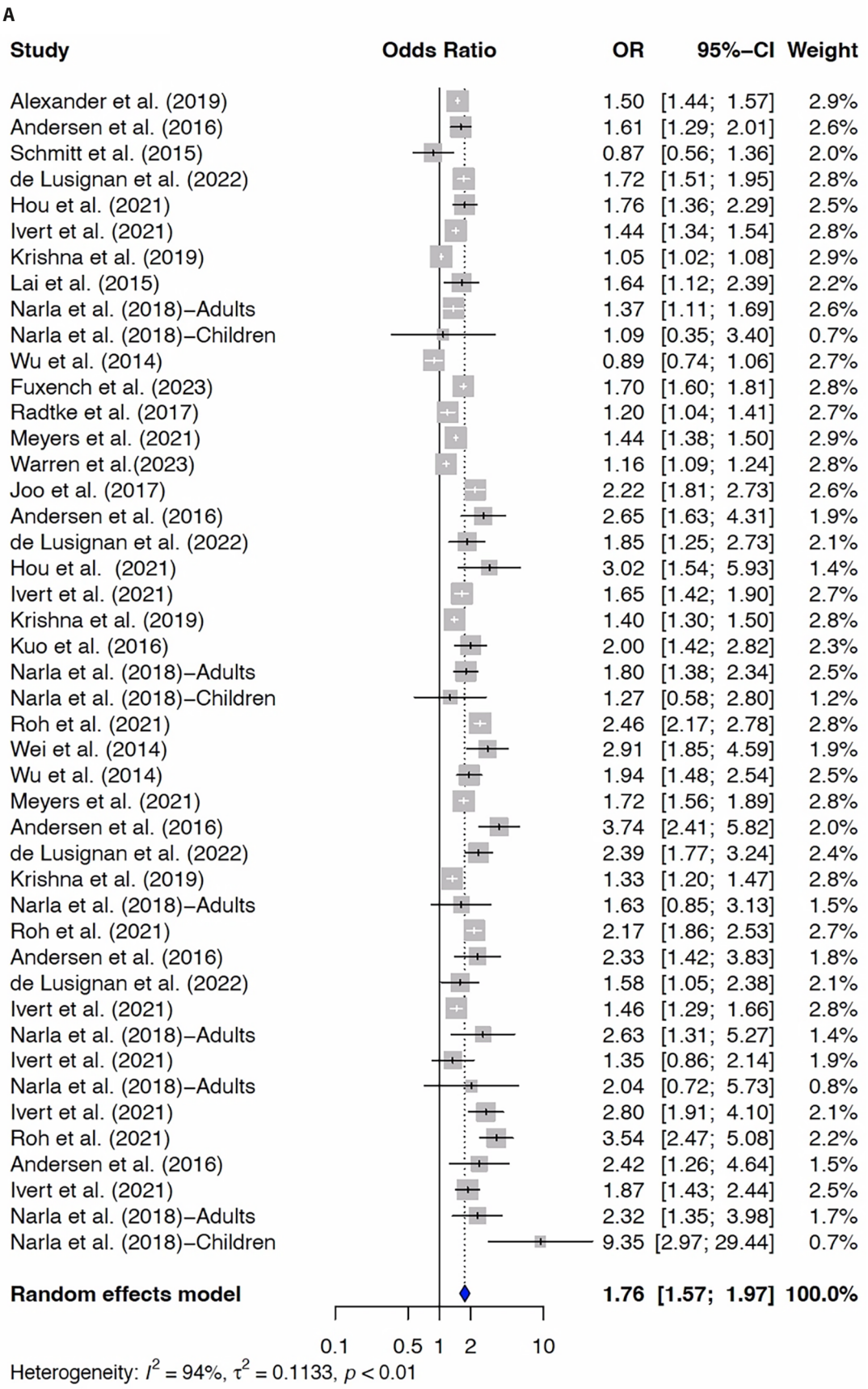
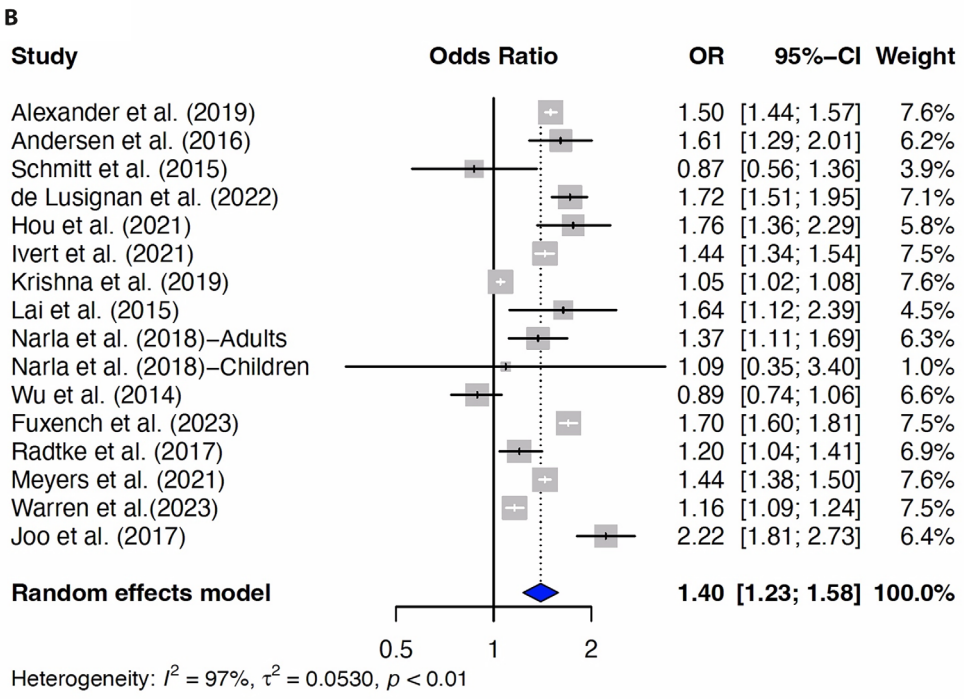
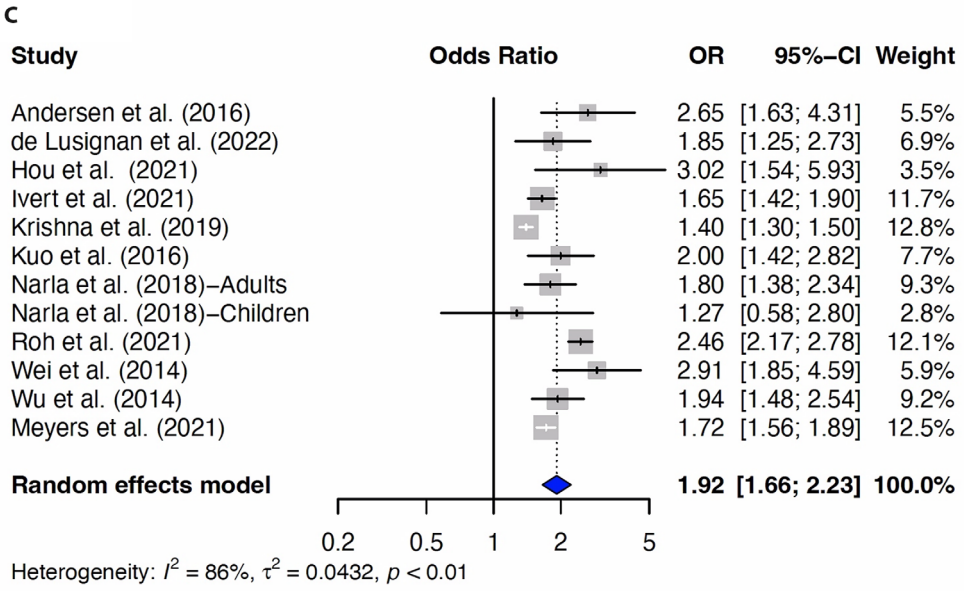
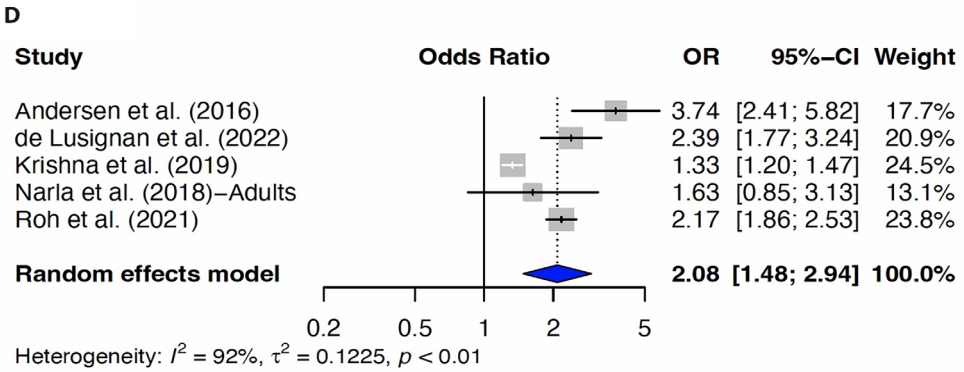


Figure 3. Forest plot for the meta-analysis of the pooled OR of ACTD in AD. (A) Any autoimmune connective tissue diseases. (B) Rheumatoid arthritis. (C) Systemic lupus erythematosus. (D) Sjögren syndrome, (E) Ankylosing spondylitis. (F) Polymyositis/dermatomyositis. (G) Systemic scleroderma. (AD, atopic dermatitis; ACTD, autoimmune connective tissue diseases; OR, odds ratio; CI, confidence interval.)







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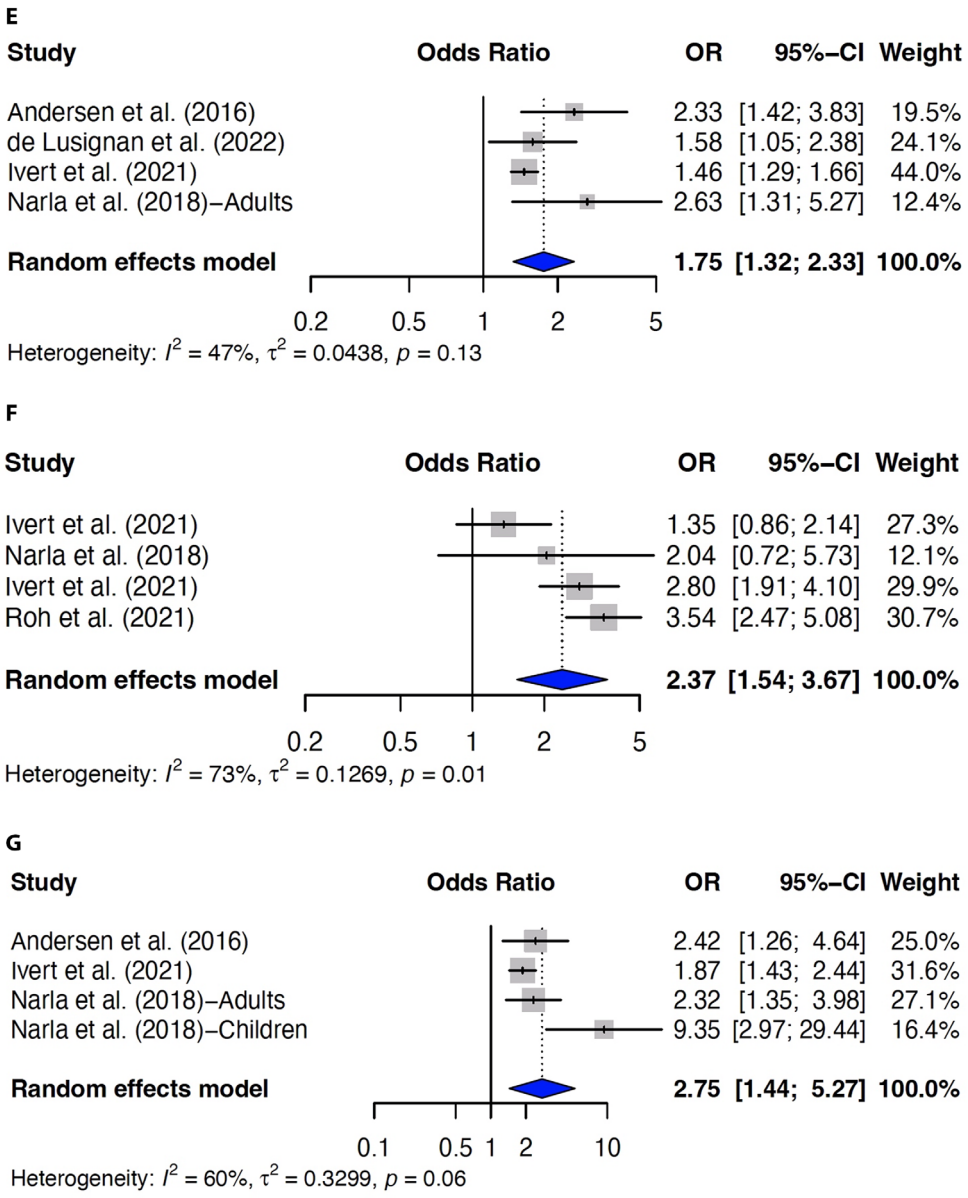

Figure 3. (*Continued*)

CI: 1.11–1.69) when compared to controls, but not in children (OR 1.09, 95% CI: 0.35–3.40). Among the associations not included in the meta-analysis due to the absence of ORs, six cohort studies examined the risk of RA in AD patients compared to controls. Five of them found a significantly increased risk: Alexander et al. [12] reported an hazard ratio (HR) of 1.41 (95% CI: 1.32–1.51), Schmitt et al. [19] reported an relative risk (RR) of 1.72 (95% CI: 1.25–2.37), de Lusignan et al. [13] reported an HR of 1.38 (95% CI: 1.21–1.57), Krishna et al. [16] reported an RR of 1.28 (95% CI: 1.22–1.34), Syed et al. [34] reported an HR of 1.18 (95% CI: 1.13–1.22) for adults and an HR of 1.38 (95% CI: 1.14–1.67) for children. However, Lai et al. [17] did not find a significant association, reporting an HR of 1.41 (95% CI: 0.98–2.02).

Association Between Atopic Dermatitis and Systemic Lupus Erythematosus

Fourteen studies examined the association between AD and SLE [11,13-14,16,18,22-24,26,28-31,33]. Eight studies reported a point prevalence of SLE in AD [13,16,18,23,26, 29-31]; the pooled point prevalence was estimated to be 0.17% (Figure 2C). Eleven studies compared the odds of SLE in AD and controls, with all reporting a statistically significant OR [13,16,18,22-24,26,28-31]. However, Narla et al. [26] only found the association to be significant in adults (OR 1.80, 95% CI: 1.38–2.34) but not children (OR 1.27, 95% CI: 0.58–2.80). We estimated the pooled OR to 1.92 (95% CI: 1.66–2.23, I^2 = 86%, P <0.01) (Figure 3C). Additionally, four cohort studies, for which the reported association could not be pooled in the meta-analysis due to the absence

of ORs, identified a significant increased risk of SLE in AD patients, as Deng et al. [14] reported an RR of 1.29 (95% CI: 1.06–1.57), Krishna et al. [16] reported an RR of 1.86 (95% CI: 1.66–2.09), and Wei et al. [22] reported a higher HR of 2.92 (95% CI: 1.85–4.60), while Ahn et al. [11] reported an HR of 1.43 (95% CI: 1.04–1.95) in children. Conversely, de Lusignan et al. [13] reported an insignificant increased risk of SLE in AD compared to controls (HR 1.44, 95% CI: 0.97–2.13).

Association Between Atopic Dermatitis and Sjögren Syndrome

Six studies investigated the association between AD and SS [11,13,16,23,26,28], four of which reporting the point prevalence of SS in AD [13,16,23,26]; the pooled point prevalence was estimated to be 0.11% (Figure 2D). Five of the studies provided data on the odds of SS in AD compared to controls; four found a statistically significant association [13,16,23,28], while one did not [26]. The meta-analysis estimated a pooled OR of 2.08 (95% CI: 1.48–2.94, I^2 = 92%, P<0.01) (Figure 3D). Three cohort studies, whose reported association could not be pooled in the meta-analysis due to the lack of ORs, similarly identified an increased risk of SS among AD patients compared to controls: de Lusignan et al. [13] reported an HR of 1.83 (95% CI: 1.34–2.48), Krishna et al. [16] reported an RR of 1.48 (95% CI: 1.30–1.69), and Ahn et al. [11] reported an HR of 1.40 (95% CI: 1.01-1.94) in children.

Association Between Atopic Dermatitis and Ankylosing Spondylitis

Six of the identified studies investigated the association between AD and AS [11,13,23,26,29,33], with four reporting the point prevalence [13,23,26,29]; the pooled point prevalence was estimated to be 0.11% (Figure 2E). A statistically significant increased odds for comorbid AS in AD patients was reported in four studies [13,23,26,29], with a pooled OR estimated to be 1.75 (95% CI: 1.32 –2.33, I^2 = 47%, P=0.13) (Figure 3E). One cohort study, which could not be included in the meta-analysis due to the absence of ORs, found an increased risk of AS in children: Ahn et al. [11] reported an HR of 1.41 (95% CI: 1.02-1.94). However, de Lusignan et al. [13] reported a non-significant increased risk of AS in AD patients compared to controls (HR 1.33, 95% CI: 0.87–2.01).

Association Between Atopic Dermatitis and Polymyositis/Dermatomyositis

The association between AD and PM was reported in two studies [26,29], one study investigated the association between AD and DM [29], and two studies reported on the association between AD and PM/DM [11,28], with the point prevalence reported in two [26,29]; the combined prevalence of PM/DM in AD was estimated to 0.04% (Figure 2F). Three studies reported an OR, which were significant for DM and PM/DM. However, none of the studies reporting an OR for the association between AD and PM was significant. The combined OR of the association between AD and PM/DM was estimated to be 2.37 (95% CI: 1.54–3.67, P<0.01) (Figure 3F). Ahn et al. [11], whose reported association could not be pooled in the meta-analysis, identified an increased risk of PM/DM, with an HR of 1.59 (95% CI: 1.03–2.45).

Association Between Atopic Dermatitis and Systemic Scleroderma

Three studies investigated the association between AD and SSc [23,26,29], with all reporting both a point prevalence and an OR. The pooled point prevalence was estimated to be 0.1% (Figure 2G). All the studies found a statistically significant association, with a pooled OR of 2.75 (95% CI: 1.44–5.27, I^2 = 60%, P=0.06) (Figure 3G).

Publication Bias

Publication bias was assessed using funnel plots. The funnel plot for the association between AD and any ACTD showed an almost symmetrical distribution, indicating little to no publication bias (Figure 4A). The funnel plot for RA showed symmetry, indicative of no publication bias (Figure 4B), while the funnel plot for SLE was somewhat asymmetric, indicating potential publication bias (Figure 4C). Due to the limited numbers of studies of SS, AS, PM/DM, and SSc, funnel plots were not constructed for these associations.

Discussion

Main Findings

In this systematic review and meta-analysis, we estimated the prevalence of any ACTD at 0.17%, RA at 0.43%, SLE at 0.17%, SS at 0.11%, AS at 0.11%, PM/DM at 0.04%, and SSc at 0.1% among patients with AD. Additionally, AD had an overall significant association with any ACTD; the estimated ORs for the association between AD and the ACTD were statistically significant for RA, SLE, SS, and PM/DM. However, the association with AS and SSc was not statistically significant. The association between AD and MCTD could not be investigated due to the absence of studies available on this topic.

Interpretation

Our results are consistent with previous research, supporting the evidence for the potential association between AD and systemic autoimmune diseases. Previous reviews based on relatively fewer studies reported positive associations between AD and RA [35-38] and SLE [35-36,39-41].

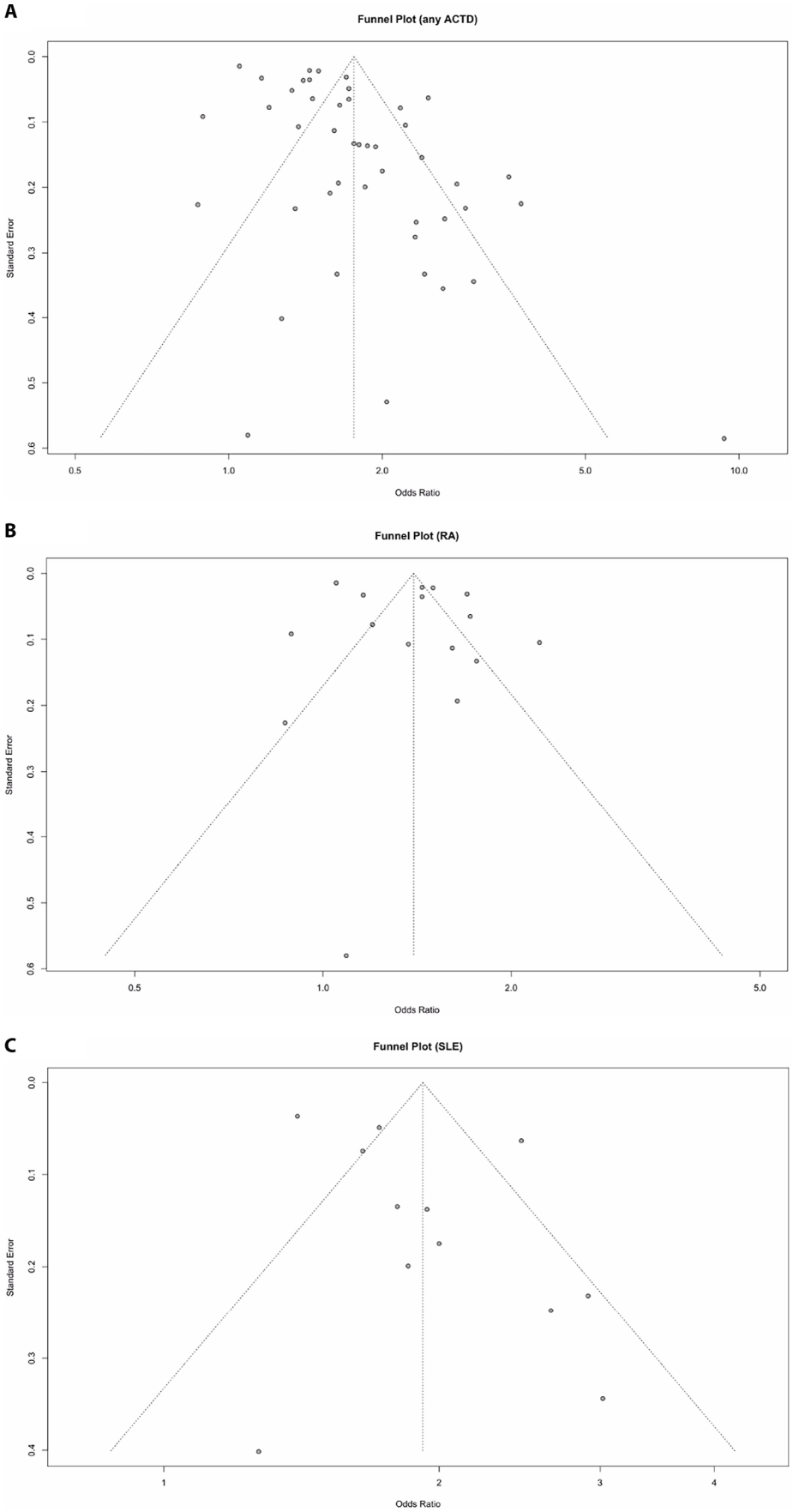

Figure 4. Funnel plots of the meta-analyses. (A) Any autoimmune connective tissue diseases. (B) Rheumatoid arthritis. (C) Systemic lupus erythematosus. (AD, atopic dermatitis; ACTD, autoimmune connective tissue diseases; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.)

Additionally, Chester et al. [40] similarly reported positive associations between AD and SS, AS, and SSc. Our study investigates the association between AD and RA, SLE, SS, AS, PM/DM, and SSc.

While research has uncovered associations between AD and autoimmune diseases, further supporting that AD extends beyond cutaneous manifestations [5-6], the underlying pathophysiological mechanism connecting AD and these conditions remains unclear. AD is characterized by a dysregulated innate immune response with an immunological T helper 2 (Th2) cell reaction characterized by the release of proinflammatory cytokines such as interleukin (IL)-4, IL-5, and IL-13, and subsequent increased levels of immunoglobulin E (IgE) [42]. While Th1 and Th17 are well-recognized contributors to autoimmune diseases [43], emerging evidence suggests their involvement in the pathogenesis of AD as well [44-46]. This proinflammatory response might not be limited to the skin. One possible explanation is the activation of common immunologic pathways, resulting in increased autoreactivity [47] and risk of subsequent autoimmune diseases. These conditions are characterized by a dysregulated immune response, leading to pathological autoimmunity and ultimately tissue damage [48]. The positive association between AD and ACTD could potentially be attributed to shared immunologic dysregulation in T cell activity. Th1 and Th17 are widely recognized as contributors to the pathogenesis of RA [43,49]. Similarly, SS has gained interest in recent research, and both experimental and clinical evidence suggest that both Th1 and Th17 play a crucial role in the development and progression of SS [50]. SLE has long been considered a Th1- and Th17-mediated disease. However, more recent insight suggest that Th2 cells also play an active role in its pathogenesis, eventually resulting in elevated levels of IgE [51-52]. Additionally, regulatory T cells (Treg), which play an essential role in immune suppression and self-tolerance, thereby preventing autoimmunity, have been found to be dysfunctional in AD [53], RA, SLE [54], and SS [50], potentially resulting in the formation of autoantigens, and thus promoting autoreactivity. Interestingly, antinuclear antibody (ANA), a cluster of autoantibodies targeting nuclear cellular components strongly associated with ACTD, especially SLE, SS, SSc, PM, and DM, but also RA [55-56], has been detected in patients with AD [57-59]. These similarities in pathophysiological mechanism strongly indicate a correlation between AD and ACTD.

Our findings underscore the need for future studies investigating the association between AD and ACTD.

Given the potential association between AD and ACTD, dermatologists should be aware of their possible coexistence and the challenges this may present in differential diagnosis. Increased vigilance and interdisciplinary collaboration, particularly with rheumatologists, are essential to ensure timely recognition and appropriate management of both conditions. In clinical practice, early detection of ACTD in AD patients can be facilitated through screening protocols, including standardized questionnaires with short and simple questions, to assess symptoms such as joint swelling, muscle pain, stiffness, and dryness of the eyes, mouth, and skin. At-risk patients may benefit from additional serological testing, such as ANA, rheumatoid factor, and anti-CCP antibodies, to detect early signs of autoimmunity.

Emerging systemic treatments for AD, such as dupilumab and Janus kinase (JAK) inhibitors, have shown significant efficacy in managing the condition. However, their long-term impact on autoimmune disease risk remains an area of ongoing research. Clinicians should carefully consider individual patient profiles, including the presence of autoimmune comorbidities and family history, when selecting treatment options.

Limitations

This systematic review and meta-analysis investigated the association between AD and ACTD, which included RA, SLE, SS, AS, PM/DM, and SSc. However, several limitations should be acknowledged. Given the relatively low incidence and prevalence of ACTD, the number of available studies was limited. Furthermore, the availability of data varied across the studies, including discrepancies in the reporting of prevalence and risk estimates of ACTD in AD.

Moderate-to-high levels of heterogeneity were observed in some analyses, which can be attributed to several factors. Different study designs were included, with variations in recruitment methods, sample sizes, and population characteristics, including sex and age distribution. The assessment of AD varied across studies, and diagnosis varied from physician-verified to self-reports, introducing potential recall bias and misclassification. Furthermore, studies were conducted in different geographic regions, and with AD having geographic variation in prevalence [60], this may contribute to the heterogeneity. These factors may influence the interpretation and comparison of the pooled estimates. We extracted and analyzed the adjusted effects with 95% CI when available. However, inconsistencies in confounder adjustment were observed across included studies. Due to the nature of the meta-analysis, we were unable to account for these variations, which may have introduced bias and affected the pooled results.

Given that studies were conducted across Europe, North America, and Asia, with only one study being international, with Africa not being represented, it is important to note that the result do not reflect a global perspective.

Conclusion

AD was significantly associated with an increased risk of any ACTD, especially RA, SLE, SS, and PM/DM. However, the

association between AS and SSc was not significant. We also estimated the point prevalence of ACTD in AD patients, but it is important to note that these may not be completely representative of the general population. Large-scale prospective studies are needed to further investigate the association between AD and ACTD. Furthermore, an increased awareness of the burden of comorbid ACTD in the AD population should be emphasized.

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