

ORIGINAL ARTICLE

Association between atopic dermatitis and contact sensitization: A systematic review and meta-analysis

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Background: It is unclear whether patients with atopic dermatitis (AD) have an altered prevalence or risk for contact sensitization. Increased exposure to chemicals in topical products together with impaired skin barrier function suggest a higher risk, whereas the immune profile suggests a lower risk.

Objective: To perform a systematic review and meta-analysis of the association between AD and contact sensitization.

Methods: The PubMed/Medline, Embase, and Cochrane databases were searched for articles that reported on contact sensitization in individuals with and without AD.

Results: The literature search yielded 10,083 citations; 417 were selected based on title and abstract screening and 74 met inclusion criteria. In a pooled analysis, no significant difference in contact sensitization between AD and controls was evident (random effects model odds ratio [OR] = 0.891; 95% confidence interval [CI] = 0.771-1.03). There was a positive correlation in studies that compared AD patients with individuals from the general population (OR 1.50, 95% CI 1.23-1.93) but an inverse association when comparing with referred populations (OR 0.753, 95% CI 0.63-0.90).

Limitations: Included studies used different tools to diagnose AD and did not always provide information on current or past disease. Patch test allergens varied between studies.

Conclusion: No overall relationship between AD and contact sensitization was found. We recommend that clinicians consider patch testing AD patients when allergic contact dermatitis is suspected. (J Am Acad Dermatol <http://dx.doi.org/10.1016/j.jaad.2017.02.001>.)

Key words: allergic contact dermatitis; atopic dermatitis; atopic risk factors; atopy; chromium; contact allergy; contact sensitization; eczema.

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Atopic dermatitis (AD) is a chronic relapsing, pruritic inflammatory skin condition that most often begins in early childhood.¹ The risk for AD is increased in individuals with primary skin-barrier impairment, eg, mutations in the common *filaggrin* gene, but also in individuals with primary immune dysregulation.^{2,3}

Allergic contact dermatitis (ACD) is a type IV hypersensitivity reaction caused by re-exposure to a cutaneous contact allergen in a presensitized individual. ACD is diagnosed via patch testing, the process of applying contact allergens to the skin under occlusion and visually grading the skin inflammatory response. Contact sensitivity is the term used to describe a positive patch test reaction. To diagnose ACD in a patient, he or she must have a contact sensitivity, and a dermatitis with clinically relevant exposure to said contact allergen. It has long been debated whether or not patients with AD have an altered prevalence or increased risk for contact sensitization when compared with controls. Several factors might affect this relationship as recently discussed in detail.⁴ In favor of the increased occurrence of contact sensitization among patients with AD includes evidence of a nearly two-fold-increased skin absorption of chemicals including irritants and contact allergens in AD skin.^{3,5,6} In addition, patients with AD frequently use, as a part of recommended treatment, topical medicaments and moisturizers.⁷ Unfortunately, moisturizers might contain contact allergens, as illustrated in a recent study from the United States where a large proportion of 187 so-called hypoallergenic, pediatric cosmetic products contained contact sensitizers, including the potent preservative methylisothiazolinone (seen in 10%).⁸

However, there is also compelling evidence in favor of reduced contact sensitization in AD populations; notably, experimental studies have found an increased elicitation threshold in AD patients compared with controls.⁹⁻¹²

Epidemiologic studies investigating contact sensitization prevalence in patients with AD compared with those without have shown mixed results.^{10,11,13-16} To increase insight of this relationship, we performed a systematic review and meta-analysis of the literature.

MATERIALS AND METHODS

Literature search

We searched the databases PubMed/Medline (1946-present), EMBASE (1947-present), and Cochrane Library (1992-present) through October 2016 using the search terms (“atopic dermatitis” OR “atopic eczema” OR “atopy”) AND (“allergic contact dermatitis” OR “contact allergy” OR “contact sensitization” OR “patch test”). Title and abstract review was performed, and articles were excluded if there was no indication that they reported prevalence of contact sensitization in AD and non-AD populations. Studies published online, in-print, and in-press from all years, written in any language were considered. Studies that used nonscreening patch testing series or only evaluated contact sensitization to specific allergens were included.

Studies that evaluated prevalence of contact sensitization in the general population, contact sensitization in populations of patients referred for patch testing, and pre-established AD patients with matched controls were all included. For this analysis, we focused on studies evaluating individuals specifically with AD. Studies that evaluated patients with undifferentiated atopic syndrome or atopy, ie, a combination of AD, allergic asthma, or allergic rhinoconjunctivitis, were excluded. Articles that evaluated atopy patch test sensitivity or aeroallergen sensitivity were also excluded.

Data extraction and exclusion

Manuscripts were reviewed and the following data points were extracted: total number of individuals patch tested, total number of individuals with and without AD in the patch tested population, total number of AD patients and non-AD patients who had at least 1 positive patch test reaction. In addition, individual allergen patch test data were collected for the allergens nickel, cobalt, chromium, sesquiterpene lactone mix (SL), and Compositae mix, given previous research highlighting their possible relationship to AD.^{17,18} Mode of AD diagnosis, patch testing series allergens used, reading days, and location and dates of patch testing were noted for each study. The

CAPSULE SUMMARY

- It is unclear whether individuals with atopic dermatitis have an altered risk for contact sensitization.
- This meta-analysis showed no significant association between atopic dermatitis and contact sensitization. However, contact sensitization was increased in individuals with atopic dermatitis in general population studies.
- Individuals with atopic dermatitis have similar rates of contact sensitization as individuals without, and clinicians should consider patch testing when allergic contact dermatitis is suspected.

Abbreviations used:

ACD:	allergic contact dermatitis
AD:	atopic dermatitis
CI:	confidence interval
CQP:	Cochrane Q statistic <i>P</i> value
OR:	odds ratio
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-analysis
SL:	sesquiterpine lactone mix

Newcastle-Ottawa scale, a scoring system that assesses quality of nonrandomized studies, was used to enable sensitivity analysis.¹⁹

Included studies were grouped into 4 broad categories. Studies that included a baseline or screening patch test series were grouped into the total category. This category was further subdivided into studies that analyzed individuals taken from the general population versus studies that analyzed patients taken from a body of consecutive patients referred for patch testing. Pediatric patient-only studies were also analyzed separately. Studies that reported contact sensitization to individual allergens were grouped according to allergen, (ie, nickel and cobalt). In cases of repeated patient data in separate studies, the most recent or complete data was included.

Statistical analysis

Statistical analyses were performed using StatsDirect version 3.0.183 (StatsDirect Ltd, Cheshire, UK). Odds ratios (OR) with 95% confidence intervals (CI) of contact sensitization in individuals with AD compared with no AD were estimated. Forest plots were constructed for each study category. Heterogeneity of results were assessed with Cochrane Q statistic *P* values (CQP). Because of significant between-study heterogeneity, random effects models with the DerSimonian and Laird method were used to estimate the pooled OR in all groups. Funnel plot progression of logarithmic OR and standard errors was used to assess for publication bias. All statistical tests were 2-sided, with a significance level of <.05.

RESULTS

The literature search yielded 10,083 citations, of which 9666 were excluded in title and abstract review. Of the 417 manuscripts reviewed, 74 met inclusion criteria (published from 1964-2016). Reasons for exclusion are reported in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram (Fig 1). Funnel plot analysis showed no evidence of publication bias.

The categories total; total, referred population; pediatric; nickel; cobalt; chromium; and SL showed significant heterogeneity with a CQP <.05. The remaining categories showed less significant heterogeneity: total, general population (CQP = 0.957) and Compositae mix (0.519).

In the 74 studies analyzed, the average number of patients was 2632 (max 74,940; min 38; median 456). Most studies (60/74) in this analysis were performed in Europe,^{13-15,18,20-75} Two studies were performed in Asia,^{76,77} 2 in the Middle East,^{78,79} 8 in North America,⁸⁰⁻⁸⁷ and 1 in both Africa⁸⁸ and South America.⁸⁹

Fifty-six studies that performed a baseline test or screening test series were grouped into the total category. Overall, no significant correlation between AD and contact sensitization was evident (random effects pooled OR 0.891, 95% CI 0.771-1.03). Further sensitivity analysis on articles with Newcastle-Ottawa scale 6 or higher showed similar nonsignificant results (random effects pooled OR 0.941; 95% CI 0.830-1.07). Subanalysis on studies published before 2006 and on or after 2006 also showed no significant relationships.

Five of these total studies, using a screening or baseline series, evaluated patients from the general population (Fig 2). In this general population group (n = 6161 individuals), the average prevalence of contact sensitization in individuals with AD was 29.6% compared with 22.5% in those without. All 5 studies reported a higher prevalence of contact sensitization in individuals with AD than without AD. Among the general population screening studies, there was a significant correlation between AD and contact sensitization (random effects pooled OR 1.54, 95% CI 1.23-1.93).

Thirty-one of the studies in the total category drew from a body of patients referred for patch testing (Fig 3). In this referred population group (n = 50,544), the average prevalence of contact sensitization in individuals with AD was 49.9%, compared with 54.9% in individuals without AD. Ten (24.4%) of these studies found a higher prevalence of contact sensitization in individuals with AD compared with those without.^{23,34,47,50,60,72,75,83,86,87} Among these referred population studies there was an inverse correlation (random effects pooled OR 0.753; 95% CI 0.629-0.901).

Twenty-four studies were performed in pediatric populations.^{28,33,34,36,37,43,47,48,54,56,58-61,63,64,69,71,73-75,83,84,86} In the pediatric group (n = 17,951), the prevalence of contact sensitization in patients with AD was 45.6%, compared with 47.0% in those without. Ten studies (41.7%) reported a higher prevalence of contact sensitization in individuals with AD compared with those

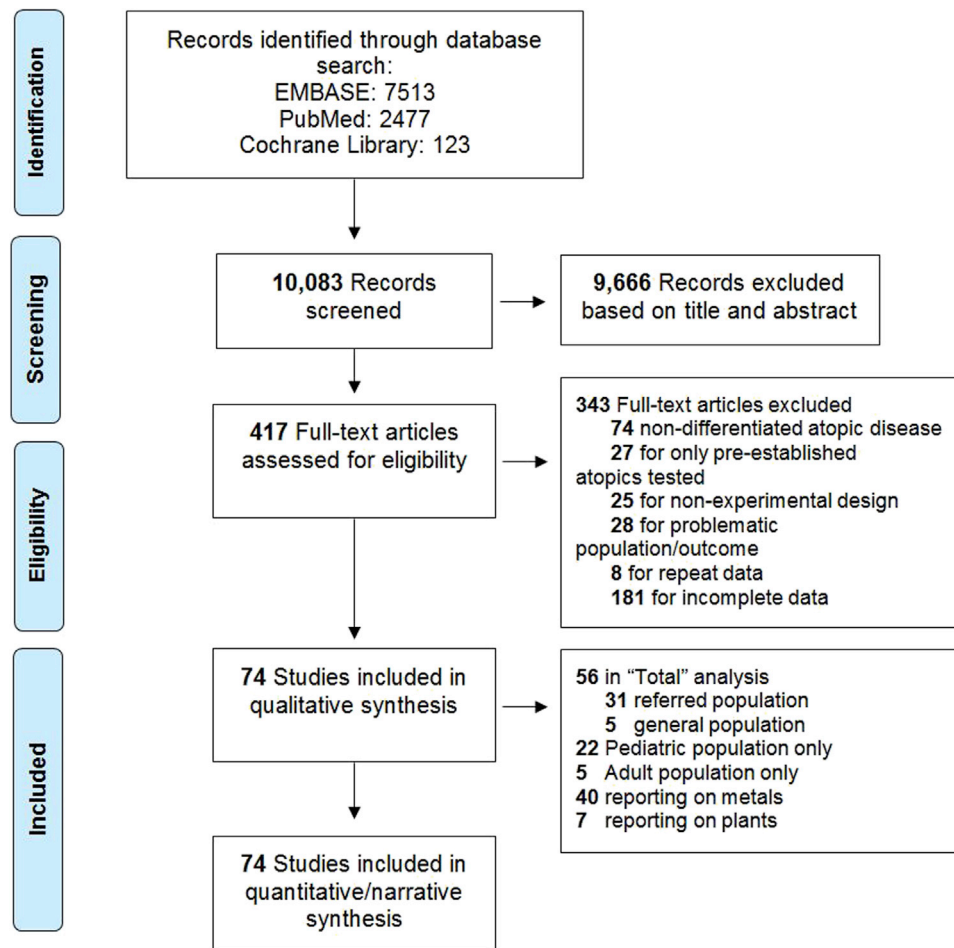


Fig 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of literature review and study selection.

without AD.^{28,33,34,43,47,60,63,75,83,86} In a pooled analysis, there was no significant difference in contact sensitization prevalence between AD and non-AD populations (random effects OR 0.910, 95% CI 0.790-1.05).

In total, 38 studies reported on nickel sensitization among AD versus non-AD populations. Twenty-two reported on cobalt and 29 on chromium sensitization. In the 38 studies reporting on nickel testing (n = 170,593), the prevalence of nickel contact sensitization was lower among AD (17.2%) than among non-AD populations (18.2%) (random effects OR 0.985, 95% CI 0.842-1.15).

In the 22 studies reporting on cobalt testing (n = 51,058), the average cobalt contact sensitization prevalence was 8.65% among AD and 7.51% among non-AD populations (random effects OR 1.08, 95% CI 0.914-1.29). In the 29 studies reporting on chromium (n = 56,300), the average chromium contact sensitization prevalence was 9.56% and 7.13% among AD and non-AD populations, respectively (random effects OR 1.25, 95% CI 1.01-1.56).

Four studies (n = 4612) included in our analysis reported on contact sensitization to SL,^{46,49,68,71} and 3 studies reported on Compositae mix sensitization.^{50,58,85} Average SL sensitization prevalence estimates in AD versus non-AD populations were 8.95% and 1.38%, respectively. In pooled analysis, the relationship was strong but not significant (random effects OR 5.71, 95% CI 0.949-34.3). Similarly, all 3 studies reporting on Compositae mix sensitization (n = 13,115) reported a higher prevalence of contact sensitization among AD than among non-AD populations, with average prevalences of 4.03% and 1.93%, respectively (random effects OR 1.42, 95% CI 1.15-1.74).

DISCUSSION

This meta-analysis showed that individuals with and without AD have a similar prevalence of contact sensitization. While a higher prevalence of contact sensitization was observed among individuals with AD in general population studies, we found an inverse association in patients referred for patch

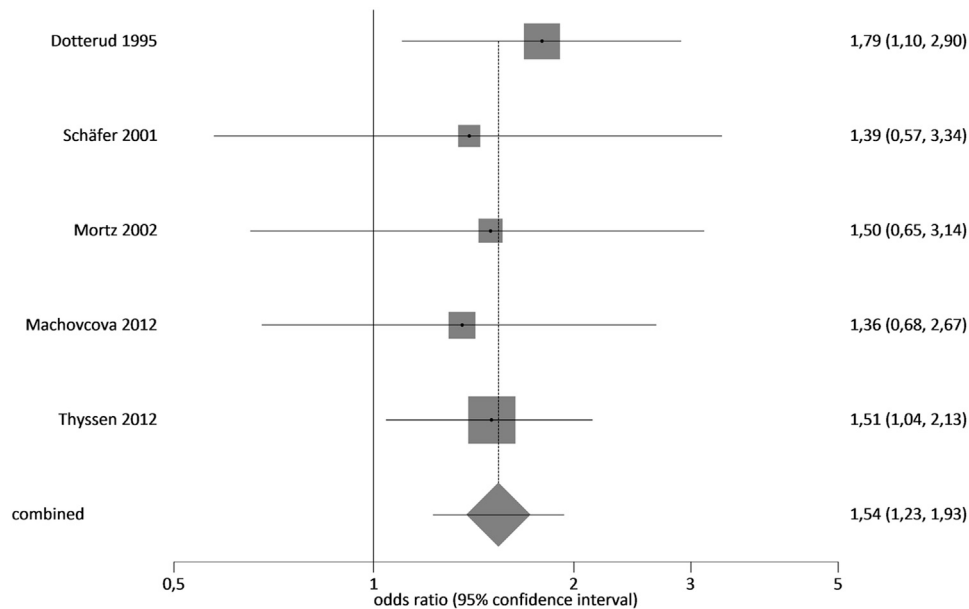


Fig 2. Forrest plot depicting odds ratios and random effects pooled odds ratio for general population studies using a screening or standard series.

testing. In subanalyses, we found that chromium and Compositae mix sensitization occurred more frequently in patients with AD.

Early experimental studies investigating the nuances of contact sensitization found an increased elicitation threshold to experimental allergens, such as dinitrochlorobenzene and urushiol, in AD patients compared with controls, and it was more pronounced in patients with severe AD than patients with mild AD.⁹⁻¹² This prompted a slew of epidemiologic studies, many of which, had similar clinical conclusions, namely a decreased prevalence of contact sensitization in AD patients than in non-AD patients.¹³⁻¹⁶ This might, in part, explain the observed inverse association between AD status and contact sensitization in referred populations in our study, in which moderate-to-severe AD is likely over-represented. An additional possible explanation for these results is a skewed referral pattern of AD patients for patch testing because it is the practice of some clinics to rule out contact sensitization in patients with AD without clear clinical suspicion, eg, when eczema is hard to control or before subscribing systemic therapy.⁹⁰

All 5 of the studies that evaluated the general population found higher rates of contact sensitization in individuals with AD. General population studies are typically less prone to bias than clinical studies. We posit that these general population results are likely more representative of the AD population as a whole because they include AD patients with a wide spectrum of disease severity. A

possible relationship between low allergenic substances and an increased risk for contact sensitization in AD individuals has recently been suggested.^{91,92} We found no statistically significant relationship between AD and contact sensitization in pediatric studies, but this was probably, at least in part, caused by having too few general population studies in this group (3/24, 12.5%).

Previous epidemiologic studies have suggested that there might be an increased prevalence of nickel sensitization in persons with AD.^{62,82} Moreover, an increased prevalence of nickel sensitization and dermatitis has been observed in carriers of *filaggrin* loss-of-function mutations.⁹³ However, we did not find a positive correlation between nickel sensitization and AD in our meta-analysis. We speculate that the role of ear-piercing partly could explain this. Ear piercing remains the most important etiology of nickel sensitization, and the correlation between *filaggrin* loss-of-function mutations and nickel sensitization shown by Novak et al was only evidenced in a Danish cohort when those with ear-piercings were excluded.⁹⁴⁻⁹⁶ The bypass hypothesis suggests that ear-piercing bypasses the epidermal barrier hence reducing the possible nickel-chelating effects of filaggrin and other proteins that are down-regulated in AD.⁹⁷

We found a statistically significant positive relationship between chromium sensitization and AD status. In mouse models, it has been shown that chromium (III) more readily penetrates the stratum corneum in filaggrin-deficient skin.⁹⁸ Chromium is

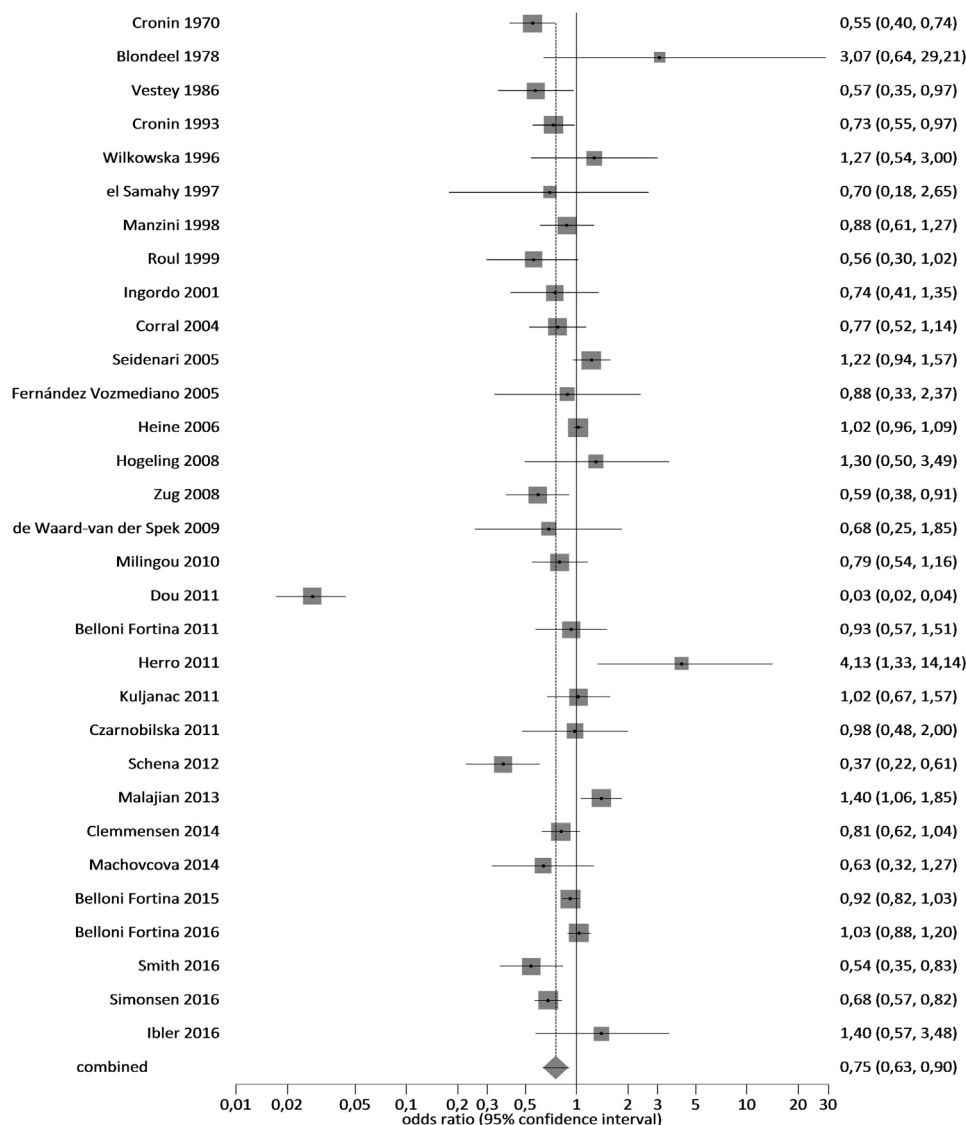


Fig 3. Forrest plot depicting odds ratios and random effects pooled odds ratio for referred population studies using a screening or standard series.

seldom released by jewelry, including earrings.⁹⁶ As stated, the intradermal exposure of nickel during ear-piercing seems to negate the increased risk individuals with AD might have for the development of nickel ACD.⁹⁴ The primarily percutaneous exposure to chromium might be a better model to study the increased risk for metal allergy among individuals with AD, as suggested by many immunologic studies.^{5,99} Another possible explanation for the association we found is that positive chromium patch tests are difficult to differentiate from irritant reactions and could have been falsely read as positive reactions in AD patients at a higher rate than in non-AD patients.¹⁰⁰

We found a statistically significant positive relationship between contact sensitization to Compositae mix and AD status, and a nearly

significant five-fold relationship between SL sensitivity and AD status. SL and Compositae mixes are used as markers for Compositae contact sensitization and have significant overlap. Plants in the Compositae family include the sunflower (*Helianthus annuus*), mugwort (*Artemisia vulgaris*), chrysanthemum (*Chrysanthemum indicum*), and tansy (*Tanacetum vulgare*) and can cause ACD, in particular airborne and occupational ACD.¹⁰¹ The phenomenon of increased plant contact sensitization among AD individuals has previously been reported.^{46,102} But, the exact cause of this relationship is unclear. SL allergy might be related to atopic disease as a whole; historically, ragweed dermatitis was noted to often complicate other atopic diseases¹⁰³ and the positive relationship between AD and Compositae mix sensitization seems to extend to

atopic diseases in general.¹⁰⁴ Inhaled Compositae pollen eliciting or worsening asthma or mucosal membrane atopy could cause concomitant SL or Compositae allergen sensitization. An alternative possibility is that patients with AD have increased exposure to Compositae allergens through use of topical emollients. Botanical extracts containing Compositae allergens, such as chamomile extract and arnica Montana flower extract, are used in some topical products, including those marketed as hypoallergenic and dermatologist-recommended.⁸

Limitations and strengths

We used strict exclusion criteria, so we could present data that was most amenable to meta-analysis. This might have led to the exclusion of some relevant studies that reported on the possible association between AD and contact sensitization. In addition, many factors can complicate a straightforward comparison of the included studies, including the definition of AD used, current or only past AD diagnosis, severity of AD, history of elevated IgE or atopic diseases, the patch test series applied, the day of patch test reading (patients with AD tend to react earlier than patients without AD), and the referral pattern of the reporting clinic. Some weak positive reactions could have been due to irritancy, particularly in patients with AD.

Conclusions

We found no significant difference in the overall prevalence of contact sensitization to common allergens in AD versus non-AD individuals. However, in general population studies patients with AD had a higher prevalence of contact sensitization, whereas a lower prevalence was observed in referred populations. Individuals with AD had higher rates of chromium and Compositae mix contact sensitization. Clinicians caring for patients with AD should be cognizant that contact sensitization is not uncommon among the AD population, and should therefore recommend safe low-allergenic products to their patients and consider patch testing when ACD is suspected.

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