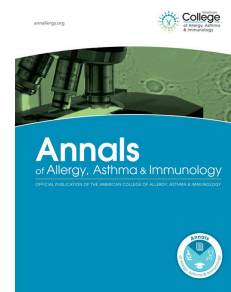


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Rhinitis prevalence and association with atopic dermatitis: A systematic review and meta-analysis

Mette Hjorslev Knudgaard, MD, Thomas Holger Andreassen, MD, Nanna Ravnborg, MD, Thomas Bieber, MD, PhD, MDRA, Jonathan I. Silverberg, MD, PhD, MPH, Alexander Egeberg, MD, PhD, Anne-Sofie Halling, MD, Jacob P. Thyssen, MD, PhD, DMSci



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Title Page**Title**

Rhinitis prevalence and association with atopic dermatitis: A systematic review and meta-analysis

Author names, academic degrees, affiliation(s) of the authors

Mette Hjorslev Knudgaard MD^{1,2}; Thomas Holger Andreasen MD^{1,2}; Nanna Ravnborg MD^{1,2};
Thomas Bieber MD, PhD, MDRA³; Jonathan I Silverberg MD, PhD, MPH⁴; Alexander Egeberg
MD, PhD^{1,2}; Anne-Sofie Halling MD^{1,2}; Jacob P Thyssen MD, PhD, DMSci^{2,5,6}.

1) Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of
Copenhagen, Gentofte Hospitalsvej 15, Hellerup, Denmark

2) Copenhagen Research Group for Inflammatory Skin (CORGIS), Hellerup, Denmark

3) Department of Dermatology and Allergy and Christine Kühne-Center for Allergy Research and
Education (CK-CARE) Davos, University Hospital, Bonn, Germany.

4) Department of Dermatology, The George Washington University School of Medicine and Health
Sciences, Washington, DC 20037, USA

5) Department of Dermatology, Bispebjerg and Frederiksberg Hospital, University of Copenhagen,
Bispebjerg Bakke 23, Copenhagen, Denmark

6) LEO Pharma Foundation Skin Research Centre

Corresponding author

Jacob P. Thyssen, MD PhD DMSci

Department of Dermatology, Bispebjerg and Frederiksberg Hospital, University of Copenhagen,
Bispebjerg Bakke 23, 2400 Copenhagen, Denmark

E-mail: jacob.pontoppidan.thyssen@regionh.dk

Phone number: +45 3867 3150

Author Contributions

Knudgaard and Andreassen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Thyssen, Halling, Egeberg and Silverberg. *Acquisition, analysis, and interpretation of data:* All authors. *Drafting of the manuscript:* All authors. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Halling and Egeberg. *Administrative, technical, or material support:* None. *Study supervision:* Thyssen.

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Dr. Thyssen has attended advisory boards for Sanofi-Genzyme, Abbvie, Union Therapeutics, Pfizer, and Eli Lilly & Co, and received speaker honorarium from LEO Pharma and Sanofi-Genzyme, and been an investigator for Sanofi-Genzyme, Eli Lilly & Co, LEO Pharma and Abbvie. Dr. Egeberg has received research funding from Pfizer, Eli Lilly & Co, the Danish National Psoriasis Foundation, and the Kgl Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from AbbVie, Almirall, Bristol-Meyers Squibb, Dermavant, Leo Pharma, Samsung Bioepis Co., Ltd., UCB, Pfizer, Eli Lilly & Co, Novartis, Galderma, and Janssen Pharmaceuticals. Dr. Silverberg has received honoraria as an advisory board member or consultant from Abbvie, Anaptysbio, Asana, Eli Lilly, Galderma, GlaxoSmithKline, Kiniksa, Leo, Menlo, Pfizer, Regeneron-Sanofi, Realm, Roivant, and as a speaker for Regeneron-Sanofi. Dr. Bieber was speaker¹, and/or consultant² and/or Investigator³ for: AbbVie^{1, 2, 3}, Allmiral^{1, 2, 3}, AnaptysBio², Arena², Asana Biosciences², Astellas^{1, 2, 3}, BioVerSys², Böhringer-Ingelheim², Celgene², Daichi-Sankyo², Dermavant/Roivant², DermTreat³, DS Pharma², RAPT/FLX Bio², Galapagos/MorphoSys^{2, 3}, Galderma^{2, 3}, Glenmark^{2, 3}, GSK^{2, 3}, Incytes², Kymab^{2, 3}, LEO^{1, 2, 3}, Lilly^{1, 2, 3}, L'Oréal^{1, 2, 3}, MenloTx^{2, 3}, Novartis^{1, 2, 3}, Pfizer^{1, 2, 3}, Pierre Fabre², Sanofi/Regeneron^{1, 2, 3}, UCB². Thomas Bieber is founder of the non-profit biotech company "Davos Biosciences". Knudgaard, Andreasen, Ravnborg and Halling have no relevant interests to declare.

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Abbreviations used

AD: Atopic dermatitis

CI: Confidence interval

NOS: Newcastle-Ottawa scale

OR: Odds ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

sIgE: Specific IgE

SPT: Skin Prick Test

21-01-0009R1

Background: Atopic dermatitis (AD) and rhinitis are common atopic diseases that may co-occur due to an overlap in pathophysiology. While most cases of both diseases are mild and managed with topical anti-inflammatory medicaments, the advent of new systemic and biologic treatments targeting type 2 inflammation in both diseases warrant further insight in the exact overlap of AD and rhinitis.

Objective: To determine the association between AD and rhinitis.

Methods: A systematic review and meta-analysis of the databases Pubmed, Embase and CNKI was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Pooled prevalence and pooled odds ratios (OR) with 95% confidence intervals (95% CI) were calculated.

Results: The search resulted in 10,422 citations, and, respectively, 341 articles and 302 were included in the qualitative and quantitative analyses. The pooled prevalence of rhinitis was 40.5% (95% CI 39.0-42.0) in patients with atopic dermatitis and 18.0% (95% CI 16.7-19.2) in the reference individuals without atopic dermatitis. The pooled prevalence of having both rhinitis and asthma was 14.2% (95% CI 13.0-15.5) in patients with AD. There was an association between AD and, respectively, rhinitis (OR 3.00, 95% CI 2.83-3.18), allergic rhinitis (OR 3.25, 95% CI 2.26-4.66) and non-allergic rhinitis (OR 1.99, 95% CI 1.39-2.86).

Conclusion: Rhinitis, both allergic and non-allergic forms, is very common in patients with AD. Future investigations should clarify how medications targeting both diseases should be indicated in these patients.

1 Introduction

2 Atopic dermatitis (AD) is a common chronic and recurrent inflammatory skin disease that
3 often begins in early childhood, but which may persist as well as begin or recur in
4 adulthood^{1,2}.

5 It has been recognized for a long time that AD patients have an increased risk of developing
6 atopic conditions such as food allergy, rhinitis and asthma³. Atopy, i.e. the capacity to
7 synthesize IgE and develop allergic disease to common aero and food allergens, is found in
8 high proportions of patients with atopic conditions. However, it is becoming increasingly
9 apparent that type 2 (T2) inflammation is highly expressed across these disorders and
10 independent of atopy^{4,5}. The T2 immune response is characterized by production of
11 interleukin (IL)-4, IL-5, IL-9, IL-13, and IL-31 from e.g. mast cells, basophils, innate
12 lymphoid cells and T-helper (Th) 2 cells^{1,4}.

13 Since it has become possible to treat T2 inflammation in different tissues with the same
14 therapy^{1,6-8,9,10}, it is important to determine the proportion of AD patients who suffer from
15 airway disease with T2 inflammation as well as subtypes, as this may affect future treatment
16 strategies. In a recent systematic review and meta-analysis, a strong association was identified
17 between AD and asthma¹¹. In this article, we examined the prevalence of rhinitis as well as
18 combined rhinitis and asthma in AD patients, and the association between these conditions.

Methods

Protocol

Prior to study start, a protocol was submitted to PROSPERO (ID CRD42019138986)¹².

Literature search

The systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two authors (M.H.K and T.H.A) independently searched the databases PubMed, Embase and CNKI from their date of inception until June 2019. The search was restricted to human studies and English language studies and the utilized search terms are available as eSupplement material, see eTable 1. All titles and abstracts were screened for relevant studies and duplicates were removed. Full-text articles were retrieved if they fulfilled the inclusion criteria. Additional studies were identified from manual searches of reference lists found in included articles, including a recently completed meta-analysis, which examined the association between atopic dermatitis and asthma¹¹.

Inclusion and exclusion criteria

Studies were included if they reported data on the prevalence of rhinitis in AD patients, and irrespective of type and/or definition of rhinitis. Both studies with and without a control group were included. If a study had a sample size of less than 50 AD patients, it was excluded. There were no restrictions regarding age of participants, type of study design, or year of publication.

Data extraction

Data extraction was performed independently by two authors (M.H.K and T.H.A). The following data were collected from each study: study design, country of study, gender, age of participants, sample size, method used to diagnose AD and rhinitis, severity of AD and rhinitis, current or past clinical activity of AD and rhinitis, patients with both rhinitis and asthma, type of rhinitis (rhinoconjunctivitis, allergic rhinitis, non-allergic rhinitis), result of skin prick test (SPT), specific-IgE (sIgE) tests and age of AD onset. ~~Rhinitis was defined as being allergic in case of concomitant positive sIgE and/or a SPT test. Non-allergic rhinitis was defined in case of negative sIgE and/or a negative SPT test.~~ Allergic rhinitis was defined as rhinitis along with a positive sIgE and/or SPT test. Non-allergic rhinitis was defined as rhinitis along with a negative sIgE and/or SPT test. If sIgE and/or SPT test results were not presented, it was classified as rhinitis. AD and rhinitis were categorized as ‘clinical diagnoses’ when a physician had established the diagnosis, whereas questionnaire-based participant reported clinical diagnoses were categorized as ‘rhinitis’. Post hoc cut-offs defining early childhood-onset and late childhood-onset AD were made based on the respective studies definitions. Therefore, early childhood-onset of AD was defined as onset ≤ 2 years of age, and late childhood-onset of AD was defined as onset after 1-3 years of age, resulting in an overlap between early childhood- and late childhood-onset of AD. Adult-onset AD was defined as onset ≥ 18 years of age. If the same study population was presented in multiple publications, the publication with the most comprehensive data was included or, if data could fit into different analyses, data from both publications were included. All studies that examined the association between AD and rhinitis were included in the qualitative analysis. If study publications contained extractable data on the prevalence of rhinitis, or the association between AD and rhinitis, they were also included in the quantitative analysis. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of studies included in the

quantitative analysis¹³. NOS is a quality assessment tool used for cohort and case-control studies. It is based on the three variables: selection of study population, comparability, and ascertainment of exposure/outcomes (case-control studies and cohort studies, respectively) and results in a maximum score of nine points. An adapted version of NOS was used for cross-sectional studies with a maximum score of ten points. A score of six or higher were considered as a study of high quality for case-control and cohort studies and for cross-sectional studies a score of seven or higher were considered as a study of high quality. Work to identify and validate threshold scores for high- and low quality studies is still ongoing¹³, but earlier studies have used the above-mentioned thresholds^{14,15}. All studies were included in the quantitative analysis, irrespective of their NOS score.

Statistical analysis

The quantitative analysis was performed using StatsDirect version 3 (StatsDirect Ltd, Cheshire, U.K.). Pooled proportions with 95% confidence intervals (CI) and pooled odds ratios (ORs) with 95% CI were calculated for the overall populations and for pre-specified subgroups. Random effects models with DerSimonian–Laird methods were used for calculation of both proportions and ORs in all analyses, since significant between-study heterogeneity was observed. The heterogeneity was assessed using Cochran’s Q and I^2 statistics. All analyses showed $I^2 > 70\%$ and Cochran Q statistics P-values < 0.05 . Publication bias was evaluated by visual inspection of funnel plots of the included studies and forest plots were constructed for all analyses, to visually display the results. All statistical tests were two-sided with a significant level at $p < 0.05$.

Results

The literature search yielded a total of 10,422 non-duplicate articles. After screening titles and abstracts, 1,883 articles underwent full-text review. Of these 1,542 were excluded due to reasons listed in the PRISMA flow diagram (Fig 1).

A total of 341 studies were included in the qualitative analysis (328 unique studies) comprising 922,818 patients with AD and 6,148,789 reference individuals. Of these, 302 unique studies with details on 778,908 AD patients and 4,306,063 reference individuals were further included in the quantitative analysis. Detailed information on the included studies is available upon request.

Quantitative analysis

Rhinitis prevalence in atopic dermatitis patients

The overall random-effect prevalence of rhinitis among 778,908 patients with AD was 40.5% (95% CI 39.0-42.0) based on 302 studies. Among reference individuals without AD (165 studies, 4,306,013 reference individuals) the pooled prevalence of rhinitis was 18.0% (95% CI 16.7-19.2). The pooled prevalence of having both rhinitis and asthma in patients with AD (123 studies and 416,518 patients with AD) was 14.2% (95% CI 13.0-15.5) (Fig 2). When restricting the analysis to studies with a clinical diagnosis of both AD and rhinitis, the pooled prevalence of rhinitis was 39.4% (95% CI 36.8-42.0) based on data from 115 studies and 320,566 patients with AD, whereas the pooled prevalence of rhinitis was 44.3% (95% CI 39.4-49.1) in males with AD (25 studies, 35,000 males with AD) and 36.7% (95% CI 32.1-41.5) in females with AD (25 studies, 38,191 females with AD). When comparing children (178 studies, 524,194 children with AD) and adults (51 studies, 106,516 adults with AD), the pooled prevalence of rhinitis was higher in adults with AD (pooled prevalence 49.2%, 95% CI

45.3-53.1) than in children with AD (pooled prevalence 37.2%, 95% CI 35.2-39.1). Examining the prevalence of rhinitis in 5 age groups including 0-5, 6-11, 12-17, 18-44 and >45 years, respectively, showed a tendency towards an age dependent increase of rhinitis in patients with AD (Table 1). The pooled prevalence of rhinitis was 22.8% (95% CI 17.2-29.0), 33.0% (95% CI 27.0-39.4), 39.2% (95% CI 35.5-43.1), 50.9% (95% CI 40.8-60.9) and 41.5% (95% CI 24.5-59.4), respectively, listed from the youngest to oldest age group. The prevalence was highest in the age group 18-44 years and a tendency towards a decrease was observed in the oldest age group (>45 years).

Rhinitis prevalence by subtype of rhinitis

A total of 19 studies including 4,534 patients with AD and 12,212 reference individuals examined the occurrence of allergic rhinitis defined as a positive sIgE and/or a positive SPT test, and 16 studies including 4,187 patients with AD and 11,342 reference individuals examined the occurrence of non-allergic rhinitis defined as a negative sIgE and/or a negative SPT test. None of the included studies performed nasal biopsies. The pooled prevalence of allergic and non-allergic rhinitis was 29.3% (95% CI 22.3-36.9) and 12.3% (95% CI 8.4-16.7), respectively, among patients with AD. When restricting the analysis to rhinoconjunctivitis 22 studies were included. The pooled prevalence of rhinoconjunctivitis was 31.0% (95% CI 28.2-34.0) among 133,579 patients with AD.

Rhinitis prevalence by onset of atopic dermatitis

Six studies examined the prevalence of rhinitis in patients with early childhood-onset AD (88,345 patients with AD) and those with late childhood-onset AD (27,157 patients with AD). The prevalence of rhinitis was slightly elevated in those with early childhood-onset AD (pooled prevalence 39.3%, 95% CI 15.1-66.8) compared to late childhood-onset AD (pooled prevalence 33.7%, 95% CI 12.1-59.6). No data on rhinitis subtype was available for this

analysis. The pooled prevalence of rhinitis in patients with adult-onset AD (5 studies, 949 patients with AD) was 39.4% (95% CI 26.2-53.5).

Rhinitis prevalence by disease severity and activity

Seven studies examined the prevalence of rhinitis in patients with mild AD (4,805 patients with AD) and 23 studies examined patients with moderate-to-severe AD (6,210 patients with AD). The pooled prevalence of rhinitis was 34.1% (95% CI 21.5-48.1) and 51.8% (42.3-61.3) among patients with mild, and moderate-to-severe AD, respectively. When stratifying for the activity of AD and rhinitis (current AD versus ever AD and current rhinitis versus ever rhinitis) there was no difference in the prevalence (Table 1).

Rhinitis prevalence by study sample size, study design and Newcastle-Ottawa score

A total of 193 studies were cross-sectional, 66 were cohort studies, 35 were case-control studies and 8 were clinical trials. The pooled prevalence of rhinitis was higher in cross-sectional studies (pooled prevalence 42.3%, 95% CI 40.5-44.0) when compared to cohort studies (pooled prevalence 35.3%, 95% CI 31.8-38.9). Case-control studies and clinical trials showed a prevalence of 40.2% (95% CI 36.3-44.2) and 42.6% (95% CI 29.3-56.6), respectively. Studies with a population size >3000 individuals showed a significant lower prevalence of rhinitis (35.2%, 95% CI 32.8-37.5) compared to studies with a population <3000 individuals (pooled prevalence 43.1%, 95% CI 40.4-45.9). A total of 260 studies including 752,316 patients with AD, were of high quality and 34 studies including 23,935 patients with AD were of low quality. The overall prevalence was 40.0% (95% CI 38.4-41.5) and 45.3% (95% CI 39.4-51.3), respectively.

Rhinitis prevalence by continent

Studies originated from Africa (7 studies), Asia (74 studies), Australia (9 studies), Europe

(155 studies), the Middle East (21 studies), North America (32 studies), and South America (3 studies). The pooled prevalence of rhinitis was lower among patients with AD from Europe (pooled prevalence 38.1%, 95% CI 36.1-40.1) compared to North America (pooled prevalence 46.7%, 95% CI 41.9-51.5) and South America (52.2%, 95% CI 40.8-63.5). In Asia, where a potentially different immune response has been found in patients with AD¹⁶, the pooled prevalence of rhinitis in patients with AD was 42.2% (95% CI 39.0-45.4) (Table 1).

Association between atopic dermatitis and rhinitis

Analysis of 165 studies including 616,493 patients with AD and 4,306,013 reference individuals showed a compelling association between rhinitis and AD, with an overall OR of 3.00 (95% CI 2.83-3.18) (Fig 3). The association remained significant in all sensitivity analyses (for detailed information see Table 1). The association between allergic rhinitis and AD (OR 3.25, 95% CI 2.26-4.66, 12 studies, 2,606 patients with AD) was slightly stronger than between non-allergic rhinitis and AD (OR 1.99, 95% CI 1.39-2.86, 11 studies, 2,499 patients with AD) when allergic rhinitis was defined as a positive sIgE or a positive SPT test, but the difference between these two definitions was not significant (Fig 3). A significant difference was found between studies of high quality (OR 2.82, 95% CI 2.66-3.00, 154 studies, 599,646 patients with AD) and studies of low quality (OR 6.80, 95% CI 4.82-9.58, 12 studies, 16,847 patients with AD). Moreover, when examining the association in children compared to adults, it tended to be stronger in children compared to adults, but the association was non-significant.

Qualitative analysis

A total of 341 studies were included in the qualitative analysis, of which 22 studies were not included in the quantitative analysis. These 22 studies all confirmed the positive association

178 between AD and rhinitis¹⁷⁻³⁸. Six cohort studies examined the influence of age at onset of AD,
 179 on the association between AD and rhinitis. One American study found a decreased
 180 association between late childhood-onset AD (defined as onset at age ≥ 3 years) and rhinitis
 181 when compared to early childhood-onset AD (defined as onset at age ≤ 2 years) (adjusted
 182 relative risk ratio 0.91, 95% CI 0.88-0.95)³⁹. A Swedish study only found an association
 183 between early childhood-onset AD (defined as onset < 1 year) and rhinitis (OR 5.02, 95% CI
 184 3.58-7.05) when compared to reference individuals and no significant association between
 185 late childhood-onset AD (defined as onset at age ≥ 1 year) and rhinitis (OR 0.96, 95% CI 0.46-
 186 2.00)⁴⁰. A study from Canada found an association between early childhood persistent AD
 187 (defined as onset at age ≤ 2 years) and rhinitis (OR 3.47, 95% CI 1.34-8.99), but no
 188 association with early childhood-onset of non-persistent AD (OR 1.75, 95% CI 0.77-3.94) and
 189 late childhood-onset AD (defined as onset at age > 2 years) (OR 2.47, 95% CI 0.86-7.11)⁴¹.
 190 However, there was no significant difference between early childhood-onset persistent AD,
 191 and early childhood-onset non-persistent AD and late-onset AD⁴¹. Moreover, a European
 192 study only found a significant association with early childhood-onset (defined as onset at age
 193 < 2 years) persistent AD (OR 4.04, 95% CI 1.82-8.96) and rhinitis, but no association between
 194 early childhood-onset transient AD and rhinitis (OR 1.90, 95% CI 0.88-4.12)⁴². The same
 195 study found no difference between early childhood- and late childhood-onset AD and
 196 rhinitis⁴². Two studies, both from Taiwan, also found no difference between early childhood-
 197 and late childhood-onset AD in relation to developing rhinitis^{43,44}.

Discussion

Main findings

This systematic review and meta-analysis found that the overall prevalence of rhinitis was 40.5% (95% CI 39.0-42.0) in patients with AD and showed that AD was associated both with allergic and non-allergic rhinitis. The pooled prevalence of having both rhinitis and asthma in patients with AD was 14.2% (95% CI 13.0-15.5). Regional difference in prevalence was observed with higher estimates in North and South American populations compared to European population.

Interpretation

Our study expands previous knowledge since it firmly establishes that not only allergic rhinitis, but also non-allergic rhinitis, is more common in patients with AD than reference individuals. Allergic sensitization, either defined as a clinically relevant positive SPT or sIgE, works as a useful clinical and epidemiological tool to stratify patients with atopic diseases. In patients with allergic skin or airway manifestations, allergen avoidance or immunotherapy may lead to resolution of disease, whereas use of medications targeting free and membrane bound IgE may strongly reduce signs and symptoms of the disease⁴⁵⁻⁴⁷.

In recent years, the important role of T2 inflammation in epithelial disease has become apparent and with the advent of systemic and biological medications that specifically target this pathway, it will likely soon have ramifications on disease management. Thus, patients with T2 inflammatory disease, e.g. in the skin and airways, and where allergen management prove to be inadequate, may benefit from targeted therapy controlling T2 inflammation⁴⁸. We recently showed that 25.7% of AD patients had comorbid asthma, and in the current study, we also found that 14.2% of AD patients had concomitant asthma and rhinitis. Importantly,

allergic forms of these respiratory diseases have long been recognized as belonging to the same spectrum of diseases⁴⁹. There is reason to believe that certain forms of AD belong to the same disease spectrum. As to nasal polyposis, which is often characterized by T2 inflammation, current data are insufficient to determine whether an association between AD and nasal polyposis exists⁵⁰.

Our large systematic review and meta-analyses failed to capture enough studies with severe AD patients to show a significant difference in comorbid asthma or rhinitis between patients with mild, moderate and severe AD¹¹. Nonetheless, clinical trials including patients with very severe AD showed very high proportions of patients with a history of asthma and rhinitis, e.g. in the SOLO 1 and SOLO 2 trials in adult patients with moderate to severe AD, the prevalence of rhinitis was 50.2%⁵¹, and in the LIBERTY AD ADOL trial of adolescents with moderate to severe AD, a personal history of allergic rhinitis was found in 65.6% of the patients⁵². These findings indicate that, particularly patients with severe AD, might benefit from medication targeting T2 inflammatory pathways in several tissues and not only the skin. However, at present, the severity of rhinitis and asthma in patients with severe AD is unknown and future studies are needed to examine this to inform clinicians about treatment needs and management strategies. A retrospective cohort study from United Kingdom showed that patients with AD have a higher risk of common cutaneous and non-cutaneous infections and that the magnitude of the odds increased with the occurrence of allergic rhinitis or asthma⁵³, implying that a shared genetic link or inflammatory pathway between the atopic diseases might result in a higher susceptibility to infections.

This systematic review and meta-analysis found a tendency towards an increased prevalence of rhinitis in patients with early childhood-onset of AD (defined as onset ≤ 2 years of age) compared to later childhood-onset³⁹⁻⁴¹. The notion that late childhood-onset AD is associated

with a lower occurrence of other atopic traits, is also supported by recent studies where IgE levels were lowered in those with late childhood-onset disease⁵⁴⁻⁵⁶. While the difference, at least in part, may be explained by less severe AD in those with late disease onset, it is also possible that filaggrin gene (*FLG*) mutations may explain this observation. These are associated with both early childhood-onset of AD as well as persistent and severe disease⁵⁷⁻⁵⁹, whereas individuals with onset of AD after 8 years rarely have these mutations⁶⁰. A German study showed that *FLG* mutations increase the risk of allergic rhinitis, irrespective of AD status⁶¹, perhaps due to primary allergic sensitization which then leads to allergic airway disease following subsequent allergen exposure⁶².

We found a significantly stronger association between AD and rhinitis in studies of low quality compared to studies of high quality, indicating that the association could be overestimated in studies of low quality. However, most studies were of high quality and the OR for studies of high quality did not differ from our overall OR, indicating that the studies of low quality did not have any considerable effect on our results.

Strength and limitations

This systematic review and meta-analysis has many strengths including the strict methodology following the PRISMA guidelines and the large number of included studies showing similar results. The diagnosis of AD and rhinitis varied across studies leading to a potential misclassification of both diseases. We acknowledge that a positive SPT or sIgE test by no means can be used to determine whether rhinitis was of allergic origin, as it does not inform about exposure or clinical relevance. However, the analysis on rhinoconjunctivitis showed a similar prevalence suggesting that it was a fair assumption. We also acknowledge that the articles on which figure 2 was based may not be exhaustive, and selected studies may

not have examined both asthma and rhinitis in the target populations. As we only included studies in English, our results may not be generalizable to all populations. Moreover, only limited studies were included from the geographical regions; Africa, Australia and South America, which might also have affected the generalizability of our results. When restricting the analysis to studies with a large sample size, a slightly lower prevalence was found when compared to studies with a small sample size. The implication for this is unknown. Also, the cause for a higher prevalence in cross-sectional studies compared to cohort studies is unknown. Sub-analysis on perennial allergens, seasonal allergens, and mean age of onset of rhinitis were not examined due to limited data. Also, the pathophysiologic mechanism behind the association of non-allergic rhinitis and AD remains to be examined further. Future studies should address these topics.

In conclusion, the occurrence of rhinitis, both allergic and non-allergic, is very frequent in patients with AD in turn warranting the attention of physicians who care for these patients. New research indicates that epithelial diseases characterized by T2 inflammation belong to the same disease spectrum⁶. With the development of novel biological treatments that can target the T2 inflammatory response in different tissues at the same time, it is of great importance to further examine this relationship as it may affect future treatment strategies.

eTable 1. Search strategy

Database	Search strategy
EMBASE	(exp 'atopic dermatitis'/ OR 'atopic dermatitis' OR 'dermatitis atopic' OR exp 'eczema'/ OR 'eczema' OR 'childhood eczema' OR 'infantile eczema' OR 'neurodermatitis' OR exp 'neurodermatitis'/ OR 'Besnier's prurigo' OR ('Besnier's' AND 'prurigo')) AND (exp 'rhinitis'/ OR 'rhinitis' OR ('allergic' AND 'rhinitis') OR ('non-allergic' AND 'rhinitis') OR ('hay fever'))
MEDLINE (Pubmed)	("Dermatitis, Atopic"[Mesh] OR "atopic dermatitis"[all fields] OR "dermatitis atopic"[all fields] OR "Eczema"[Mesh] OR "eczema"[all fields] OR "childhood eczema"[all fields] OR "infantile eczema"[all fields] OR "neurodermatitis"[all fields] OR "Neurodermatitis"[Mesh] OR "Besnier's prurigo"[all fields] OR ("Besnier's"[all fields] AND "prurigo"[all fields])) AND ("rhinitis"[MeSH Terms] OR "rhinitis"[all fields] OR "allergic rhinitis"[all fields] OR "non-allergic rhinitis"[all fields] OR "hay fever")
CNKI	((Atopic dermatitis OR eczema) AND (rhinitis OR hay fever))

Table 1. The prevalence of rhinitis among patients with atopic dermatitis (left gray columns) and the association between atopic dermatitis and rhinitis (right brown columns).

Variable	Number of studies	Number of study participants with AD	Prevalence % (95% CI)	Number of studies	Number of study participants with AD	OR (95% CI)
Overall	302	778,908	40.5 (39.0-42.0)	165	616,493	3.00 (2.83-3.18)
Definition of disease						
Clinically diagnosed AD	153	461,130	40.2 (38.0-42.3)	38	310,073	2.45 (2.16-2.78)
Clinically diagnosed AD and rhinitis	115	320,566	39.4 (36.8-42.0)	34	191,069	2.13 (1.82-2.49)
Allergic rhinitis	19 [†]	4,534	29.3 (22.3-36.9)	12	2,606	3.25 (2.26-4.66)
Non-allergic rhinitis	16 [‡]	4,187	12.3 (8.4-16.7)	11	2,499	1.99 (1.39-2.86)
Rhinoconjunctivitis	22	133,579	31.0 (28.2-34.0)	17	132,820	3.74 (3.41-4.10)
Participants with both AD, rhinitis and asthma	123	416,518	14.2 (13.0-15.5)	71	309,338	3.16 (2.75-3.63)
Sex						
Female	25	38,191	36.7 (32.1-41.5)	16	15,202	2.17 (1.63-2.90)
Male	25	35,000	44.3 (39.4-49.1)	16	15,769	2.80 (2.37-3.29)
Age						
Children <18	178	524,194	37.2 (35.2-39.1)	109	446,548	3.15 (2.96-3.35)
Adults ≥18	51	106,516	49.2 (45.3-53.1)	28	51,427	2.40 (1.73-3.32)
0-5	20	5,025	22.8 (17.2-29.0)	13	4,285	3.43 (2.63- 4.47)
6-11	31	45,535	33.0 (27.0-39.4)	31	45,533	3.10 (2.64-3.64)
12-17	16	89,782	39.2 (35.5-43.1)	13	71,507	3.21 (2.75-3.74)
18-44	14	6,272	50.9 (40.8-60.9)	10	5,639	2.40 (1.82-3.15)
45+	3	8,945	41.5 (24.5-59.4)	2	8,866	4.35 (2.43-7.80)
Age of onset						
Early childhood-onset ≤2	6	88,345	39.3 (15.1-66.8)	-	-	-
Late childhood onset 1-3	6	27,157	33.7 (12.1-59.6)	-	-	-
Adult onset ≥18	5	949	39.4 (26.2-53.5)	-	-	-
Region						
Europe	155	298,017	38.1 (36.1-40.1)	86	164,705	2.85 (2.58-3.14)
Asia	74	289,389	42.2 (39.0-45.4)	35	216,288	2.70 (2.44-2.99)
North America	32	60,565	46.7 (41.9-51.5)	19	47,575	3.03 (2.58-3.55)
Middle-East	21	5,719	42.0 (32.8-51.4)	17	8,969	3.20 (2.29-4.48)
Australia	9	9,327	36.3 (30.0-42.9)	6	8,189	4.03 (2.73-5.94)
Africa	7	10,479	33.3 (17.2-51.7)	6	10,379	4.90 (2.13-11.28)
South America	3	598	52.2 (40.8-63.5)	-	-	-
AD severity						
Mild	7	4,805	34.1 (21.5-48.1)	-	-	-
Moderate/severe	23	6,210	51.8 (42.3-61.3)	5	684	3.78 (2.29-6.33)

Disease activity						
AD current	141	214,362	40.7 (38.5-43.0)	69	185,814	2.99 (2.73-3.28)
AD lifetime	49	138,532	39.1 (34.9-43.3)	36	134,490	3.31 (2.95-3.71)
Rhinitis current	101	193,804	41.3 (38.9-43.8)	60	177,253	2.84 (2.61-3.10)
Rhinitis lifetime	64	146,612	39.4 (35.3-43.6)	42	139,839	3.27 (2.91-3.68)
Study design, sample size						
Cross-sectional	193	444,557	42.3 (40.5-44.0)	109	312,825	3.15 (2.94-3.37)
Cohort	66	160,768	35.3 (31.8-38.9)	42	137,235	2.54 (2.24-2.89)
Case-control	35	170,693	40.2 (36.3-44.2)	19	168,257	3.43 (2.72-4.32)
Clinical trials	8	2,571	42.6 (29.3-56.6)	-	-	-
n <3000	208	48,401	43.1 (40.4-45.9)	85	19,343	2.92 (2.58-3.31)
n ≥3000	94	730,198	35.2 (32.8-37.5)	79	591,240	3.21 (2.96-3.47)
NOS score						
High quality	260	752,316	40.0 (38.4-41.5)	154	599,646	2.82 (2.66-3.00)
Low quality	34	23,935	45.3 (39.4-51.3)	12	16,847	6.80 (4.82-9.58)

AD = Atopic dermatitis, CI = Confidence interval, NOS = Newcastle-Ottawa Scale, OR = Odds ratio

†: 14 studies tested for aeroallergens, 5 studies for food and aeroallergens

‡: 11 studies tested for aeroallergens, 5 studies for food and aeroallergens

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram

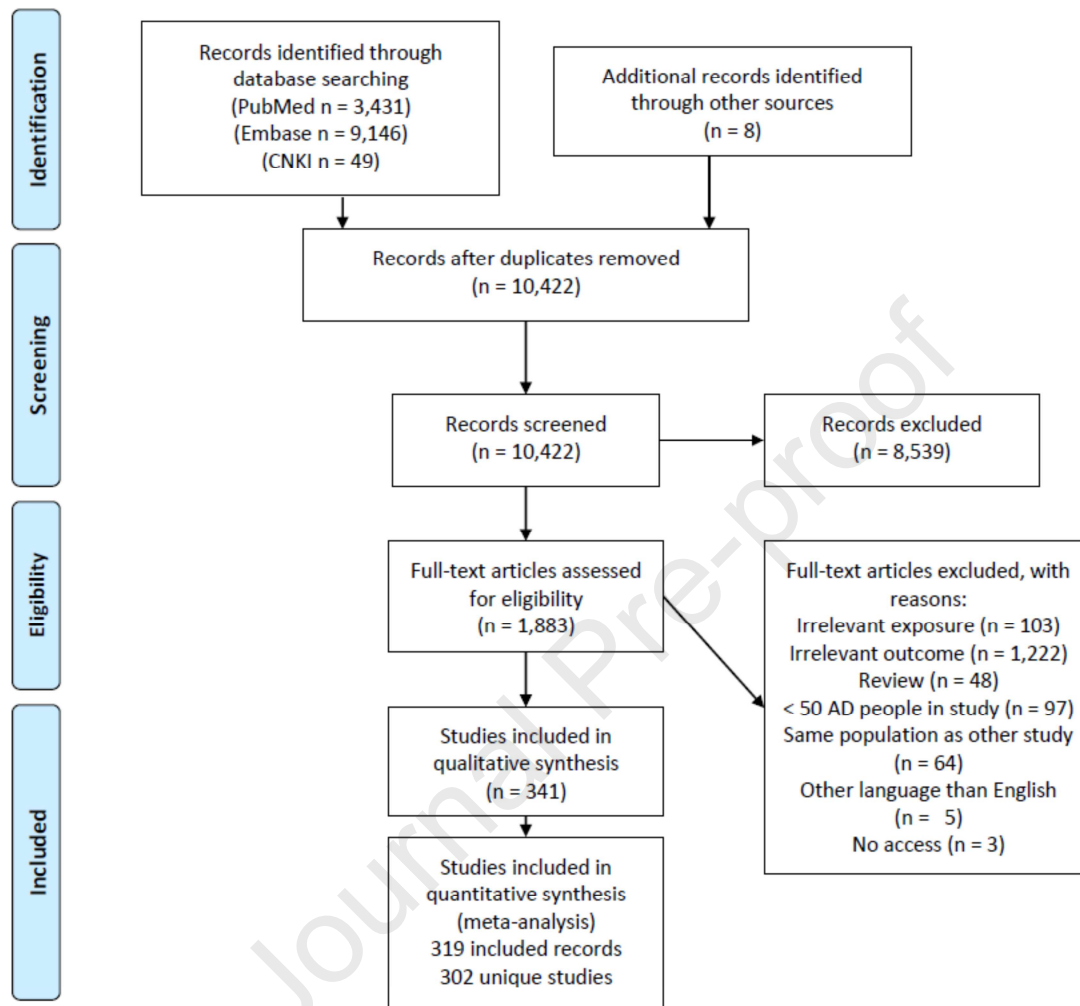


Figure 2. The prevalence of rhinitis and asthma in patients with atopic dermatitis (a) and in reference individuals (b) ¹

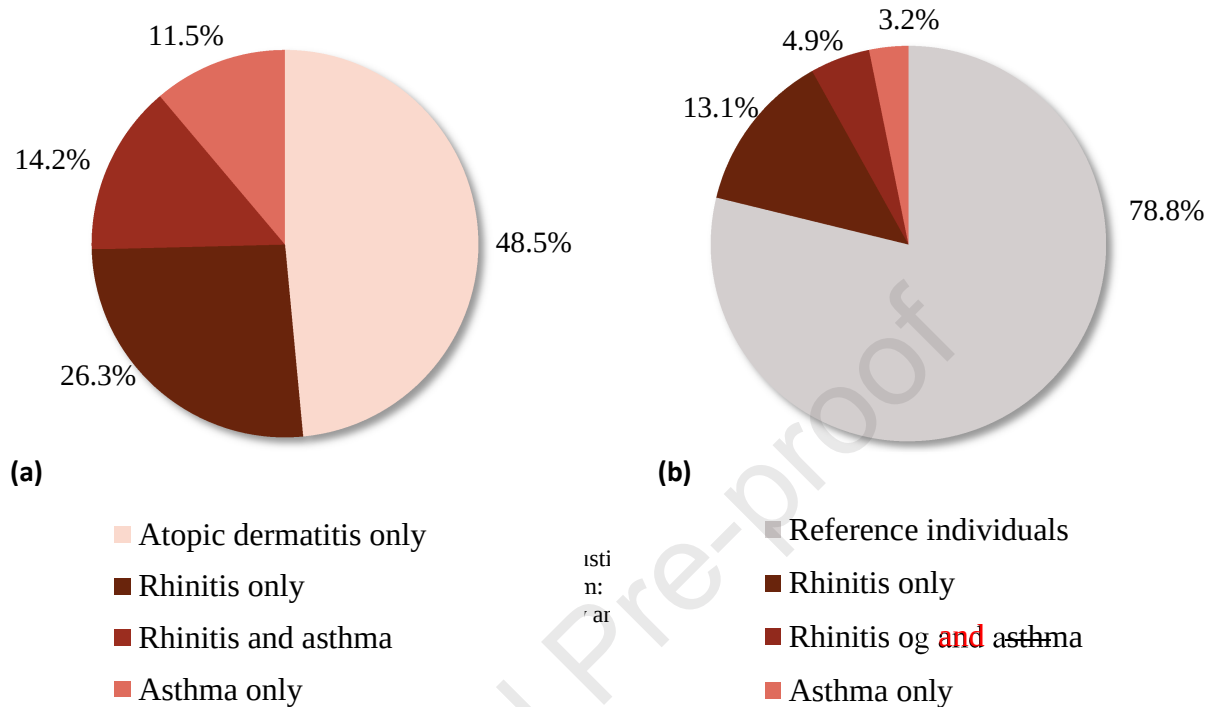


Figure 2. The prevalence of rhinitis and asthma in patients with atopic dermatitis (a) and in reference individuals (b) ¹

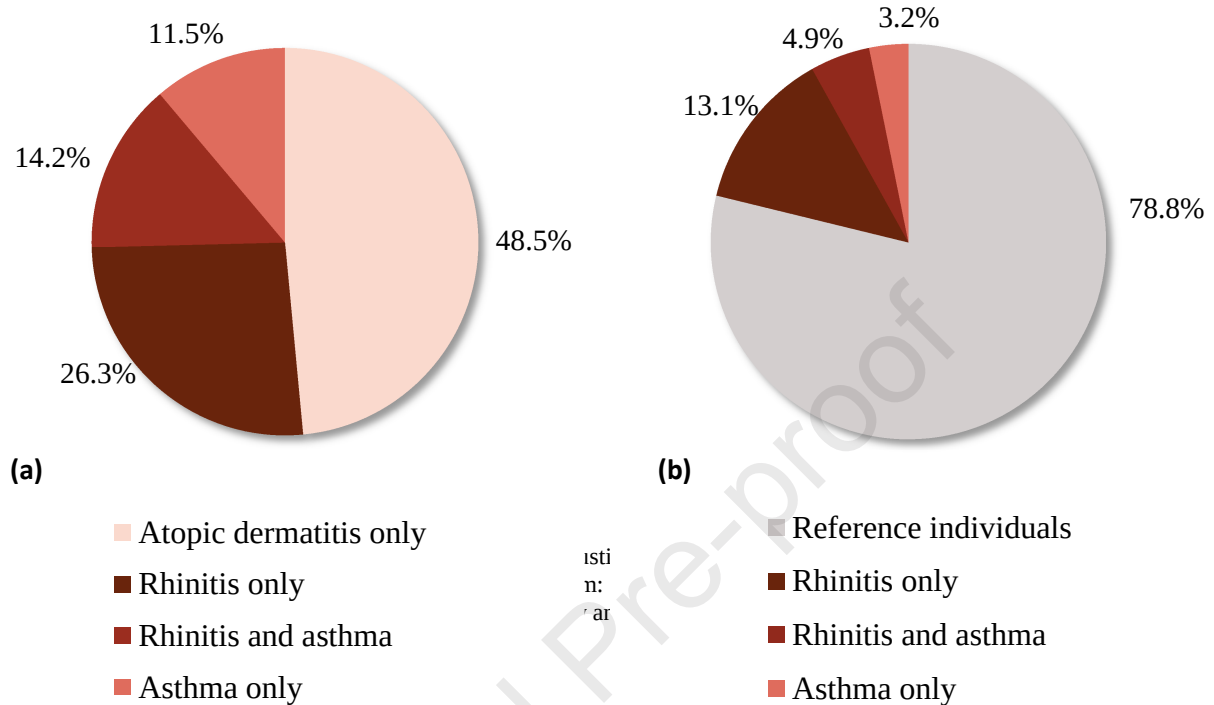
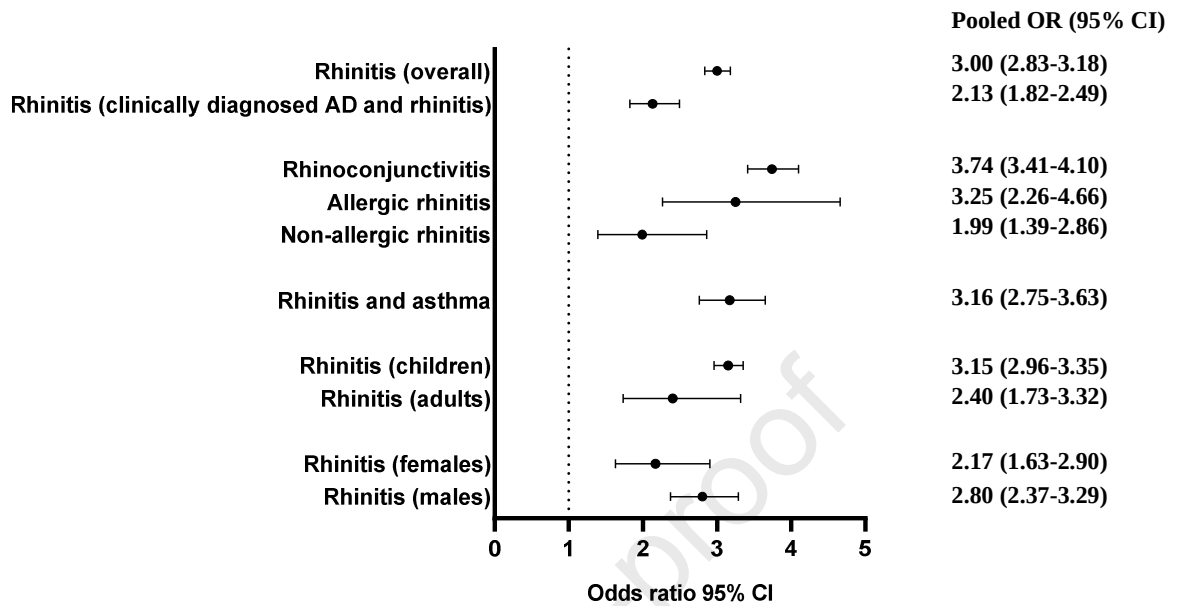


Figure 3. Forest plot of the pooled odds ratios (OR) with 95% confidence intervals (CI) calculated for the association between atopic dermatitis (AD) and rhinitis.



Title Page**Title**

Rhinitis prevalence and association with atopic dermatitis: A systematic review and meta-analysis

Author names, academic degrees, affiliation(s) of the authors

Mette Hjorslev Knudgaard MD^{1,2}; Thomas Holger Andreasen MD^{1,2}; Nanna Ravnborg MD^{1,2};
Thomas Bieber MD, PhD, MDRA³; Jonathan I Silverberg MD, PhD, MPH⁴; Alexander Egeberg
MD, PhD^{1,2}; Anne-Sofie Halling MD^{1,2}; Jacob P Thyssen MD, PhD, DMSci^{2,5,6}.

1) Department of Dermatology and Allergy, Herlev and Gentofte Hospital, University of
Copenhagen, Gentofte Hospitalsvej 15, Hellerup, Denmark

2) Copenhagen Research Group for Inflammatory Skin (CORGIS), Hellerup, Denmark

3) Department of Dermatology and Allergy and Christine Kühne-Center for Allergy Research and
Education (CK-CARE) Davos, University Hospital, Bonn, Germany.

4) Department of Dermatology, The George Washington University School of Medicine and Health
Sciences, Washington, DC 20037, USA

5) Department of Dermatology, Bispebjerg and Frederiksberg Hospital, University of Copenhagen,
Bispebjerg Bakke 23, Copenhagen, Denmark

6) LEO Pharma Foundation Skin Research Centre

Corresponding author

Jacob P. Thyssen, MD PhD DMSci

Department of Dermatology, Bispebjerg and Frederiksberg Hospital, University of Copenhagen,
Bispebjerg Bakke 23, 2400 Copenhagen, Denmark

E-mail: jacob.pontoppidan.thyssen@regionh.dk

Phone number: +45 3867 3150

Author Contributions

Knudgaard and Andreassen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Thyssen, Halling, Egeberg and Silverberg. *Acquisition, analysis, and interpretation of data:* All authors. *Drafting of the manuscript:* All authors. *Critical revision of the manuscript for important intellectual content:* All authors. *Statistical analysis:* Halling and Egeberg. *Administrative, technical, or material support:* None. *Study supervision:* Thyssen.

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Dr. Thyssen has attended advisory boards for Sanofi-Genzyme, Abbvie, Union Therapeutics, Pfizer, and Eli Lilly & Co, and received speaker honorarium from LEO Pharma and Sanofi-Genzyme, and been an investigator for Sanofi-Genzyme, Eli Lilly & Co, LEO Pharma and Abbvie. Dr. Egeberg has received research funding from Pfizer, Eli Lilly & Co, the Danish National Psoriasis Foundation, and the Kgl Hofbundtmager Aage Bang Foundation, and honoraria as consultant and/or speaker from AbbVie, Almirall, Bristol-Meyers Squibb, Dermavant, Leo Pharma, Samsung Bioepis Co., Ltd., UCB, Pfizer, Eli Lilly & Co, Novartis, Galderma, and Janssen Pharmaceuticals. Dr. Silverberg has received honoraria as an advisory board member or consultant from Abbvie, Anaptysbio, Asana, Eli Lilly, Galderma, GlaxoSmithKline, Kiniksa, Leo, Menlo, Pfizer, Regeneron-Sanofi, Realm, Roivant, and as a speaker for Regeneron-Sanofi. Dr. Bieber was speaker¹, and/or consultant² and/or Investigator³ for: AbbVie^{1, 2, 3}, Allmiral^{1, 2, 3}, AnaptysBio², Arena², Asana Biosciences², Astellas^{1, 2, 3}, BioVerSys², Böhringer-Ingelheim², Celgene², Daichi-Sankyo², Dermavant/Roivant², DermTreat³, DS Pharma², RAPT/FLX Bio², Galapagos/MorphoSys^{2, 3}, Galderma^{2, 3}, Glenmark^{2, 3}, GSK^{2, 3}, Incytes², Kymab^{2, 3}, LEO^{1, 2, 3}, Lilly^{1, 2, 3}, L'Oréal^{1, 2, 3}, MenloTx^{2, 3}, Novartis^{1, 2, 3}, Pfizer^{1, 2, 3}, Pierre Fabre², Sanofi/Regeneron^{1, 2, 3}, UCB². Thomas Bieber is founder of the non-profit biotech company "Davos Biosciences". Knudgaard, Andreasen, Ravnborg and Halling have no relevant interests to declare.

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Abbreviations used

AD: Atopic dermatitis

CI: Confidence interval

NOS: Newcastle-Ottawa scale

OR: Odds ratio

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

sIgE: Specific IgE

SPT: Skin Prick Test

1 Introduction

2 Atopic dermatitis (AD) is a common chronic and recurrent inflammatory skin disease that
3 often begins in early childhood, but which may persist as well as begin or recur in
4 adulthood^{1,2}.

5 It has been recognized for a long time that AD patients have an increased risk of developing
6 atopic conditions such as food allergy, rhinitis and asthma³. Atopy, i.e. the capacity to
7 synthesize IgE and develop allergic disease to common aero and food allergens, is found in
8 high proportions of patients with atopic conditions. However, it is becoming increasingly
9 apparent that type 2 (T2) inflammation is highly expressed across these disorders and
10 independent of atopy^{4,5}. The T2 immune response is characterized by production of
11 interleukin (IL)-4, IL-5, IL-9, IL-13, and IL-31 from e.g. mast cells, basophils, innate
12 lymphoid cells and T-helper (Th) 2 cells^{1,4}.

13 Since it has become possible to treat T2 inflammation in different tissues with the same
14 therapy^{1,6-9}, it is important to determine the proportion of AD patients who suffer from airway
15 disease with T2 inflammation as well as subtypes, as this may affect future treatment
16 strategies. In a recent systematic review and meta-analysis, a strong association was identified
17 between AD and asthma¹⁰. In this article, we examined the prevalence of rhinitis as well as
18 combined rhinitis and asthma in AD patients, and the association between these conditions.

Methods

Protocol

Prior to study start, a protocol was submitted to PROSPERO (ID CRD42019138986)¹¹.

Literature search

The systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two authors (M.H.K and T.H.A) independently searched the databases PubMed, Embase and CNKI from their date of inception until June 2019. The search was restricted to human studies and English language studies and the utilized search terms are available as eSupplement material, see eTable 1. All titles and abstracts were screened for relevant studies and duplicates were removed. Full-text articles were retrieved if they fulfilled the inclusion criteria. Additional studies were identified from manual searches of reference lists found in included articles, including a recently completed meta-analysis, which examined the association between atopic dermatitis and asthma¹⁰.

Inclusion and exclusion criteria

Studies were included if they reported data on the prevalence of rhinitis in AD patients, and irrespective of type and/or definition of rhinitis. Both studies with and without a control group were included. If a study had a sample size of less than 50 AD patients, it was excluded. There were no restrictions regarding age of participants, type of study design, or year of publication.

Data extraction

Data extraction was performed independently by two authors (M.H.K and T.H.A). The following data were collected from each study: study design, country of study, gender, age of participants, sample size, method used to diagnose AD and rhinitis, severity of AD and rhinitis, current or past clinical activity of AD and rhinitis, patients with both rhinitis and asthma, type of rhinitis (rhinoconjunctivitis, allergic rhinitis, non-allergic rhinitis), result of skin prick test (SPT), specific-IgE (sIgE) tests and age of AD onset. Allergic rhinitis was defined as rhinitis along with a positive sIgE and/or SPT test. Non-allergic rhinitis was defined as rhinitis along with a negative sIgE and/or SPT test. If sIgE and/or SPT test results were not presented, it was classified as rhinitis. AD and rhinitis were categorized as 'clinical diagnoses' when a physician had established the diagnosis, whereas questionnaire-based participant reported clinical diagnoses were categorized as 'rhinitis'. Post hoc cut-offs defining early childhood-onset and late childhood-onset AD were made based on the respective studies definitions. Therefore, early childhood-onset of AD was defined as onset ≤ 2 years of age, and late childhood-onset of AD was defined as onset after 1-3 years of age, resulting in an overlap between early childhood- and late childhood-onset of AD. Adult-onset AD was defined as onset ≥ 18 years of age. If the same study population was presented in multiple publications, the publication with the most comprehensive data was included or, if data could fit into different analyses, data from both publications were included. All studies that examined the association between AD and rhinitis were included in the qualitative analysis. If study publications contained extractable data on the prevalence of rhinitis, or the association between AD and rhinitis, they were also included in the quantitative analysis. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of studies included in the quantitative analysis¹². NOS is a quality assessment tool used for cohort and case-control studies. It is based on the three variables: selection of study population, comparability, and

ascertainment of exposure/outcomes (case-control studies and cohort studies, respectively) and results in a maximum score of nine points. An adapted version of NOS was used for cross-sectional studies with a maximum score of ten points. A score of six or higher were considered as a study of high quality for case-control and cohort studies and for cross-sectional studies a score of seven or higher were considered as a study of high quality. Work to identify and validate threshold scores for high- and low quality studies is still ongoing¹², but earlier studies have used the above-mentioned thresholds^{13,14}. All studies were included in the quantitative analysis, irrespective of their NOS score.

Statistical analysis

The quantitative analysis was performed using StatsDirect version 3 (StatsDirect Ltd, Cheshire, U.K.). Pooled proportions with 95% confidence intervals (CI) and pooled odds ratios (ORs) with 95% CI were calculated for the overall populations and for pre-specified subgroups. Random effects models with DerSimonian–Laird methods were used for calculation of both proportions and ORs in all analyses, since significant between-study heterogeneity was observed. The heterogeneity was assessed using Cochran’s Q and I^2 statistics. All analyses showed $I^2 > 70\%$ and Cochran Q statistics P-values < 0.05 . Publication bias was evaluated by visual inspection of funnel plots of the included studies and forest plots were constructed for all analyses, to visually display the results. All statistical tests were two-sided with a significant level at $p < 0.05$.

Results

The literature search yielded a total of 10,422 non-duplicate articles. After screening titles and abstracts, 1,883 articles underwent full-text review. Of these 1,542 were excluded due to reasons listed in the PRISMA flow diagram (Fig 1).

A total of 341 studies were included in the qualitative analysis (328 unique studies) comprising 922,818 patients with AD and 6,148,789 reference individuals. Of these, 302 unique studies with details on 778,908 AD patients and 4,306,063 reference individuals were further included in the quantitative analysis. Detailed information on the included studies is available upon request.

Quantitative analysis

Rhinitis prevalence in atopic dermatitis patients

The overall random-effect prevalence of rhinitis among 778,908 patients with AD was 40.5% (95% CI 39.0-42.0) based on 302 studies. Among reference individuals without AD (165 studies, 4,306,013 reference individuals) the pooled prevalence of rhinitis was 18.0% (95% CI 16.7-19.2). The pooled prevalence of having both rhinitis and asthma in patients with AD (123 studies and 416,518 patients with AD) was 14.2% (95% CI 13.0-15.5) (Fig 2). When restricting the analysis to studies with a clinical diagnosis of both AD and rhinitis, the pooled prevalence of rhinitis was 39.4% (95% CI 36.8-42.0) based on data from 115 studies and 320,566 patients with AD, whereas the pooled prevalence of rhinitis was 44.3% (95% CI 39.4-49.1) in males with AD (25 studies, 35,000 males with AD) and 36.7% (95% CI 32.1-41.5) in females with AD (25 studies, 38,191 females with AD). When comparing children (178 studies, 524,194 children with AD) and adults (51 studies, 106,516 adults with AD), the pooled prevalence of rhinitis was higher in adults with AD (pooled prevalence 49.2%, 95% CI

45.3-53.1) than in children with AD (pooled prevalence 37.2%, 95% CI 35.2-39.1). Examining the prevalence of rhinitis in 5 age groups including 0-5, 6-11, 12-17, 18-44 and >45 years, respectively, showed a tendency towards an age dependent increase of rhinitis in patients with AD (Table 1). The pooled prevalence of rhinitis was 22.8% (95% CI 17.2-29.0), 33.0% (95% CI 27.0-39.4), 39.2% (95% CI 35.5-43.1), 50.9% (95% CI 40.8-60.9) and 41.5% (95% CI 24.5-59.4), respectively, listed from the youngest to oldest age group. The prevalence was highest in the age group 18-44 years and a tendency towards a decrease was observed in the oldest age group (>45 years).

Rhinitis prevalence by subtype of rhinitis

A total of 19 studies including 4,534 patients with AD and 12,212 reference individuals examined the occurrence of allergic rhinitis defined as a positive sIgE and/or a positive SPT test, and 16 studies including 4,187 patients with AD and 11,342 reference individuals examined the occurrence of non-allergic rhinitis defined as a negative sIgE and/or a negative SPT test. None of the included studies performed nasal biopsies. The pooled prevalence of allergic and non-allergic rhinitis was 29.3% (95% CI 22.3-36.9) and 12.3% (95% CI 8.4-16.7), respectively, among patients with AD. When restricting the analysis to rhinoconjunctivitis 22 studies were included. The pooled prevalence of rhinoconjunctivitis was 31.0% (95% CI 28.2-34.0) among 133,579 patients with AD.

Rhinitis prevalence by onset of atopic dermatitis

Six studies examined the prevalence of rhinitis in patients with early childhood-onset AD (88,345 patients with AD) and those with late childhood-onset AD (27,157 patients with AD). The prevalence of rhinitis was slightly elevated in those with early childhood-onset AD (pooled prevalence 39.3%, 95% CI 15.1-66.8) compared to late childhood-onset AD (pooled prevalence 33.7%, 95% CI 12.1-59.6). No data on rhinitis subtype was available for this

analysis. The pooled prevalence of rhinitis in patients with adult-onset AD (5 studies, 949 patients with AD) was 39.4% (95% CI 26.2-53.5).

Rhinitis prevalence by disease severity and activity

Seven studies examined the prevalence of rhinitis in patients with mild AD (4,805 patients with AD) and 23 studies examined patients with moderate-to-severe AD (6,210 patients with AD). The pooled prevalence of rhinitis was 34.1% (95% CI 21.5-48.1) and 51.8% (42.3-61.3) among patients with mild, and moderate-to-severe AD, respectively. When stratifying for the activity of AD and rhinitis (current AD versus ever AD and current rhinitis versus ever rhinitis) there was no difference in the prevalence (Table 1).

Rhinitis prevalence by study sample size, study design and Newcastle-Ottawa score

A total of 193 studies were cross-sectional, 66 were cohort studies, 35 were case-control studies and 8 were clinical trials. The pooled prevalence of rhinitis was higher in cross-sectional studies (pooled prevalence 42.3%, 95% CI 40.5-44.0) when compared to cohort studies (pooled prevalence 35.3%, 95% CI 31.8-38.9). Case-control studies and clinical trials showed a prevalence of 40.2% (95% CI 36.3-44.2) and 42.6% (95% CI 29.3-56.6), respectively. Studies with a population size >3000 individuals showed a significant lower prevalence of rhinitis (35.2%, 95% CI 32.8-37.5) compared to studies with a population <3000 individuals (pooled prevalence 43.1%, 95% CI 40.4-45.9). A total of 260 studies including 752,316 patients with AD, were of high quality and 34 studies including 23,935 patients with AD were of low quality. The overall prevalence was 40.0% (95% CI 38.4-41.5) and 45.3% (95% CI 39.4-51.3), respectively.

Rhinitis prevalence by continent

Studies originated from Africa (7 studies), Asia (74 studies), Australia (9 studies), Europe

(155 studies), the Middle East (21 studies), North America (32 studies), and South America (3 studies). The pooled prevalence of rhinitis was lower among patients with AD from Europe (pooled prevalence 38.1%, 95% CI 36.1-40.1) compared to North America (pooled prevalence 46.7%, 95% CI 41.9-51.5) and South America (52.2%, 95% CI 40.8-63.5). In Asia, where a potentially different immune response has been found in patients with AD¹⁵, the pooled prevalence of rhinitis in patients with AD was 42.2% (95% CI 39.0-45.4) (Table 1).

Association between atopic dermatitis and rhinitis

Analysis of 165 studies including 616,493 patients with AD and 4,306,013 reference individuals showed a compelling association between rhinitis and AD, with an overall OR of 3.00 (95% CI 2.83-3.18) (Fig 3). The association remained significant in all sensitivity analyses (for detailed information see Table 1). The association between allergic rhinitis and AD (OR 3.25, 95% CI 2.26-4.66, 12 studies, 2,606 patients with AD) was slightly stronger than between non-allergic rhinitis and AD (OR 1.99, 95% CI 1.39-2.86, 11 studies, 2,499 patients with AD) when allergic rhinitis was defined as a positive sIgE or a positive SPT test, but the difference between these two definitions was not significant (Fig 3). A significant difference was found between studies of high quality (OR 2.82, 95% CI 2.66-3.00, 154 studies, 599,646 patients with AD) and studies of low quality (OR 6.80, 95% CI 4.82-9.58, 12 studies, 16,847 patients with AD). Moreover, when examining the association in children compared to adults, it tended to be stronger in children compared to adults, but the association was non-significant.

Qualitative analysis

A total of 341 studies were included in the qualitative analysis, of which 22 studies were not included in the quantitative analysis. These 22 studies all confirmed the positive association

176 between AD and rhinitis¹⁶⁻³⁷. Six cohort studies examined the influence of age at onset of AD,
177 on the association between AD and rhinitis. One American study found a decreased
178 association between late childhood-onset AD (defined as onset at age ≥ 3 years) and rhinitis
179 when compared to early childhood-onset AD (defined as onset at age ≤ 2 years) (adjusted
180 relative risk ratio 0.91, 95% CI 0.88-0.95)³⁸. A Swedish study only found an association
181 between early childhood-onset AD (defined as onset < 1 year) and rhinitis (OR 5.02, 95% CI
182 3.58-7.05) when compared to reference individuals and no significant association between
183 late childhood-onset AD (defined as onset at age ≥ 1 year) and rhinitis (OR 0.96, 95% CI 0.46-
184 2.00)³⁹. A study from Canada found an association between early childhood persistent AD
185 (defined as onset at age ≤ 2 years) and rhinitis (OR 3.47, 95% CI 1.34-8.99), but no
186 association with early childhood-onset of non-persistent AD (OR 1.75, 95% CI 0.77-3.94) and
187 late childhood-onset AD (defined as onset at age > 2 years) (OR 2.47, 95% CI 0.86-7.11)⁴⁰.
188 However, there was no significant difference between early childhood-onset persistent AD,
189 and early childhood-onset non-persistent AD and late-onset AD⁴⁰. Moreover, a European
190 study only found a significant association with early childhood-onset (defined as onset at age
191 < 2 years) persistent AD (OR 4.04, 95% CI 1.82-8.96) and rhinitis, but no association between
192 early childhood-onset transient AD and rhinitis (OR 1.90, 95% CI 0.88-4.12)⁴¹. The same
193 study found no difference between early childhood- and late childhood-onset AD and
194 rhinitis⁴¹. Two studies, both from Taiwan, also found no difference between early childhood-
195 and late childhood-onset AD in relation to developing rhinitis^{42,43}.

Discussion

Main findings

This systematic review and meta-analysis found that the overall prevalence of rhinitis was 40.5% (95% CI 39.0-42.0) in patients with AD and showed that AD was associated both with allergic and non-allergic rhinitis. The pooled prevalence of having both rhinitis and asthma in patients with AD was 14.2% (95% CI 13.0-15.5). Regional difference in prevalence was observed with higher estimates in North and South American populations compared to European population.

Interpretation

Our study expands previous knowledge since it firmly establishes that not only allergic rhinitis, but also non-allergic rhinitis, is more common in patients with AD than reference individuals. Allergic sensitization, either defined as a clinically relevant positive SPT or sIgE, works as a useful clinical and epidemiological tool to stratify patients with atopic diseases. In patients with allergic skin or airway manifestations, allergen avoidance or immunotherapy may lead to resolution of disease, whereas use of medications targeting free and membrane bound IgE may strongly reduce signs and symptoms of the disease^{44,45}.

In recent years, the important role of T2 inflammation in epithelial disease has become apparent and with the advent of systemic and biological medications that specifically target this pathway, it will likely soon have ramifications on disease management. Thus, patients with T2 inflammatory disease, e.g. in the skin and airways, and where allergen management prove to be inadequate, may benefit from targeted therapy controlling T2 inflammation⁴⁶. We recently showed that 25.7% of AD patients had comorbid asthma, and in the current study, we also found that 14.2% of AD patients had concomitant asthma and rhinitis. Importantly,

allergic forms of these respiratory diseases have long been recognized as belonging to the same spectrum of diseases⁴⁷. There is reason to believe that certain forms of AD belong to the same disease spectrum. As to nasal polyposis, which is often characterized by T2 inflammation, current data are insufficient to determine whether an association between AD and nasal polyposis exists⁴⁸.

Our large systematic review and meta-analyses failed to capture enough studies with severe AD patients to show a significant difference in comorbid asthma or rhinitis between patients with mild, moderate and severe AD¹⁰. Nonetheless, clinical trials including patients with very severe AD showed very high proportions of patients with a history of asthma and rhinitis, e.g. in the SOLO 1 and SOLO 2 trials in adult patients with moderate to severe AD, the prevalence of rhinitis was 50.2%⁴⁹, and in the LIBERTY AD ADOL trial of adolescents with moderate to severe AD, a personal history of allergic rhinitis was found in 65.6% of the patients⁵⁰. These findings indicate that, particularly patients with severe AD, might benefit from medication targeting T2 inflammatory pathways in several tissues and not only the skin. However, at present, the severity of rhinitis and asthma in patients with severe AD is unknown and future studies are needed to examine this to inform clinicians about treatment needs and management strategies. A retrospective cohort study from United Kingdom showed that patients with AD have a higher risk of common cutaneous and non-cutaneous infections and that the magnitude of the odds increased with the occurrence of allergic rhinitis or asthma⁵¹, implying that a shared genetic link or inflammatory pathway between the atopic diseases might result in a higher susceptibility to infections.

This systematic review and meta-analysis found a tendency towards an increased prevalence of rhinitis in patients with early childhood-onset of AD (defined as onset ≤ 2 years of age) compared to later childhood-onset³⁸⁻⁴⁰. The notion that late childhood-onset AD is associated

with a lower occurrence of other atopic traits, is also supported by recent studies where IgE levels were lowered in those with late childhood-onset disease⁵²⁻⁵⁴. While the difference, at least in part, may be explained by less severe AD in those with late disease onset, it is also possible that filaggrin gene (*FLG*) mutations may explain this observation. These are associated with both early childhood-onset of AD as well as persistent and severe disease⁵⁵⁻⁵⁷, whereas individuals with onset of AD after 8 years rarely have these mutations⁵⁸. A German study showed that *FLG* mutations increase the risk of allergic rhinitis, irrespective of AD status⁵⁹, perhaps due to primary allergic sensitization which then leads to allergic airway disease following subsequent allergen exposure⁶⁰.

We found a significantly stronger association between AD and rhinitis in studies of low quality compared to studies of high quality, indicating that the association could be overestimated in studies of low quality. However, most studies were of high quality and the OR for studies of high quality did not differ from our overall OR, indicating that the studies of low quality did not have any considerable effect on our results.

Strength and limitations

This systematic review and meta-analysis has many strengths including the strict methodology following the PRISMA guidelines and the large number of included studies showing similar results. The diagnosis of AD and rhinitis varied across studies leading to a potential misclassification of both diseases. We acknowledge that a positive SPT or sIgE test by no means can be used to determine whether rhinitis was of allergic origin, as it does not inform about exposure or clinical relevance. However, the analysis on rhinoconjunctivitis showed a similar prevalence suggesting that it was a fair assumption. We also acknowledge that the articles on which figure 2 was based may not be exhaustive, and selected studies may

not have examined both asthma and rhinitis in the target populations. As we only included studies in English, our results may not be generalizable to all populations. Moreover, only limited studies were included from the geographical regions; Africa, Australia and South America, which might also have affected the generalizability of our results. When restricting the analysis to studies with a large sample size, a slightly lower prevalence was found when compared to studies with a small sample size. The implication for this is unknown. Also, the cause for a higher prevalence in cross-sectional studies compared to cohort studies is unknown. Sub-analysis on perennial allergens, seasonal allergens, and mean age of onset of rhinitis were not examined due to limited data. Also, the pathophysiologic mechanism behind the association of non-allergic rhinitis and AD remains to be examined further. Future studies should address these topics.

In conclusion, the occurrence of rhinitis, both allergic and non-allergic, is very frequent in patients with AD in turn warranting the attention of physicians who care for these patients. New research indicates that epithelial diseases characterized by T2 inflammation belong to the same disease spectrum⁶. With the development of novel biological treatments that can target the T2 inflammatory response in different tissues at the same time, it is of great importance to further examine this relationship as it may affect future treatment strategies.

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