

The association between contact sensitization and atopic disease by linkage of a clinical database and a nationwide patient registry

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Abstract

Background: Experimental studies have shown that individuals with atopic dermatitis are likely to have suppressed contact sensitivity secondary to their disease whereas some clinical and epidemiological studies have shown that individuals with atopic dermatitis might have a higher prevalence of contact sensitization than controls. The objective was to study the association between contact sensitization and, respectively, atopic dermatitis and asthma using clinical databases.

Methods: Record linkage of two different registers was performed: (i) a tertiary hospital register of dermatitis patient's patch tested for contact sensitivity and (ii) the Danish National Patient Register containing nationwide hospital discharge diagnoses and outpatient contacts.

Results: An inverse association was found between contact sensitization and, respectively, presumed severe atopic dermatitis (OR, 0.70; 95% CI, 0.61–0.81) and asthma (OR, 0.61; 95% CI, 0.42–0.90) when linkage was performed. Inverse associations were found for all groups of chemicals and metals except for sensitization to fragrances and topical drugs where positive associations were identified. A significant positive association between fragrance sensitization and presumed mild–moderate atopic dermatitis was also found when data from hospital register only were used, suggesting an overall higher prevalence of fragrance sensitization in patients with atopic dermatitis.

Conclusions: Our findings support that patients with severe atopic dermatitis and asthma have an overall lower prevalence of contact sensitization when compared with controls, whereas mild-to-moderate disease does not suppress contact sensitization. The prevalence of contact sensitization to fragrance chemicals was higher in patients with atopic dermatitis. Patients should be instructed to avoid scented moisturizers and products containing highly sensitizing substances.

Contact sensitization (CS) affects up to 20% of adults from the general population. Induction of CS and elicitation of allergic contact dermatitis depend on the sensitizing potency of the hapten, dose per unit area, the presence of irritants, race, gender, age and genetic predisposition (1). Epidemiological and experimental studies have investigated the relationship between CS and atopic dermatitis (AD) (2–16). Despite the individuals with AD are likely to have suppressed contact sensitivity secondary to their disease (7,11,12), the prevalence of CS may be similar or even increased in individuals with AD

as shown in general population studies (4,13,15,16). Indeed, a recent study, taking the likely route of hapten exposure into account, found a strong positive association between AD and CS, which was mainly driven by fragrance sensitization (17). A positive association between nickel sensitization and filaggrin loss-of-function mutations was also recently identified (18,19), and the prevalence of CS to ingredients used in topical medications tend to be higher in individuals with AD (8,20,21). A positive association between AD and CS might be explained by frequent exposure to contact sensitizers from

topical products used to treat dry and itchy skin together with a skin barrier abnormality allowing penetration of chemicals. We investigated the association between CS and AD (and asthma) by cross-linking two registers.

Materials and Methods

Study population

Patients with dermatitis were patch tested for CS at Gentofte University Hospital, a tertiary clinic. The outcome of patch testing, sex, date of birth and past/present AD (only since 2004) was recorded in the sensitization database. The European baseline series was used for patch testing (Trolab allergens (Hermal, Reinbek, Germany) and Finn Chambers® (8 mm Epitest Ltd, Oy, Finland) on Scanpor tape® (Norgesplaster A/S, Alfarma, Vennesla, Norway)). Occlusion time was 48 h, and the patches were read on day 2, on day 3 or 4, and on day 5 or 7 according to the criteria from the International Contact Dermatitis Research Group (ICDRG). A positive reaction was defined as at least homogeneous erythema and infiltration in the test area, and CS was defined as a positive reaction at any day of reading to any hapten in the European baseline series.

Association by linkage with a nationwide register (patients with presumed severe AD)

For this study, 15 641 (9960 female) patients patch tested between November 1984 and December 2006 were included. At birth, or on immigration, Danish residents are given a unique and personal identifier number. This enables linkage of individual data between registers (22). Using the unique identifier number, the CS database from Gentofte Hospital was linked with the nationwide Danish National Patient Register (DNPR) that contains discharge diagnoses from 1977 and outpatient contacts from 1995 in all-over Denmark (23). The DNPR is coded according to the International Classification of Diseases, version 8 (ICD8), between 1977 and 1993, and version 10 (ICD10) from 1994 and onwards. An individual with the ICD8 code 691 (except code 69 101 'diaper dermatitis') or the ICD10 code DL20 was considered to have AD, whereas an individual with the ICD8 code 493 or the ICD10 code DJ45–46 was considered to have asthma.

Association by comparing clinical data obtained by the treating physician (patients with presumed mild–moderate AD)

For this substudy, 4336 (2860 female and 1476 male) patients patch tested between January 1, 2004 and December 31, 2010 were included. AD was defined by the treating physician at Gentofte Hospital as the occurrence of AD at some point in life.

Statistical analysis

Age was defined as the age at first positive patch test reaction, or in case of negative reactions, as the age at first

patch testing. Logistic regression analyses were conducted with, respectively, AD and asthma (asthma only for the DNPR study part) as the dependent variable and different CS variables as the independent variables. The strength of patch test reactivity in patients with AD and asthma was also investigated and compared with controls. The relative onset of dermatitis (atopic or allergic contact) could not be investigated. Odds ratios (ORs) with 95% confidence intervals (CIs) were given. All data analyses were done using SPSS version 18 (SPSS Inc., Chicago, IL, USA).

Results

Prevalence rates

A total of 5572 (35.6%) patients had a positive patch test reaction to at least one sensitizer on at least one occurrence (Table 1). The prevalence was 26% ($n = 1478$) in male and 41% ($n = 4094$) in female patients ($P < 0.001$). The difference was mainly driven by nickel (3.3% vs. 17.9%) and fragrances (8.1% vs. 11.7%). The prevalence of CS was 18.6% ($n = 51$) in 0- to 15-year-olds, 30.6% ($n = 959$) in 16- to 30-year-olds, 38.8% ($n = 2112$) in 31- to 50 year-olds, 36.6% ($n = 1703$) in 51- to 70-year-olds and 35.1% ($n = 747$) in >70 year-olds. The high prevalence in middle-aged patients was mainly explained by nickel sensitization (24). The prevalence of CS to metals (nickel, cobalt and chromium), fragrances (fragrance mix I and Myroxylon pereirae), preservatives (formaldehyde, quarternium-15, methylisothiazolinone/methylchloroisothiazolinone and paraben mix) and topical drugs (neomycin sulphate, clioquinol, quinoline, and benzocaine) was 15.8%, 10.4%, 5.2%, and 4.5%, respectively. Between 2004 and 2010, 1788 (41.2%) of 4336 patients were contact sensitized, and the distribution was similar to the one observed between 1984 and 2006.

Association by linkage with the DNPR (presumed severe AD)

After linkage with the DNPR, AD was identified in 7.8% ($n = 1218$), asthma in 0.9% ($n = 146$), and asthma in combination with AD in 0.6% ($n = 92$) of the patch-tested patients. These patients were suspected of having severe AD. Both AD and asthma were associated with low age, and AD was associated with female gender (Tables 2 and 3). The overall prevalence of CS was 27.4% ($n = 334$) in patients with AD, 24.7% ($n = 36$) in patients with asthma and 20.7% ($n = 19$) in patients with both diseases. The prevalence of CS was 31.9% ($n = 268$) and 26.6% ($n = 25$) in female patients with AD and asthma, respectively, and 17.5% ($n = 66$) and 21.2% ($n = 11$) in male patients with AD and asthma, respectively. Asthma and AD were found to be inversely associated with CS to at least one sensitizer in crude and adjusted analyses. Inverse associations were found for all groups of chemicals and metals except for sensitization to fragrances in patients with AD and to topical drugs in patients with AD and asthma; however, none of these reached statistical significance. The positive association between fragrance sensitization and AD was caused by a borderline significant positive

Table 1 The prevalence of contact sensitizations to baseline sensitizers in dermatitis patients patch tested during the period 1984–2006

		Contact sensitization prevalence% (<i>n</i> / <i>n</i> _{total})		
Hapten	Concentration and vehicle	All <i>n</i> = 15 461	Patients with atopic dermatitis <i>n</i> = 1218	Patients with asthma <i>n</i> = 146
Metals				
Potassium dichromate	0.5% pet.	2.6 (412)	3.28 (40)	2.05 (3)
Cobalt chloride	1% pet.	3.8 (600)	3.94 (48)	2.05 (3)
Nickel sulphate	5% pet.	12.6 (1 966)	9.69 (118)	7.53 (11)
Fragrances				
Fragrance mix I	8% pet.	7.9 (1 232)	7.72 (94)	4.11 (6)
Myroxylon pereirae (Balsam of Peru)	25% pet.	4.5 (703)	2.63 (32)	2.74 (4)
Preservatives				
Formaldehyde	1% aq.	3.0 (474)	1.81 (22)	0.68 (1)
Quaternium-15	1% pet.	0.9 (148)	0.74 (9)	0
Methylisothiazolinone/ methylchlorisothiazolinone	0.01% aq.	1.8 (275)	1.23 (15)	0.68 (1)
Paraben mix	16% pet.	0.6 (93)	0.16 (2)	0.68 (1)
Topical Drugs				
Neomycin sulphate	20% pet.	2.9 (453)	2.30 (28)	3.42 (5)
Clioquinol*	5% pet.	0.3 (53)	0.41 (5)	0.68 (1)
Quinoline mix*	6.0 pet	0.4 (66)	0.16 (2)	0
Benzocaine	5% pet.	0.5 (87)	0.33 (4)	0.68 (1)
Other chemicals				
p-phenylenediamine	1% pet.	2.3 (352)	1.64 (20)	0.68 (1)
Thiuram mix	1% pet.	2.8 (436)	1.81 (22)	2.05 (3)
Colophonium	20% pet.	4.0 (625)	3.37 (41)	1.37 (2)
N-Isopropyl-N'-phenylparaphenylenediamine (IPPD)	0.1% pet.	0.3 (52)	0.25 (3)	0.68 (1)
Wool alcohols (lanolin alcohol)	30% pet.	1.0 (154)	0.41 (5)	0.68 (1)
Mercapto mix	1% pet.	0.7 (109)	0.41 (5)	1.37 (2)
Epoxy resin	1% pet.	1.2 (180)	0.90 (11)	2.05 (3)
para-tertiary-butylphenol-formaldehyde resin (PTBP resin)	1% pet.	1.3 (200)	1.15 (14)	0
Mercaptobenzolthiazole	2% pet.	0.6 (109)	0.33 (4)	0.68 (1)
Primin	0.01% pet.	1.1 (176)	0.25 (3)	0
Sesquiterpene lactone mix	0.1% pet.	1.2 (183)	1.07 (13)	0.68 (1)
Ethylenediamine	1.0% pet	0.3 (44)	0	0
Carba mix	3.0% pet	0.8 (126)	0.49 (6)	0.68 (1)
Black rubber mix	0.6% pet	0.3 (42)	0.08 (1)	0.68 (1)

*Between 1984 and 1994, quinoline mix 6.0% in petrolatum was used for testing but was replaced by clioquinol 5% in petrolatum in 1994 and used onwards.

association in female dermatitis patients as a negative association was found in male patients. Similar for CS to topical drugs, a stronger association was found in women with AD when compared with men. No other gender differences were found. When the strength of patch test reactivity was investigated in patients with AD and asthma and compared with controls, no significant differences were identified.

Association by comparing clinical data obtained by the treating physician (presumed mild–moderate AD)

The prevalence of AD as registered by the treating physician at Gentofte Hospital was 16.8% (732/4336). These patients

were suspected of having mild–moderate AD. Adjusted regression analyses between CS and AD for the period 2004–2010 are shown in Table 4. There was no overall association between AD and CS whereas a positive and significant association was found for fragrance sensitization (OR, 1.45; 95% CI, 1.13–1.86). Fragrance sensitization was associated with AD in both male (OR, 1.20; 95% CI, 0.68–2.12) and female (OR, 1.50; 95% CI, 1.13–1.99) patients.

Discussion

Contact sensitization was inversely associated with AD and asthma in patch-tested patients with presumed severe AD (linkage with the DNPR) whereas no association was found

Table 2 Logistic regression analyses with the outcome 'atopic dermatitis' as registered in the Danish National Patient Register (DNPR) and with different explanatory variables performed in dermatitis patients from Gentofte University Hospital patch tested between 1984 and 2006

Explanatory variables	Atopic Dermatitis% (<i>n</i> / <i>n</i> _{total})	Crude OR with 95% CI	Adjusted OR* with 95% CI
Sex			
Male	6.65 (378/5681)	1 (reference)	1 (reference)
Female	8.43 (844/9960)	1.29 (1.14–1.47)	1.23 (1.08–1.41)
Age (years)			
0–15	34.67 (95/274)	1 (reference)	1 (reference)
16–30	17.36 (544/3134)	0.40 (0.30–0.52)	0.41 (0.31–0.53)
31–50	7.16 (390/5447)	0.15 (0.11–0.19)	0.15 (0.12–0.20)
51–70	3.48 (162/4656)	0.07 (0.05–0.09)	0.07 (0.05–0.10)
70<	1.27 (27/2130)	0.03 (0.02–0.04)	0.03 (0.02–0.04)
Contact sensitization to at least one hapten			
No	8.78 (884/10 069)	1 (reference)	1 (reference)
Yes	5.99 (334/5572)	0.66 (0.58–0.76)	0.70 (0.61–0.81)
Nickel sensitization			
No	8.04 (1100/13 675)	1 (reference)	1 (reference)
Yes	6.00 (118/1966)	0.73 (0.60–0.89)	0.56 (0.46–0.69)
Metal sensitization [†]			
No	8.04 (1058/13 163)	1 (reference)	1 (reference)
Yes	6.46 (160/2478)	0.79 (0.67–0.94)	0.67 (0.56–0.80)
Fragrance Sensitization [‡]			
No	7.90 (1107/14 010)	1 (reference)	1 (reference)
Yes	6.81 (111/1631)	0.85 (0.70–1.04)	1.11 (0.90–1.37)
Preservative Sensitization [§]			
No	7.98 (1182/14 820)	1 (reference)	1 (reference)
Yes	4.38 (36/821)	0.53 (0.38–0.74)	0.61 (0.43–0.87)
Topical Drug Sensitization [¶]			
No	7.86 (1171/14 876)	1 (reference)	1 (reference)
Yes	6.14 (47/765)	0.77 (0.57–1.04)	1.11 (0.81–1.51)

OR, Odds ratio; CI, Confidence intervals.

*Adjusted for sex and age.

†Contact sensitization to nickel, cobalt and/or chromium.

‡Contact sensitization to fragrance mix I (pet.) and/or Myroxylon pereirae 25% (pet.)

§Contact sensitization to formaldehyde 1% aq., quaternium-15 1% petrolatum (pet.), paraben mix 16% pet. (between 1985 and 1995, 15% pet. was used), methylchloroisothiazolinone/methylisothiazolinone 0.01% aq., and/or methyldibromo glutaronitrile 0.5% pet.

¶Contact sensitization to neomycin sulphate 20% in pet., cliquinol 5% in pet and/or benzocaine 5% in pet.

in those with presumed mild–moderate AD (linkage with in-house data). Patients suffering from mild-to-moderate AD and asthma are typically diagnosed and treated by their general practitioners or private dermatologists and are not registered in the DNPR. Hence, cases in the DNPR study are expected to mainly suffer from severe AD and asthma as these are hospitalized and/or treated in an ambulatory setting. Dermatitis patients who underwent patch testing constituted a heterogeneous group being referred from various other specialties. It is our clear impression that throughout the study period, patients have suffered from mild, moderate and occasionally severe AD in equal distributions and that most suffered from AD during their childhood. Hence, this population represented a mixed population having presumed mild–moderate AD as an average.

Study limitations include the retrospective design and that we were not able to determine causation; that is, we could not establish whether AD decreased the risk of CS, or whether CS prevented the development of AD in those

with presumed severe AD. The risk of bias should be considered: (i) patients with severe AD and asthma were diagnosed and treated in a tertiary clinic possibly resulting in patch testing albeit the suspicion of CS was small, and this would result in a lower prevalence of CS; (ii) patients with negative patch test reactions could theoretically have been coded as having AD more often as the dermatologists might tend to make this diagnosis in the absence of positive reactions; (iii) patients with allergic contact dermatitis may have been incorrectly categorized as having AD as it is clear that AD and allergic contact dermatitis may sometimes be indistinguishable clinically and that epidemiological, clinical and animal data support a close overlap between the two conditions (discussed in (17)). Moreover, recent studies have clearly documented the diagnostic benefits of patch testing juvenile patients with dermatitis, and not restricting the diagnosis to clinical expression, and outcome of specific serum-IgE levels and skin prick testing alone (25,26).

Table 3 Logistic regression analyses with the outcome 'asthma' as registered in the Danish National Patient Register (DNPR) and with different explanatory variables performed in dermatitis patients from Gentofte University Hospital patch tested between 1984 and 2006

Explanatory variables	Asthma% (n/n _{total})	Crude OR with 95% CI	Adjusted OR* With 95% CI
Sex			
Male	0.92 (52/5681)	1 (reference)	1 (reference)
Female	0.94 (94/9960)	1.03 (0.73–1.45)	1.05 (0.74–1.48)
Age (years)			
0–15	2.92 (8/274)	1 (reference)	1 (reference)
16–30	1.47 (46/3134)	0.50 (0.23–1.06)	0.52 (0.24–1.12)
31–50	0.95 (52/5447)	0.32 (0.15–0.68)	0.36 (0.16–0.74)
51–70	0.60 (28/4656)	0.20 (0.09–0.44)	0.22 (0.10–0.48)
70<	0.56 (12/2130)	0.19 (0.08–0.47)	0.20 (0.08–0.50)
Contact sensitization to at least one hapten			
No	1.09 (110/10 069)	1 (reference)	1 (reference)
Yes	0.64 (36/5572)	0.59 (0.40–0.86)	0.61 (0.42–0.90)
Nickel sensitization			
No	0.99 (135/13 675)	1 (reference)	1 (reference)
Yes	0.56 (11/1966)	0.56 (0.31–1.05)	0.51 (0.27–0.95)
Metal sensitization [†]			
No	1.01 (133/13 030)	1 (reference)	1 (reference)
Yes	0.52 (13/2465)	0.52 (0.29–0.92)	0.48 (0.27–0.86)
Fragrance Sensitization [‡]			
No	0.97 (136/14 010)	1 (reference)	1 (reference)
Yes	0.61 (10/1631)	0.63 (0.33–1.20)	0.71 (0.37–1.36)
Preservative Sensitization [§]			
No	0.97 (136/14 010)	1 (reference)	1 (reference)
Yes	0.61 (10/1631)	0.37 (0.12–1.18)	0.41 (0.129–1.28)
Topical Drug Sensitization [¶]			
No	0.93 (139/14 876)	1 (reference)	1 (reference)
Yes	0.91 (7/765)	0.98 (0.46–2.10)	1.16 (0.54–2.51)

OR, Odds ratio; CI, Confidence intervals.

*Mutually adjusted for variables shown in Table.

†Contact sensitization to nickel, cobalt, and/or chromium.

‡Contact sensitization to fragrance mix I (pet.) and/or Myroxylon pereirae 25% (pet.)

§Contact sensitization to formaldehyde 1% aq., quaternium-15 1% petrolatum (pet.), paraben mix 16% pet. (between 1985 and 1995, 15% pet. was used), methylchloroisothiazolinone/methylisothiazolinone 0.01% aq. and/or methylidibromo glutaronitrile 0.5% pet.

¶Contact sensitization to neomycin sulphate 20% in pet., cliquinol 5% in pet. and/or benzocaine 5% in pet.

This is one of the very few large-scale epidemiological studies that partly support an overall inverse association between CS and AD identified by experimental studies (7,11,12,27). Whether the patients were truly not contact sensitized or disease activity suppressed immune reactivity at the time of patch testing resulting in false negative reactions is unknown. The Th1/Th2-dichotomy, suggesting an inverse association between mainly Th1 (e.g. CS) and Th2 (e.g. AD) driven diseases, was for long a useful working hypothesis, but it is now clear that the innate immune response plays an important role for CS (28) and that a mixed Th1 and Th2 response is observed in allergic contact dermatitis (29,30). In mice, it appears that for potent haptens the sensitization is dependent on CD8+Tc1 cells (31) while re-exposure can lead to a mixed CD4+-dominated response that might resemble AD (32). Moreover, IL-17-producing cells are involved in the pathogenesis of CS (33). Although the exact pathomechanisms are unclear, a sensitization study using dinitrochlorobenzene (DNCB) showed that challenge gave positive

reactions in 33% of 24 patients with severe AD, 95% of 86 patients with moderate AD and in 100% of 40 patients with mild AD (7). When re-challenge was performed in patients who did not react on the first occasion, 18 with now controlled dermatitis reacted to DNCB. Another experimental study showed that 3% of 40 atopic individuals and 37% of 131 health controls had contact sensitivity to *Rhus* and that the active sensitization frequencies to *Rhus* were 6% vs. 31%, respectively (12). The frequency of positive patch test reactions was lower in patients with high IgE values than in those with IgE less than or equal to 1000 U/ml (11). A sensitization trial using DNCB evaluated the dose-response relationship for CS in 22 patients with minimal AD and 27 nonatopic controls and found that atopic patients were significantly less responsive (27). A prospective study found a lower prevalence of CS in the group with severe dermatitis when compared with the group with moderate AD (34). A low prevalence of CS was also shown in individuals with asthma from Finland (6). Finally, the peripheral blood

Table 4 Separate logistic regression analyses, adjusted for age and sex, and with the outcome 'atopic dermatitis' as registered by the treating physician in the medical chart. Patients were seen at the Gentofte University Hospital patch tested between 2004 and 2010.

Explanatory variables	Adjusted OR* with 95% CI
Contact sensitization to at least one hapten	
No	1 (reference)
Yes	1.02 (0.86–1.21)
Nickel sensitization	
No	1 (reference)
Yes	0.89 (0.70–1.11)
Metal sensitization [†]	
No	1 (reference)
Yes	1.01 (0.82–1.25)
Fragrance Sensitization [‡]	
No	1 (reference)
Yes	1.44 (1.12–1.85)
Preservative Sensitization [§]	
No	1 (reference)
Yes	0.99 (0.72–1.37)
Topical Drug Sensitization [¶]	
No	1 (reference)
Yes	0.82 (0.47–1.46)

OR, Odds ratio; CI, Confidence intervals.

*Mutually adjusted for age and sex.

[†]Contact sensitization to nickel, cobalt, and/or chromium.

[‡]Contact sensitization to fragrance mix I (pet.) and/or Myroxylon pereirae 25% (pet.)

[§]Contact sensitization to formaldehyde 1% aq., quaternium-15 1% petrolatum (pet.), paraben mix 16% pet. (between 1985 and 1995, 15% pet. was used), methylchloroisothiazolinone/methylisothiazolinone 0.01% aq. and/or methylidibromo glutaronitrile 0.5% pet.

[¶]Contact sensitization to neomycin sulphate 20% in pet., cliquinol 5% in pet, and/or benzocaine 5% in pet.

mononuclear cells (PBMC) of patients with allergic nickel contact dermatitis and concomitant AD displayed impaired *in vitro* reactivity to nickel stimulation when compared with nickel allergic controls without AD (35).

Although the accumulation of findings convincingly suggests that severe AD and asthma might prevent the development and expression of CS, it is wise to put these into clinical, immunological and epidemiological context. This is necessary as we could not confirm an association between AD and CS when only using the data registered in the patch test database (Table 4). In fact, several authors have found a similar or even higher prevalence of CS in atopic individuals when compared with controls (4,6,14–17). General population studies with high participation rates are often useful for association analyses because they tend to be unbiased and mimic real-life conditions integrating most exposures and biological interactions. Experimental studies do not mimic real-life exposure situations as they reflect isolated exposures. Klas et al. stated that 'reduced poison oak and DNCB sensitization among patients with AD may be the clinical reflection of cellular abnormalities. This does not mean that

atopics are anergic, but that they may have varying degrees of reduced responsiveness' (14). However, remember that individuals with AD in general population studies typically have mild disease.

Patients with AD have an inherited or acquired dysfunctional skin barrier as well as an elevated level of hapten exposure due repeated topical application of drugs and moisturizers used to treat the condition. Although this would expectedly increase the level of CS, and indeed does so (8,20,21), the activated immune response has traditionally been used to explain the lower overall rate of sensitization (likely to be graded depending on the severity of AD). Individuals with AD and/or asthma typically suffer from diseases that are characterized not only by their chronicity but also by their recurrent episodes of aggravation. The skin barrier is dysfunctional not only in all individuals with AD during active disease but also in some individuals during periods without skin inflammation, for example the flaggrin mutation carriers. Assuming that atopic individuals are generally exposed to the same variety of chemicals as nonatopic individuals, CS might mainly develop in periods of rest where the immune system is not alerted. This could also explain the findings from experimental sensitization trials where extreme sensitizers have alerted the system and prevented sensitization. Patch testing of atopic individuals should, when possible, be performed in periods where dermatitis is absent or limited to prevent false negative patch test reactions.

A general population study found a strong and positive association between AD and CS, mainly driven by fragrance sensitization (17). In the present study, sensitization to fragrances was also positively, but not significantly, associated with AD in the DNPR study despite an overall inverse association. Moreover, a significant association was found between AD and fragrance sensitization when the in-house data from the Gentofte patch test database were analysed. These findings suggest that despite Th-2-dominated immune reactivity would tend to prevent CS, high or sustained cutaneous chemical exposure during times with and without skin inflammation may indeed result in CS. Patients should be instructed to avoid scented moisturizers and products containing highly sensitizing substances. Clinicians should consider patch testing their patients with AD and probably repeat this several times.

In conclusion, we showed that presumed severe AD was inversely associated with CS, whereas no association was found with presumed mild-to-moderate AD. Fragrance sensitization seems to be positively associated with AD in those with mild-moderate as well as severe AD.

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Authors contribution

Jacob Thyssen outlined the data analysis and wrote the manuscript. Kaare Engkilde conducted the data analyses. Torkil Menné and Jeanne Johansen collected the data and

established the database. All authors critically reviewed the manuscript and were involved the interpretation of data.

Conflict of interests

The authors declare that they have no conflict of interest to disclose.

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