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Association between Atopic Dermatitis and Hypertension: A Systematic Review and Meta-Analysis

Running Header: AD and hypertension

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ADE=adverse drug event, NOS=Newcastle-Ottawa Scale

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What's already known about this topic?

- Previous studies showed conflicting results regarding the association between atopic dermatitis and hypertension.

What does this study add?

- This systematic review and meta-analysis found that atopic dermatitis, particularly moderate-severe disease, is associated with increased odds of hypertension compared to healthy controls, especially amongst the US population.

Abstract

Background: Previous studies found conflicting results about the association of atopic dermatitis (AD) with hypertension.

Objectives: Determine whether AD and AD severity are associated with hypertension.

Methods: A systematic review was performed of published studies in MEDLINE, EMBASE, Scopus, Web of Science, and GREAT databases. At least 2 reviewers conducted title/abstract, full-text review, and data extraction. Quality of evidence was assessed using the Newcastle-Ottawa Scale.

Results: Fifty-one studies met inclusion criteria; 19 had sufficient data for meta-analysis. AD was associated with higher odds of hypertension compared to healthy controls (increased in 9 of 16 studies; pooled prevalence: 16.4% vs 13.8%; random-effects regression, pooled unadjusted odds ratio [OR][95% confidence interval <CI95>]: 1.16 [1.04-1.30]), but lower odds of hypertension compared to psoriasis (decreased in 5 of 8 studies; 15.4% vs 24.8%; 0.53 [0.37-0.76]). In particular, moderate-severe AD were associated with hypertension compared to healthy controls (increased in 4 of 6 studies; 24.9% vs 14.7%; 2.33 [1.10-4.94]). Hypertension was commonly reported as an adverse-event secondary to AD treatments, particularly systemic cyclosporine A. Limitations include lack of longitudinal studies or individual-level data and potential confounding.

Conclusions: AD, particularly moderate-to-severe disease, was associated with increased hypertension compared to healthy controls, but lower odds than psoriasis.

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting 13% of children and 7% of adults^{1,2} in the US and up to 20% of children and 3% of adults globally.^{3,4} AD is associated with pruritus, skin pain^{5,6}, sleep disturbance⁷⁻¹⁰, symptoms of anxiety and depression¹¹⁻¹⁴, lower health-rating and life satisfaction scores.¹⁵⁻¹⁷ AD is also associated with more sedentary behavior¹⁸⁻²⁰, cigarette smoking²¹, and obesity²²⁻²⁶, and multiple comorbid health disorders, including asthma, autoimmune disease³²⁻³⁵ and malignancy.³⁶ All of these could potentially contribute toward increased cardiovascular risk factors, such as hypertension. Systemic inflammation may also increase cardiovascular disease risk in certain subsets of AD patients.^{37,38}

The relationship between AD and hypertension was examined in multiple studies, with conflicting results.^{22,39-41} We hypothesized that AD, particularly more severe AD, is associated with higher prevalence of hypertension. This systematic review (SR) determined whether AD is associated with hypertension. We further determined whether hypertension was related to AD severity. Finally, we determined how commonly hypertension was reported as a treatment-related adverse-event.

Methods

Literature search

The following databases were searched from the earliest record through June 27, 2019: Ovid MEDLINE, EMBASE, Scopus, Web of Science, and the Global Resource of Eczema Trials (GREAT). Our search strategy was adapted from previous reviews of AD¹¹ and hypertension⁴² and institutional librarian input (Supplemental Table 1)(PROSPERO ID: CRD42019135746).

Inclusion criteria were: any primary studies assessing AD/eczema (exposure) and hypertension or blood pressure (BP) with a reported hypertension/BP measure (i.e. prevalence) (outcome); had ≥ 10 subjects; cross-sectional or longitudinal; in any language. Title, abstract, and full-text review were conducted by ≥ 2 reviewers. Manuscripts were excluded in title and/or abstract review if the study did not clearly mention both AD and hypertension-related items, or if the study was a case report or series, non-human study, review, editorial, abstract, unpublished study or study protocol. Studies were excluded in title/abstract or full-text review if they did not discuss a relationship of AD with hypertension, BP or hypertensive symptoms. Foreign language studies were translated by trained healthcare providers who were fluent in those languages to ensure they met inclusion criteria. If identical data were used in multiple studies, only the most current study was used. Corresponding authors were contacted up to three times for manuscripts that were unavailable. All included manuscripts were hand searched for additional references. AD and hypertension were defined across studies using physician-diagnosis, chart review, ICD codes, and/or self-reported questionnaires.

This study was exempt from Institutional Review Board as data were gathered from published literature.

Data extraction

The following data were extracted after full-text screening: primary author and year published; study language; funding source/type; study location; study design; number of subjects, age and gender; methods to diagnose and assess severity of AD and hypertension; number of subjects with and without AD or hypertension; adverse drug events related to hypertension, and mean BP where specified.

Data analysis

Given the relative dearth of well-constructed studies regarding this topic, we decided *a priori* to include all studies in the meta-analysis regardless of study quality. Statistical analyses were performed using OpenMetaAnalyst 10.12 (Brown University, Providence, RI). Comparable outcomes of all studies of AD (exposure) and hypertension (outcome) were combined, and measures of consistency were obtained. Studies with a healthy or psoriasis control group underwent pooled meta-regression analysis. Pooled unadjusted odds ratio (OR) of association between AD and hypertension with 95% confidence interval (CI) were estimated using random-effects logistic regression models owing to significant heterogeneity ($I^2 > 90\%$ for all analyses). Sensitivity analyses were performed based on AD and hypertension definitions, and region. Forest-plots were constructed for all studies included in meta-analysis. A 2-sided P-value of 0.05 was taken as significant. The Newcastle-Ottawa Scale was utilized to assess the quality of studies in the meta-analysis, with a scoring system based on 8 aspects and a maximum of 9 points (Supplemental Table 3). Egger regression, Begg rank correlation and funnel plot regression were used to assess for potential publication bias.

Results

Literature search

In total, 2,355 non-duplicate articles were identified in the database search, of which 2,225 were excluded during title and abstract review, and 79 were excluded during full-text review. Fifty-one studies were included in this SR^{22,35,39,41,43-89} (Figure 1); 19 had sufficient data for inclusion in the quantitative meta-analyses.^{22,35,39,43,45,46,51,62,64,66,70,73-76,78,80,82,90}

Study characteristics

The studies were published from 1975-2019. Nineteen (37.3%) were cohort studies^{41,44-46,48,49,52,56-59,67,71,74,82-84,86,89}, 16 (31.4%) were cross-sectional^{22,35,39,51,60,62,64-66,69,70,73,76,77,90,91}, 8 (15.7%) were randomized control trials^{50,53-55,61,72,85,88}, 7 (13.7%) were case-control studies^{43,47,68,75,78,80,87}, and 1 (1.9%) was a cross-over study.⁶³ The studies were conducted in Europe (n=29)^{43,44,47-55,57-59,63,68,69,72-75,77,80,83-87,89,91}, Asia (n=12)^{41,56,60-62,65-67,71,76,82,83}, North America (n=9)^{22,35,39,45,46,64,70,78,90}, and internationally (n=1).⁸⁸ Thirty (58.8%) included adults^{35,39,41,45,46,48,50-54,59,62,63,65,66,68-71,73,74,76,83-88,90}, 7 (13.7%) children^{22,43,47,55,58,78,89}, 9 (17.6%) children and adults^{44,49,56,61,67,72,75,82,91}, and 5 (9.8%) with unspecified age range.^{57,60,64,77,80} Nineteen studies included >50% females^{22,35,39,48,51,54,62,65,66,68,72,74-77,82,83,87,88}, 18 had ≤50% females^{44,46,49,50,52,53,55-59,61,63,67,69,84-86}, 1 all males⁴¹, 1 all females⁴⁵, and 12 did not specify sex distribution.^{43,47,60,64,70,71,73,78,80,89-91}

Overall 488,190 AD patients and 73,334,352 controls were included, with 97,411 AD and 434,225 controls from Europe^{43,44,47-55,57-59,63,68,69,72-75,77,80,83-87,89,91}, 256,998 AD and 72,674,850 controls from North America^{22,35,39,45,46,64,70,78,90}, 133,678 AD and 225,420 controls from Asia^{41,56,60-62,65-67,71,76,82,83}, and 103 AD patients internationally.⁸⁸ 269,861 AD adults and 718,873 control adults were included and 52,530 AD children and 340,356 AD control children were included (5 studies did not report age range). The diagnostic criteria and outcome measures used across studies are presented in the Supplemental Results.

Quantitative analyses

Association of AD with hypertension

Overall, the prevalence of hypertension in AD patients across all studies was 15.2% (min-max: 8.4%-23.5%; n=19 controlled and 5 uncontrolled studies). AD was associated with higher odds of hypertension compared to healthy controls (increased in 9 of 16 studies; pooled prevalence: 16.4% vs 13.8%; pooled unadjusted OR [95% CI]: 1.16 [1.04-1.30]) (Figure 2A), but lower odds of hypertension compared to psoriasis (decreased in 5 of 8 studies; pooled prevalence: 15.4% vs 24.8%; OR [95% CI]: 0.53 [0.37-0.76]) (Figure 2B).

Sensitivity analyses

Hypertension was significantly increased among cohort studies (3 of 4 studies; pooled prevalence: 8.8% vs 6.3%; OR [95% CI]: 1.31 [1.21-1.42]), but not among cross-sectional and case-control studies (7 of 15 studies; pooled prevalence: 18.5% vs 17.6%; OR [95% CI]: 1.05 [0.83-1.33]).

Based on study region, hypertension was significantly increased in AD among studies performed in the US (increased in 6 of 8 studies; pooled prevalence: 24.0% vs 18.5%; OR [95% CI]: 1.34 [1.22-1.47]), but not in Europe (increased in 3 of 6 studies; pooled prevalence: 10.0% vs 11.5%; OR [95% CI]: 0.92 [0.53-1.59]) or Asia (increased in 3 of 4 studies; pooled prevalence: 13.6% vs 12.4%; OR [95% CI]: 1.09 [0.91-1.30]). Of note, most studies in Europe (66.7%) and all studies in Asia (100%) had healthy control groups.

Among studies with a healthy control group, hypertension was associated with physician-diagnosed AD (8 of 13 studies; pooled unadjusted OR [95% CI]: 1.18 [1.04-1.33]), but not self-reported AD (1 of 3 studies; pooled unadjusted OR [95% CI]: 1.09 [0.72-1.66]). Similarly, AD was associated with physician-reported hypertension (6 of 10 studies; pooled unadjusted OR [95% CI]: 1.13 [1.04-1.23]), but not self-reported hypertension (2 of 4 studies; pooled unadjusted OR [95% CI]:

1.11 [0.71-1.75]). The association between AD and hypertension was significant among higher-quality studies (NOS score ≥ 6 ; 8 of 14 studies; pooled OR [95% CI]: 1.15 [1.02-1.29]), but not among lower-quality studies (NOS score < 6 ; 3 of 5 studies; pooled OR [95% CI]: 0.96 [0.46-2.03]).

Association of AD severity with hypertension

Mild AD was not associated with hypertension compared to healthy controls (increased in 0 of 3 studies; pooled prevalence: 17.9% vs 18.2%; OR [95% CI]: 0.98 [0.83-1.15]). Whereas, moderate and/or severe AD were associated with hypertension compared to healthy controls (increased in 4 of 6 studies; pooled prevalence: 24.9% vs 14.7%; OR [95% CI]: 2.33 [1.10-4.94]).

Association of AD treatment with hypertension

The pooled-random effects prevalence of hypertension as an adverse-event from cyclosporine was 7.8% overall (min-max: 5.0%-11.1%; n=20 studies), 0.8% in children (min-max: 0.0%-3.2%; n=4 studies) and 11.6% in adults (min-max: 7.1%-17.1%; n=10 studies). The pooled-random effects prevalence of hypertension as an adverse-event from systemic glucocorticoids was 4.9% in adults (min-max: 0.2%-15.2%; n=2 studies).

Whereas, a RCT investigating three separate doses of oral pimecrolimus reported a low prevalence of hypertension in adults with ADE prevalence of 0.98% in the AD population.⁸⁸

Qualitative analysis

Two studies provided qualitative data regarding hypertension prevalence in AD. A prospective study investigating multiple German cohorts, found an increased odds of hypertension in the AOK PLUS cohort (n=1.2 million; adjusted RR [95%

CI]: 1.04 [1.02-1.06]; $P < 1 \times 10^{-16}$), but not in the GINIplus/LISA birth cohort ($n=2286$; $P=0.66$) or KORA cohort ($n=2990$; $P=0.65$).⁹¹ A cross-sectional Korean study utilizing KNHANES found no association of hypertension with AD in young adult males (adjusted OR [95% CI]: 0.94 [0.56-1.60]) or females (1.74 [0.84-3.61]).⁶⁵

Two studies provided data regarding mean BP in the AD population. A German case-control study measured mean BP in 15 hospitalized AD patients and controls on two separate occasions to account for daily variation and found no significant differences. From the two measurements, this study found a combined mean BP of 111.3/68.5 mmHg (SD: 9.4/9.9) among the AD patients and a combined mean BP of 111.6/71.9 mmHg (SD: 8.2/10.0) among the controls.⁶⁸ A US multicenter, cross-sectional clinical study investigating AD in children found an association with higher systolic and diastolic BP for age, sex, and height percentile as compared to children coming to clinic for non-AD treatment (SBP: OR [95% CI]: 2.96 [1.16-7.51] and DBP: OR [95% CI]: 2.72 [1.01-7.36]).²²

Assessment of publication bias

Publication bias was not detected as judged by non-significant Egger regression or Begg rank correlation for any of the above mentioned outcomes ($P=0.76$ and 0.55).

Discussion

This SR and meta-analysis found that approximately 1 in 6 patients with AD had hypertension. AD patients had significantly higher odds of hypertension compared to healthy controls. In particular, moderate-severe AD, but not mild AD, was associated with higher odds of hypertension. The association of AD with hypertension is likely multifactorial, with contributions from systemic inflammation, chronic sleep disturbance, higher rates of obesity and mental health disturbances, decreased physical activity, increased cigarette smoking and alcohol consumption and use of systemic corticosteroids, cyclosporine A and other medications in AD patients.^{19,21,26,35,79,92-95} Interestingly, AD was most consistently associated with hypertension in studies conducted in the United States, but less so in European and Asian studies. These results are similar to a previous SR and meta-analysis that found that AD was most consistently associated with overweight and obesity in North America and Asia, but less so in Europe. AD, hypertension and cardiovascular disease overall are associated with environmental, socio-demographic, cultural and/or lifestyle factors.⁹⁶⁻⁹⁹ The observed regional differences of association between AD, hypertension and other cardiovascular disease risk factors may be confounded by such factors, and suggest that these factors may play a more important role in the association than does systemic inflammation.²⁶ Though, future studies are needed to better understand the relative contributions of these different factors.

These results are clinically relevant for multiple reasons. First, increased BP screening is warranted in AD patients, especially in those with moderate-severe disease. However, previous studies found that BP screening was performed significantly less commonly in patients with AD or psoriasis vs. without them¹⁰⁰. Our results underscore the need for increased BP screening in AD patients. However, dermatologists or allergists are often the only providers that AD patients see, i.e. they may not have regular follow-up with a primary care provider. Thus, it is important that AD patients at increased risk of hypertension establish continuing care with a primary care provider. Finally, there are simple, safe and feasible lifestyle interventions that dermatologists and allergists can recommend to AD patients, including increasing exercise and improving

diet. AD patients have increased sedentary activity^{19,93,95,101-103}, often related to their itch being triggered by heat and sweat. Moderate and vigorous physical activity should be encouraged in AD patients combined with adequate treatment to control their skin disease despite the increased heat and sweat.¹⁰⁴

AD was associated with lower odds of hypertension when compared to psoriatic controls. Previous SR and meta-analyses have demonstrated higher likelihood of hypertension among adults and/or children with psoriasis, particularly moderate-severe psoriasis, compared to health controls.^{105,106} It may be that multiple chronic inflammatory skin diseases are associated with hypertension owing to shared risk factors, including systemic inflammation and immune dysregulation, symptoms of anxiety and depression^{11,13,14,107,108}, sleep disturbance^{8,10,94,108,109}, sedentary lifestyle and decreased physical activity^{19,79,93,95,110,111}, smoking^{21,112,113}, increased alcohol consumption^{79,114}, and adverse-events from systemic immunosuppressants and corticosteroids.¹¹⁵

Many systemic treatments are used off-label and have not been well studied in AD. However, AD affects far more children and young adults than many other autoimmune diseases, such as psoriasis and rheumatoid arthritis. It is largely unknown whether previously reported AEs of these systemic therapies occur at similar rates in AD and other autoimmune disorders. In this SR, hypertension was primarily reported as an AE due to systemic cyclosporine A treatment for AD. It is well-established that cyclosporine increases BP.¹¹⁶ Hypertension is also a well-established AE of systemic glucocorticoid treatment in AD and other disorders.¹¹⁵ As such, systemic cyclosporine A and glucocorticoid may best be avoided in patients with pre-existing hypertension. However, further research is needed to better understand the short-term and long-term safety of commonly used systemic therapies in AD *per se*.

Strengths of this study include the use of a validated comprehensive search strategy, inclusion of studies of all languages from multiple regions, and multiple sensitivity analyses. The multitude of studies allowed for adequate statistical power to generate precise prevalence estimates of hypertension in patients with AD. The use of random-effects models

accounted for heterogeneity among the studies. The limitations of this SR include the lack of longitudinal studies, thereby precluding assessment of the temporal relationship between AD and hypertension. Causality cannot be determined since most studies were cross-sectional. There may be confounding variables that were not controlled for across studies (e.g. age, gender and treatment). Heterogeneity of results and potentially limited generalizability may arise from differences of study inclusion criteria and sampling methods. For example, some studies only examined children or adults; some compared AD to healthy controls or other dermatologic disorders. Further, data on AD phenotype and treatment, hypertension, and individual-level patient data were not available. Some studies relied on self-reported assessment of AD, which may be subject to misclassification.¹¹⁷ Some studies relied on self-reported assessment of hypertension, which may be subject to misclassification. However, in sensitivity analyses, studies using clinician diagnosis of AD and hypertension were associated with significant associations of AD with hypertension. Only one study accounted for patient gender, which may be a cofounder, as men have been shown to have more hypertension than women.¹¹⁸ Future studies are needed to address these points.

In conclusion, AD patients have higher odds of hypertension than the general population, but less so than psoriasis patients. Clinicians should be aware of this association and consider increased screening for hypertension in AD patients, particularly in patients with moderate-to-severe disease, and closer monitoring for hypertension as an AE of systemic cyclosporine A and glucocorticoids. Future studies are needed to determine the temporal relationship between AD and hypertension, as well as mechanisms and optimal interventions to prevent and treat hypertension in AD.

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Figure Legends

Figure 1. PRISMA flow diagram.

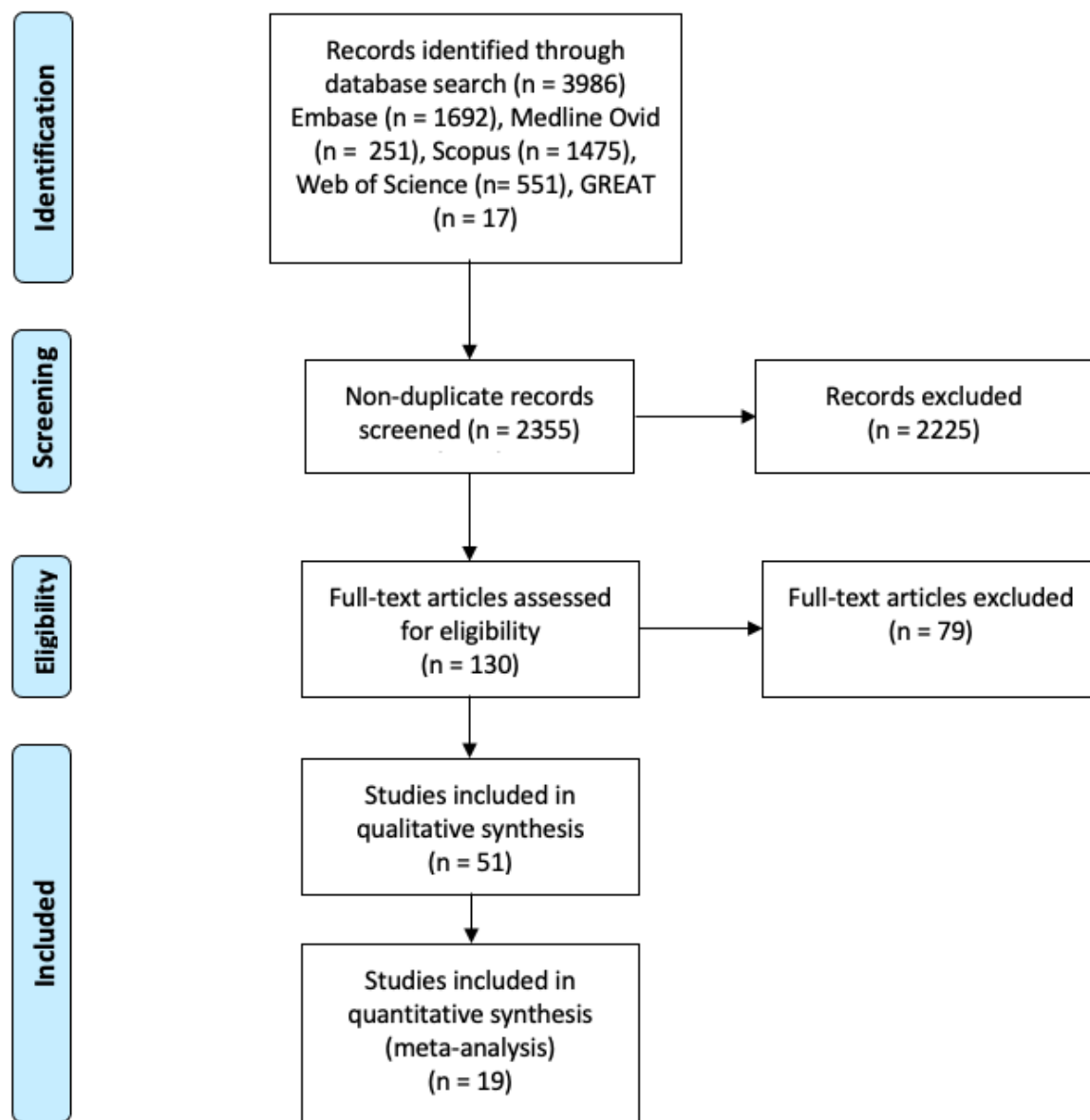
PRISMA AD Hypertension

Figure 2. Forest-plots of the proportion of hypertension in persons with AD vs healthy (A) or psoriasis (B) controls. 95% confidence intervals (squares), pooled proportions (diamond) are presented.

Figure 2A

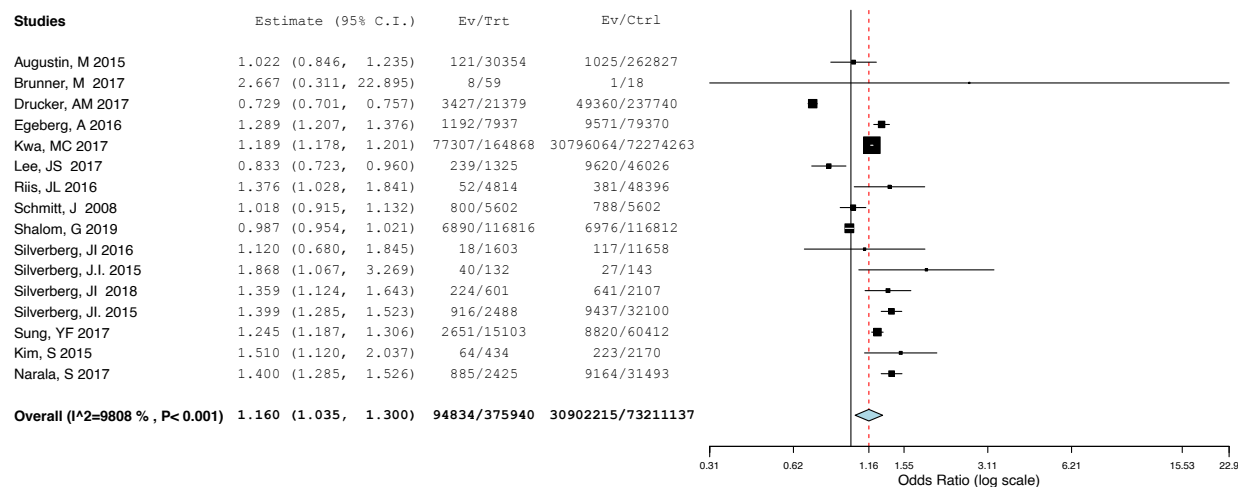
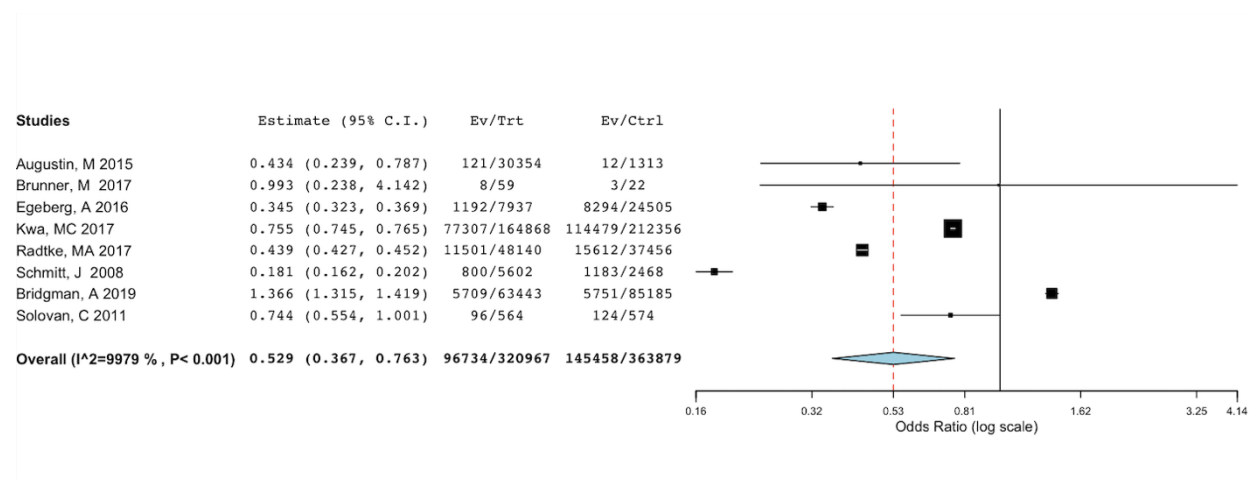


Figure 2B

Supplemental Table I. Search strategies.**OID MEDLINE** : June 27, 2019. 251 results.

1. Dermatitis, atopic.mp. or exp DERMATITIS, ATOPIC/
2. atopic dermatitis.mp.
3. dermatitis atopic.mp
4. exp ECZEMA/ or eczema.mp.
5. childhood eczema.mp.
6. infantile eczema.mp.
7. neurodermatitis.mp. or exp Neurodermatitis/
8. Besnier's prurigo.mp.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp Hypertension/ or hypertension.mp.
11. hypertens*.mp.
12. Idiopathic hypertension.mp.
13. Malignant hypertension.mp. or exp Hypertension, Malignant/
14. Essential hypertension.mp. or exp Essential Hypertension/
15. Hypertensive crisis.mp.
16. (((elevat* or high or raised or excessive) adj2 (diastolic or systolic or arterial) adj ((blood adj1 pressure) or bloodpressure)) or bp).mp.
17. ((elevat* or high or raised or excessive) adj2 ((blood adj1 pressure) or bloodpressure or bp)).mp.
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
19. 9 AND 18

EMBASE - June 27, 2019. 1692 results.

#1 ('atopic dermatitis'/exp OR 'atopic dermatitis' OR 'dermatitis atopic' OR 'eczema'/exp OR 'eczema' OR 'childhood eczema' OR 'infantile eczema' OR 'neurodermatitis' OR 'neurodermatitis'/exp OR 'Besnier/s prurigo' OR ('Besnier/s' AND 'prurigo'))
 #2 'hypertension'/exp OR hypertension
 #3 hypertens*
 #4 idiopathic NEAR/1 hypertension
 #5 'malignant hypertension'/exp OR 'malignant hypertension'
 #6 'essential hypertension'/exp OR 'essential hypertension'
 #7 'hypertensive crisis'/exp OR 'hypertensive crisis'
 #8 (elevat* OR high OR raised OR excessive) NEXT/1 (diastolic OR systolic OR arterial) NEXT/1 ('blood pressure' OR 'bloodpressure' OR 'bp')
 #9 (elevat* OR high OR raised OR excessive) NEXT/1 ('blood pressure' OR 'bloodpressure' OR 'bp')
 #10 #2 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 or #8 OR #9
 #11 #1 AND #10

SCOPUS - June 27, 2019. 1,475 RESULTS

TITLE-ABS-KEY ("atopic dermatitis" OR "dermatitis atopic" OR "eczema" OR "childhood eczema" OR "infantile eczema" OR "neurodermatitis" OR "Besnier prurigo" AND "hypertens*" OR (idiopathic W/2 hypertension) OR "malignant hypertension" OR "essential hypertension" OR "hypertensive crisis" OR ("elevat*" W/15 diastolic OR systolic OR arterial OR "blood pressure" OR bloodpressure OR bp) OR (high W/15 diastolic OR systolic OR arterial OR "blood pressure" OR bloodpressure OR bp) OR (raised W/15 diastolic OR systolic OR arterial OR "blood pressure" OR bloodpressure OR bp) OR (excessive W/15 diastolic OR systolic OR arterial OR "blood pressure" OR bloodpressure OR bp))

Web of Science June 27, 2019. 551 results.

#3 #2 AND #1

#2 ALL=(hypertension OR "essential hypertension" OR "malignant hypertension" OR "idiopathic hypertension" OR "hypertensive crisis" OR "high blood pressure" OR "raised blood pressure" OR "elevated blood pressure" OR "excessive blood pressure" OR "systolic blood pressure" OR "diastolic blood pressure" OR "arterial blood pressure" OR BP OR "blood pressure" OR bloodpressure)

#1 ALL=("atopic dermatitis" OR "dermatitis atopic" OR eczema OR "childhood eczema" OR "infantile eczema" OR neurodermatitis OR besnier*)

GREAT - June 27, 2019. 16 results.

1. (atopic dermatitis) OR (dermatitis atopic) OR (eczema) OR (childhood eczema) OR (infantile eczema) OR (neurodermatitis) OR (besniers prurigo)
2. (hypertension) OR (hypertensive) OR (blood pressure) OR (BP) OR (bloodpressure) OR (blood-pressure)
3. #1 AND #2

1
2
3

4Supplemental Results

5AD Diagnosis and Severity

6 Included in this systematic review were 51 total studies that assessed a relationship
7between atopic dermatitis and hypertension. Among these studies, AD was defined by
8physician diagnosis (82.4%) or was self-reported (7.8%). 5 studies did not specify how the
9patients were diagnosed with AD. Of the studies defining AD with physician diagnosis, 11 used
10Hanifin and Rajka criteria, 3 used UK Working Party criteria, 1 used American Academy of
11Dermatology Consensus Criteria, 6 used ICD codes, and the others did not specify further.
12Furthermore, 30 studies discussed AD severity but of these only 10 divided their results into
13subgroups. AD severity was assessed in a variety of ways including SCORing AD (SCORAD)
14(2 studies), Body Surface Area (BSA) (2 studies), Physician's Global Assessment (PGA) (1

15study), systemic therapy use (2 studies), total number of physician visits due to condition (1
16study), multiple clinical indicators (1 study), and by treatment (1 study).

17

18Diagnosis and Severity of Hypertension

19 Thirty-seven of the studies looked at diagnosed hypertension, while no studies looked at
20hypertension symptoms. 14 studies did not specify diagnosed hypertension vs symptomatic
21hypertension. Only 1 study reported on hypertension severity, which divided hypertension into
22prehypertension, stage 1, 2, 3 hypertension.

23

24

25Manuscripts included in the systematic review

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Supplemental Table 2. Characteristics of included studies.

	First author last name, Initials	Year published	Funding Source	Continent	Country	Study design	Disease group	Drug with ADE	No. w/ Hypertension	Total No.	AD severity	Specified hypertension severity	Assessment of AD (ie clinical, scord, charts, physician diagnoses, ICD10, ect)	Hypertensive symptoms vs Diagnosis	Assesment of Hypertension	Age	Mean Age (yr)	Median Age (yr)	Female Sex (%)
177 178 179	Augustin, G	2015	Industry	Europe	Germany	Retrospective case-control	AD Healthy Control Psoriasis		121 1025 12	30354 262827 1313			191 ICD10	Diagnosed	ICD9	Children			
195 196 197 198 199 200 201 202	Berth-Jones J	1997	Industry	Europe	UK	Prospective, multicenter	AD	Cyclosporine	5	100	Severe	Diastolic>95	screening visits for treatment	Both	Physician diagnoses	Both	34		43
206 207	Brunner, M	2017	Federal + Foundation	North America	US	Prospective cohort + case-control	AD Healthy Control		8 1	59 18	Moderate-severe		SCORAD	Diagnosed		Adults	40.5 41.3		47.5 33.3
217 218 219 220	Caputo, R	1993	Not specified	Europe	Italy	Prospective case series	Psoriasis		3	22							46.8		18.2
219 220	Dagaze, J	2017	Not specified	Europe	France	Single-center retrospective study	AD	Cyclosporine	0	18	Severe		Hanifin-Rajka			Adults	26		77.8
224 225 226 227 228 229 230 231 232 233 234 235 236	Drucker, AM	2017	Federal	North America	Canada	Cross-sectional	AD No AD	Cyclosporine	10	88			SCORAD	Diagnosed		Both	29.4		25
237 238 239 240 241 242 243 244 245 246 247 248 249	Egeberg, A	2016	Industry + Foundation	Europe	Denmark	Cross-sectional	AD General population Psoriasis		1192 9571 8294	7937 21379 237740	Mild or severe	Severe if they recieved systemic therapy	Diagnosed	ICD10		Adults	34.3 34.3 45.5		61.8 61.8 51.2
255 256 257 258 259 260 261 262 263 264 265 266 267 268 269 270 271 272 273 274 275 276 277 278 279 280 281 282 283 284 285	Granlund, A	2001	Industry + University	Europe	Finland	RCT	AD	Cyclosporine	7	36			SCORAD	Diagnosed		Adults	33.3		41.7
							AD	UVAB	0	35							33.2		60
							AD	cyclosporine short cours	0	21							10.1		
276 284	Harper, JI	2007	Industry	Europe	UK	RCT	AD	osporine continuous co	0	19			SASSAD			Children	10	283	47.5
285	Hijnen, DJ																		
		2008	Not specified	Europe	Netherlands	Retrospective observational	AD AD AD	Cyclosporine short cou Cyclosporine intermedi Cyclosporine long cour	4 4 3	25 25 23			Hanifin-Rajka	Diagnosed	>160systolic or >95 diastolic for 2 consecutive	Adults	33.6 30.6 36.7		36 48 43.5
311 312 313	Karthikeyan, S	2011	Not specified	Asia	India	Prospective case-control	AD Rheumatoid arthritis	Topical corticosteroids Oral corticosteroids	0	100			Charts			Both			-
325	Kok, W	2019	Not specified	Asia	Singapore	Retrospective population-based	AD AD AD		167 334	2101 505 10077	Mild Moderate Severe		Charts	Diagnosed	Charts	Adults	20		0
330 341		348 346	330 351	352 356	350		AD		77307 30796064 3219 7915 101224 2121	164,868 72274263 6339 13,342 185,803 6872									
342 343	Kwa, M	2013	Foundation	North America	USA	Cross-sectional	No inflammatory skin disease control Pemphigus Bullous pemphigoid Psoriasis Hidradenitis					374	ICD9	Diagnosed	ICD				
							AD male AD female No AD male No AD female			94 128 2737 2048	373 386 387 388 389	(systolic blood pressure ≥130 mmHg or diastolic blood	Self-report	Diagnosed	Self-reported diagnoses	Adults	27 30 30	396	57.2
377	Lee, JH	2018	Federal	Asia	South Korea	Cross-sectional	AD No AD												
397 408	Lee, JS	2017	None	Asia	South Korea	Cross-sectional	AD No AD		239 9620	1325 46026			KHANES survey	Diagnosed	KHANES survey	Adults		407	58.8 50.3
410 411	Lee, SS	2004	Not specified	Asia	China	Retrospective observational	AD	Cyclosporine	1	15	Severe	rdeline HTN 130	Charts	Diagnosed	Physician diagnosed	Both	24		40
416							Persistent AD Persistent AD		4 59	64 59	Mild Moderate						34 36		48.4
420	Megna, A	2014	None	Europe	Italy	Cross-sectional	persistent AD Adult Onset AD Adult Onset AD			28 62 32	Severe Mild Moderate	429 430	Diagnosed	Diagnosed	Chart review	Adults	34 36 36		48.4 49.2
435									14	32							36		49.2

756 757 759	Garritsen, FM	758	2014	759	None	760	Europe	761	Netherlands	762	observational	763 764	AD		Methotrexate Systemic corticosteroids	0	17	765	Charts	766	Diagnosed	767	Chart review	768	Adults	36.89	47	
770 771	Goujon, C	772	2017	773	Federal	774	Europe	775	France	776	Clinical trial	777 778	AD AD		Cyclosporine Methotrexate	3 0	47 57	779	Moderate-severe	780	Diagnosed	781	Physician diagnosed	782	Adults	33 32	34 43	
785 786	Haw, S	2010			Not specified		Asia		Korea		Retrospective observational	787	AD		Cyclosporine	8	788 789 790 791	Moderate-severe	792	systolic blood pressure was greater than 140	793	Diagnosed	794	Chart review	Both	27.9	32.7	
793 794 795	Hegazy, S	2017			Not specified		Europe		France		Retrospective observational	797 798	AD AD		Systemic therapy Topical therapy	Not specified	139 102	Severe		799	Diagnosed	800	Physician diagnosed	801	Children	8.4	41 41	
799 800 801 802 803	Heller, M Hernandez Martin, A	2007 2016			None		Europe		Spain		Retrospective observational	803	AD		Cyclosporine	0	63	Severe	804	BP at or above t	805	Physician diagnosed	806	Children	8.4	42.9		
809	Jin, SY	2012			Federal	813	Asia	814	South Korea	815 816 817	AD AD AD			Cyclosporine	0	16						812 813	Physician diagnosed	814	Both	19.5	37.5	
827 829 830	Kim, S	2013			Not specified		Asia	834	South Korea	835 836 837	Cross-sectional Age and Sex-Matched controls	838	AD		Cyclosporine glucosamine Cyclosporine and placebo	64 223	434			821	Diagnosed	822 823	Physician diagnosed	824	Adults	39.69	842 58.5	
844 845 862	Koppelhus, U	2014			Foundation		Europe	854	Denmark	855 856	Cross over trial	857	AD AD		Cyclosporine Extracorporeal photopheresis	1	15	Severe	858	Diagnosed	859 860	Physician diagnosed	861	Adults		25		
868 869 -	Narala, S	2017			None		North America		USA	863 -	Cross-sectional	866 867	AD No AD				2607 24208											
875 876	Pacor, ML	2004			Federal		Europe		Italy	884	RCT		AD AD		Tacrolimus Cyclosporine	0 0	15 15	Moderate-severe			870 871	Physician diagnosed	872 873	Both	27.1 26.6	70 73.3		
882	Solovan, C	2011			Not specified		Europe		Romania		Retrospective case-control	877 878 879	Nonspecific endogenous Psoriasis No psoriasis			96	564		Charts				Chart review					
884 885 886 887 888	Van der Schaft, J Varonier, H	2015 1966			None		Europe		Netherlands		Retrospective observational	889 890	AD		Cyclosporine	26	356	Moderate-severe		Hanifin-Rajka	894 895		899	Adults	37.6	46.9		
900 901 904	Vedie, AL	2016			None		Europe		France		Retrospective observational	891 892	AD		Methotrexate	0	28			896	Physician assessment	897 898	Diagnosed					
905 906 907	Veller, C	913	2003	914 915	Not specified	916	Europe		Italy	917	Retrospective case- control	918 919	AD Psoriasis Lichen planus Pemphigus Pyoderma	920	Cyclosporine	2 8 2 0 0	12 67 30 12 5			921	Diagnosed	922	Physician diagnosed	923		42.4 56.9 62.1 61.4 60.4	58.3 35.8 73.3 83.3 80	
924 925	Wolff, K	2005			Industry		North America		Austria, Belgium, Canada, Finland, Poland, UK and USA		RCT		AD AD AD AD		Placebo Pimecrolimus 10mg Pimecrolimus 20mg Pimecrolimus 30mg	0 0 1 0	26 26 24 26	Moderate-severe		Hanifin-Rajka		Diagnosed		Physician diagnosed		37 35 35 37	36 33 33 35	54 35 58 69
927	Zaki, R	1996			Not specified		Europe		UK		Prospective cohort		AD		Cyclosporine	0	18	Severe refractory		Physician			Physician diagnosed					
932	Silverberg, JI	2015			Foundation		North America		USA		Cross-sectional	933 934	AD Healthy Control			40 27	132 143	Moderate-severe	>90% 5th percentile	935 936	Hanifin-Rajka	937 938 939	Diagnosed	940	Physician diagnosed	Children	10.8	52.7

Supplemental Table 3. Newcastle-Ottawa Scale Quality Assessment				
Study	Selection ★★★★★	Comparability ★★	Outcome ★★★	Total
Augustin, M 2015	★★★		★★★	6
Brunner, M 2017	★	★★	★★	5
Drucker, AM 2017	★★★	★★	★★	7
Egeberg, A 2016	★★	★★	★★★	7
Kwa, MC 2017	★★	★★	★★★	7
Lee, JS 2017	★★★	★★	★★	7
Radtke, MA 2017	★★		★★★	5
Riis, JL 2016	★★	★★	★★★	7
Schmitt, J 2008	★★	★	★★★	6
Shalom, G 2019	★★★	★★	★	6
Silverberg, JI 2016	★★★	★★	★★	7
Silverberg, JI 2015 (A46)	★★★★★	★★	★	7
Silverberg, JI 2018	★★	★★	★	5
Silverberg, JI 2015 (A49)	★★★	★★	★★	7
Sung, YF 2017	★★	★★	★★★	7
Bridgman, A 2019	★★	★★	★	5
Kim, S 2015	★★★	★★	★★	7
Narala, S 2017	★★★	★★	★★	7
Solovan, C 2011	★★		★★	4