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1. Aktuelle Fachinformation TREMFYA®.

2. Reich K et al. Lancet. 2019;394(10201):831-839.

3. Griffiths CEM et al. Poster Presentation Coastal Dermatology Symposium 2020, October 15-16th.

4. Mease P et al. The Lancet 2020; [https://doi.org/10.1016/S0140-6736\(20\)30263-4](https://doi.org/10.1016/S0140-6736(20)30263-4) (Supplementary)

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Atopic skin diathesis rather than atopic dermatitis is associated with specific contact allergies

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Summary

Background: The association of atopic dermatitis (AD) and allergic contact derma-
titis has been a matter of considerable uncertainty. Study results range from lack of
any association to increased sensitization for multiple allergens, but fail to identify
consistent allergen associations.

Objective: We studied a large patch test cohort of patients stratified by their atopic
skin diathesis using the Erlangen Atopy Score (EAS), independent of active skin disease.

Methods: Retrospective multi-center data analysis from five departments of der-
matology in Germany with 4,509 patients. Patients were grouped as “no atopic skin
diathesis” (n = 2,165) and “atopic skin diathesis” (n = 1,743), according to EAS.

Results: Significantly more individuals with atopic skin diathesis showed at least one
positive patch test reaction to the baseline series compared to individuals without
atopic skin diathesis (49.1 % vs. 38.3 %). In logistic regression analyses, atopic skin
diathesis was associated with a significantly higher risk of sensitization to methylchlo-
roisothiazolinone/methylisothiazolinone (OR 2.383) and methylisothiazolinone (OR
1.891), thiuram mix (OR 1.614), as well as nickel (OR 1.530), cobalt (OR 1.683), and chro-
mium (OR 2.089).

Conclusions: Atopic skin diathesis proved to be the most important intrinsic risk fac-
tor for contact sensitization to few, specific allergens. Past or present AD was a less
relevant variable.

Introduction

Atopic Dermatitis (AD) is a common chronic inflammatory skin disease, which severely affects the quality of the patient's life. It affects up to 10–20 % of the population in industrialized countries [1, 2]. The multifactorial pathogenesis of AD comprises complex immune dysregulation and epidermal barrier defects. In contrast, allergic contact dermatitis (ACD) requires the penetration of the epidermal barrier by an allergen or hapten. After recognition by antigen-presenting cells, the cascade of sensitization and elicitation follows a predominantly Th1-cell mediated immune response with additional roles for Th2, Th17, and Th22 cells [3]. In line with these considerations, there is a strong association of ACD with occupational dermatitis [4]. Interestingly, recent studies revealed distinct activation and polarization modalities of T cells depending on the allergen in question. Nickel exposure induced a Th1-polarization and Th17/Th22 cell activation, whereas immune responses to fragrance and rubber was mainly driven by the Th2/Th22 axis [5, 6]. Since AD patients treat their skin with emollients and medical ointments daily, this repeated exposure to potential allergens was alleged to be accountable for the frequent sensitizations in these individuals. However, the causal link between AD and ACD is still the subject of controversial discussions, as the existing data are far from clear.

A Danish study revealed no significant differences in the frequency of positive patch test results in AD patients compared to healthy controls [7]. However, the diagnosis AD was based on “past or present AD diagnosis” according to UK-criteria [8], which was partly evaluated by nurses. After adjustment for age, the authors found in patients with AD significantly more sensitizations to potassium dichromate and significantly fewer positive reactions to nickel. Another Danish study investigated 3,202 participants from the general population by patch tests and filaggrin-genotyping [9]. Again, the diagnosis of AD was based on the UK-criteria [8]. At least one positive patch test reaction was found in 13.6 % of individuals with reported AD vs. a significantly lower rate of 9.5 % in people without AD. The higher sensitization rate was mainly due to fragrances. In a large multicenter study from Germany, individuals were grouped into patients with or without physician-diagnosed AD ($n = 9,020$ and $n = 15,263$, respectively) [10]. Here, the diagnosis of AD was based on criteria by Hanifin and Rajka [11]. The frequency of positive patch test results to one or more allergens was equally distributed between both groups [10]. Interestingly, significantly elevated sensitization rates in AD patients were found for fragrance mix, compositae mix, thiuram mix, MCI/MI, and bufixamac.

Several studies investigated the presence of ACD in patients with AD, with controversial results [10, 12, 13]. Given that recent studies have shown an immunological and

barrier-compromising pre-activation of cells and cytokines even in unaffected skin of patients with atopic dermatitis [14, 15], we chose a different, more refined approach: Atopic skin diathesis can be thoroughly assessed by the Erlangen Atopy Score (EAS) which was established and validated in the 1990s by Thomas Diepgen and colleagues [16, 17]. This at least in Germany well-established and widely used score integrates 24 items to measure and calculate the probability of atopic skin diathesis (Table S1, online Supporting Information). The criteria comprise personal and family history, subjective symptoms such as itch when sweating, clinical signs, and laboratory results.

The different prevalences of ACD in AD in previous studies may be due to inconsistent AD diagnosis criteria. Unfortunately, no single parameter can unequivocally establish the diagnosis of AD. In a recently published review on “diagnostic criteria used in AD randomized controlled trials”, 212 randomized controlled AD trials with pharmacological intervention were analyzed [18]. In 37 % of the trials, “no validated criteria specified” were used for AD diagnosis. In the remaining trials with specified diagnostic criteria, the “Hanifin and Rajka” criteria were used in two thirds of these [11]. This diagnostic score contains 28 items (4 major criteria and 24 minor criteria) and is frequently used for diagnosis of AD. Importantly, three distinct features separate EAS from the “Hanifin and Rajka” criteria: First, the EAS encourages evaluation of the items with partial points (minimum 0.5 to maximum of 3 points) which consequently allows better distinction. Second, the EAS includes more lab parameters (total and specific IgE). Third, the EAS assesses probability of atopic skin diathesis without necessity of present or past eczema manifestation. Previous studies reported conflicting data regarding the association of AD with contact dermatitis. To the best of our knowledge, no data have yet been published on correlation of atopic skin diathesis with contact allergy. Thus, we stratified our study cohort of 4,509 patients into two groups with and without atopic skin diathesis.

Patients and Methods

This retrospective, multi-center study is based on clinical data collected by the Information Network of Departments of Dermatology (IVDK) during the years 2008–2014. Structure and operating procedures of the IVDK have been described elsewhere [19]. The EAS is a voluntary part of the IVDK patient data documentation. We selected data from five German centers in which the EAS was recorded routinely in all patch tested patients: BG Clinic Falkenstein, SLK Clinics Heilbronn as well as University Hospitals Erlangen, Heidelberg and Marburg. Clinical data and patch test results of all patients were documented electronically in a standardized manner

and transmitted to the IVDK central office at the University of Göttingen. Patch testing with the baseline series of the German Contact Dermatitis Research Group (DKG) was performed according to DKG guidelines [20]. From 2008–2013, tests were performed with commercial test preparations from Almirall Hermal, Reinbek, Germany. In 2014, patch test preparations were obtained from Smart Practice Europe, Reinbek, Germany. Compositae mix II was purchased from Chemotechnique, Vellinge, Sweden. ECT preparations were dispensed into Finn chambers® (8 mm inner diameter) and fixed on Scanpor tape® (Smart Practice). The patches were applied to the upper back and left for 48 h. Patches were read on days 2 (48 h), 3 (72 h), and 4 (96 h). A positive response was graded as a +, ++ or +++ reaction, corresponding to infiltration, papules and/or vesicles, respectively [21]. Erythema only (without palpable infiltrate), irritant or follicular reactions in the test fields were not considered as positive.

According to IVDK guidelines, AD was diagnosed by a dermatologist if a manifest eczema was present or had been present in the past. Minimal variants of AD such as the exclusive presence of Dennie-Morgan infraorbital fold, infraauricular fissure, or periorbital pigmentation were excluded. Allergic rhinitis was diagnosed if current/intermittent and/or persistent allergic rhinitis and/or conjunctivitis were present. Similar criteria applied to bronchial asthma. Aspirin-induced asthma, stress-induced asthma without allergic compound, and all other forms of non-allergic obstructive airway diseases were excluded. Individual atopic skin diathesis independent of active skin disease was assessed by the EAS (Table S1a, online Supporting Information) [16, 17]. The atopy score and its likelihood of atopic skin diathesis and percentages of present AD are depicted in Table S1b (online Supporting Information). An $EAS \leq 7$ is rated with “no and/or improbable risk” of atopic skin diathesis. An $EAS \geq 10$ was considered as atopic skin predisposition/diathesis [16]. A total of 4,509 patients were available for data analysis. Since scoring 8–9 points in EAS is considered to be unreliable for predicting atopic skin diathesis, all patients with a final EAS of 8–9 points were excluded from subgroup analyses. Thus, the final study cohort for subgroup analysis comprised of 3,908 patients scoring ≤ 7 or ≥ 10 , respectively, in EAS.

Additionally, clinical profile and atopic skin manifestation were investigated. The descriptive comparison of the cohorts ($EAS \leq 7$ and $EAS \geq 10$) was performed by using MOAHLFA Index [22, 23]. The MOAHLFA Index includes the parameters male sex, age ≥ 40 years and an occupationally caused dermatitis, and it differentiates between AD and hand, leg and face dermatitis. Differences in population characteristics between the two cohorts ($EAS \leq 7$ and $EAS \geq 10$) were tested for statistical significance by chi-squared test (χ^2). Statistical significance of differences in sensitization frequencies in disjunct subgroups of patients was determined

by non-overlapping 95 % confidence intervals (CI) of the age and sex-standardized proportions of positive reactions. Further, we performed logistic regression analyses with positive reactions to the ten most frequent allergens as target variables. Age (< 40 vs. ≥ 40 years), sex, atopy score ($EAS \leq 7$ and $EAS \geq 10$), past or present AD (yes/no) and medical profession (yes/no) served as explanatory variables. (The latter variable was selected because medical professions were over-represented among patients with a high EAS (18.4 % vs. 6.8 %) (Table S2, online Supporting Information). Data was managed and analyzed using the statistical analysis software SAS®, version 9.4 (SAS Institute, Cary, NC, USA). A P value of $P < 0.05$ was considered to be significant.

Results

Atopic skin diathesis is highly associated with past or present atopic diseases

The well-established MOAHLFA index [22] was used to characterize the study population regarding the effects of atopic skin diathesis according to the extensive EAS (Table S1, online Supporting Information). Briefly, $EAS \leq 7$ was rated as “no or improbable risk” of atopic skin diathesis, whereas $EAS \geq 10$ was considered as atopic skin predisposition/diathesis. Values of 8 or 9 did not allow a clear assignment (indeterminate range) and were therefore discarded. All MOAHLFA items differed significantly between patients with and without atopic skin diathesis (chi²-test, $P < 0.0001$) (Table 1). As expected, atopic skin diathesis was highly associated with past or present atopic diseases (AD, allergic rhinitis, and allergic asthma). Further, patients with atopic skin diathesis were significantly more often diagnosed with occupational (53.5 % vs. 34.5 %) and hand dermatitis (68.4 % vs. 46.1 %). Leg and face dermatitis were significantly less common in patients with atopic skin diathesis. Interestingly, there were more female patients and younger patients (< 40 years) among those with atopic skin diathesis. However, these parameters differed to a lesser extent than the other items of the MOAHLFA index. Next, we assessed relevant differences in the final main diagnosis made by the dermatologist, which was established immediately after reading of the patch test (Table 2). As expected, individuals with atopic skin diathesis were more often diagnosed with AD (37.1 % vs. 6.2 %). These patients were also more often diagnosed with “pruritus of unknown origin” and “dyshidrotic eczema”; which may be related to atopy, at least in some individuals. Interestingly, “chronic irritant contact dermatitis” was diagnosed at identical rates in both groups, independent of atopy (17.6 % vs. 17.7 %). Allergic contact dermatitis and hyperkeratotic eczema were more frequent in patients without atopic skin diathesis. Since occupational exposure is one of the most important factors

Table 1 Descriptive characterization by MOAHLFA-index, plus allergic rhinitis/asthma, in patients without atopic skin diathesis (EAS ≤ 7) versus with atopic skin diathesis (EAS ≥ 10).

MOAHLFA index	EAS ≤ 7		EAS ≥ 10	
	(n = 2165)		(n = 1743)	
	n	%	n	%
Male	1010	46.7	694	39.8
Occupational dermatitis	746	34.5	932	53.5
Atopic dermatitis	222	10.3	1142	65.5
Hand dermatitis	998	46.1	1193	68.4
Leg dermatitis	139	6.4	25	1.4
Face dermatitis	287	13.3	148	8.5
Age ≥ 40 years	1601	73.9	1128	64.7
Allergic rhinitis	227	10.5	747	42.9
Allergic asthma	67	3.1	281	16.1

in sensitization to specific compounds and subsequent development of contact dermatitis, we explored this variable in greater detail by analyzing atopic skin diathesis and the self-reported occupation (Table S2, online Supporting Information). Individuals with atopic skin diathesis worked more often in medical professions (18.4 % vs. 6.8 %). In addition, hairdressers were distinctly more frequent in the group with atopic skin diathesis (4.6 % vs. 2.0 %), albeit with an overall low number of cases.

Atopy is associated with sensitization to selected allergens

All patients received patch-tests with the DKG baseline series. Focusing on the core analysis of this study, 43.0 %

patients (1,938/4,509 patients) displayed at least one positive reaction to the tested allergens. This proportion was significantly higher among patients with atopic skin diathesis, compared to individuals without atopic skin diathesis (49.1 % vs. 38.3 %) (Table 3). As mentioned earlier, reaction frequencies to different allergens are influenced by distribution of age and sex [23]. After detailed characterization of the subgroups with and without atopic skin diathesis, respectively, we calculated frequencies of sensitization to allergens from the baseline series (Table 4). Interestingly, sensitization frequencies of most of the 32 allergens were not associated with atopy. Significantly higher sensitization rates in individuals with atopic skin diathesis were seen only to MI, MCI/MI, fragrance mix I, potassium dichromate, and compositae mix II (Table 4). However, a statistical comparison of patch

Table 2 Final main diagnosis of the dermatologist after evaluation of the patch test, in individuals without atopic skin diathesis (EAS ≤ 7) versus atopic skin diathesis (EAS ≥ 10).

Final main diagnosis	EAS ≤ 7		EAS ≥ 10		Significance
	(n = 2165)		(n = 1743)		Chi ² -test, P value
	n	%	n	%	
Atopic dermatitis	135	6.2	647	37.1	<0.0001
Chronic irritant contact dermatitis	380	17.6	308	17.7	0.92
Allergic contact dermatitis	441	20.4	191	11.0	<0.0001
Hyperkeratotic eczema	175	8.1	63	3.6	<0.0001
Dyshidrotic eczema	101	4.7	112	6.4	0.016
Pruritus of unknown origin	79	3.6	91	5.2	0.017

Table 3 Frequency of reactions (none or at least one) to allergens of the baseline series of the overall cohort, and of patients without atopic skin diathesis ($EAS \leq 7$) versus atopic skin diathesis ($EAS \geq 10$). The group of ≥ 1 reaction is described in further detail. The following reactions to the patch test substances were assessed as one positive reaction only: Methylchloroisothiazolinone /methylisothiazolinone (MCI/MI) and Methylisothiazolinone (MI); Mercaptobenzothiazole (MBT) and Mercapto mix; Fragrance mix II and hydroxyisohexyl 3-cyclohexene carboxaldehyde (HICC); Compositae mix I and Compositae mix II.

Frequency of positive ECT reactions	Overall cohort		$EAS \leq 7$		$EAS \geq 10$		Significance
	$(n = 4509)$		$(n = 2165)$		$(n = 1743)$		Chi ² -test, P value
	n	%	n	%	n	%	
0	2571	57.0	1335	61.7	888	50.9	<0.0001
≥ 1	1938	43.0	830	38.3	855	49.1	
1	1054	23.4	456	21.0	460	26.4	<0.0001
2	473	10.5	203	9.4	200	11.5	0.0321
3	206	4.6	91	4.2	94	5.4	0.0817
4	93	2.1	35	1.6	44	2.5	0.0450
5	58	1.3	20	0.9	33	1.9	0.0092
6	31	0.7	12	0.6	17	1.0	0.1274
≥ 7	23	0.5	13	0.6	7	0.4	0.3865

test results with compositae mix II must be interpreted with care since the number of patients tested was low.

Atopic skin diathesis proved to be the most important intrinsic factor for contact sensitization

To address the question whether atopic skin diathesis is an independent influencing variable for sensitization to specific contact allergens, a logistic regression analysis was performed. The effect of a high EAS on reactivity to the ten most frequent allergens, controlled for past or present AD, age, sex, and having a medical profession, is presented in Table 5. Atopic skin diathesis was found to be associated with a significantly higher risk of sensitization to MI and MCI/MI, thiuram mix, as well as nickel, cobalt and chromium. In contrast, past or present AD was identified as being a less relevant variable, increasing only the risk of sensitization to MI and fragrance mix I. Unexpectedly, past or present AD appeared as a protective factor for a sensitization to Balsam of Peru. Results regarding the influence of sex and age confirmed published knowledge. Male sex meant an increased risk of being sensitized to chromium and colophony, but was negatively associated with sensitizations to nickel, cobalt, or fragrances. A higher age (40+) increased the risk of fragrance

allergy and sensitization to MCI/MI and MI. Having a medical profession significantly increased the risk of sensitization to MCI/MI, fragrance mix II, and thiuram mix.

Discussion

The aim of this study was to investigate the overall and specific prevalence of allergic contact sensitizations in patients with and without atopic skin diathesis. Our findings revealed a significantly higher rate of at least one positive patch test in patients with atopic skin diathesis than in those without (49.1 % vs. 38.3 %). Indeed, logistic regression analysis indicated that atopic skin diathesis rather than past or present AD is the most important influencing factor in sensitizations to MCI/MI and MI, thiuram mix, as well as nickel, cobalt and chromium. All other compounds investigated of the DKG baseline series showed identical frequencies in individuals with and without atopic skin diathesis. Some compounds were generally low in number of positive reactions, thus an even larger study group is needed for verification of these results. The EAS, based on atopic signs and symptoms as well as lab results, is a standardized tool to identify atopic skin diathesis in dermatitis patients to estimate their likelihood of having AD [17]. Although the EAS is widely used in Germany to support differentiation of occupational skin

Table 4 Patch testing with 32 allergens from the DKG baseline series. The vehicle was petrolatum unless otherwise marked. Significant differences in age and sex-standardized proportions of patients with positive reactions are marked in bold print. A blue background indicates significantly decreased 95 % confidence intervals (95 % CI) whereas a red background shows significantly increased 95 % CI.

Substance	Conc.	n[test]	EAS ≤ 7 (n = 2165)			EAS ≥ 10 (n = 1743)		
			n[pos.]	Age- and sex-standardized %positive [95 % CI]	n[test]	n[pos.]	Age- and sex-standardized %positive [95 % CI]	
Nickel (II)-sulfate	5 %	2144	250	14.4 [12.6–16.3]	1725	300	17.9 [16.1–19.8]	
Fragrance mix	8 %	2155	152	6.0 [5.0–7.1]	1737	165	9.2 [7.8–10.6]	
(Chloro)-Methylisothiazolinone (MCI/MI)	0.01 % aq.	2154	60	2.7 [1.9–3.5]	1737	133	7.2 [5.9–8.4]	
Cobalt (II)-chloride	1 %	2152	92	4.8 [3.7–5.9]	1735	117	6.8 [5.5–8.0]	
Methylisothiazolinone	0.05 % aq.	1932	59	2.9 [2.1–3.8]	1681	114	6.4 [5.2–7.6]	
Fragrance-mix II	14 %	2154	90	3.7 [2.9–4.6]	1739	94	5.0 [4.0–6.0]	
Potassium dichromate	0.5 %	2156	60	2.5 [1.8–3.3]	1735	90	4.9 [3.8–5.9]	
Thiuram mix	1 %	2156	56	2.6 [1.8–3.4]	1737	78	4.4 [3.4–5.4]	
Myroxylon pereirae resin (balsam of Peru)	25 %	2156	150	6.0 [4.9–7.0]	1739	83	4.3 [3.4–5.2]	
Colophony	20 %	2153	82	3.4 [2.6–4.3]	1737	79	4.3 [3.3–5.3]	
Dibromdicyanobutan (Methyl-dibromo Glut.)	0.2 %	2157	50	2.0 [1.3–2.6]	1737	57	3.0 [2.2–3.8]	
Compositae mix II	5 %	814 [#]	8	0.8 [0.2–1.4]	876 [#]	25	2.6 [1.6–3.7]	
HICC (e.g. Lyrat [®])	5 %	2158	43	1.9 [1.3–2.5]	1739	47	2.6 [1.8–3.3]	
Wool alcohols	30 %	2157	64	2.9 [2.1–3.7]	1739	41	2.5 [1.7–3.3]	
Compositae Mix	5 %	1349 [#]	13	0.9 [0.3–1.4]	866 [#]	20	2.0 [1.1–2.9]	
Formaldehyde	1 % aq.	2159	29	1.2 [0.7–1.7]	1739	32	1.9 [1.2–2.6]	
Epoxy resin	1 %	2161	32	1.1 [0.6–1.5]	1739	32	1.7 [1.1–2.4]	
Bufexamac	5 %	2047	12	0.6 [0.2–1.0]	1553	23	1.7 [1.0–2.5]	
Propolis	10 %	2155	58	2.6 [1.8–3.3]	1738	31	1.6 [1.0–2.2]	
Ylang ylang oil (I + II)	10 %	2098	36	1.6 [1.0–2.1]	1701	25	1.5 [0.9–2.2]	
Iodopropynyl butylcarbamate	0.2 %	1933	23	1.4 [0.7–2.0]	1687	25	1.4 [0.8–1.9]	
N-isopropyl-N'-phenyl-p-phenylenediamine	0.1 %	2157	16	0.7 [0.3–1.1]	1738	26	1.4 [0.8–1.9]	
Turpentine	10 %	2158	33	1.3 [0.7–1.8]	1739	22	1.1 [0.7–1.6]	
Jasmine absolute	5 %	2098	16	0.6 [0.3–0.8]	1701	21	1.1 [0.6–1.6]	

Table 4 Continued.

Substance	EAS ≤ 7 (n = 2165)				EAS ≥ 10 (n = 1743)			
	Conc.	n[test]	n[pos.]	Age- and sex-standardized %positive [95 % CI]	n[test]	n[pos.]	Age- and sex-standardized %positive [95 % CI]	
Bronopol (2-bromo-2-nitropropane-1,3-diol)	0.5 %	2156	15	0.5 [0.2–0.7]	1738	18	0.9 [0.5–1.3]	
Sandal wood oil	10 %	2098	25	1.1 [0.6–1.6]	1701	15	0.9 [0.4–1.4]	
Zinc-diethyldithiocarbamate	1 %	2158	12	0.5 [0.2–0.8]	1737	15	0.9 [0.4–1.3]	
Mercaptobenzothiazole	2 %	2157	20	1.2 [0.6–1.7]	1738	15	0.9 [0.4–1.4]	
Mercapto-Mix without MBT (only CBS, MBTS, MOR)	1 %	2157	19	1.1 [0.6–1.7]	1739	15	0.9 [0.4–1.4]	
Cetyl stearyl alcohol	20 %	2158	22	1.0 [0.5–1.4]	1739	8	0.5 [0.1–0.8]	
P-tert-butylphenol-formaldehyde resin	1 %	2047	18	0.8 [0.4–1.2]	1539	8	0.4 [0.1–0.8]	
Paraben-Mix	16 %	2158	14	0.7 [0.3–1.2]	1739	6	0.4 [0.1–0.7]	
n [test] = total number of tested individuals. n [pos.] = total number of patients with a positive reaction. % [pos.] = percentage of patients with positive reaction. #Reduced number of patients tested because the allergen preparation was not part of the DKG baseline series through the entire study period.								

Table 5 Odds ratios with 95 % confidence intervals (95 % CI) resulting from logistic regression analyses with positive reactions (sensitization) to the respective allergen as target variables and five influencing variables. Significant differences are marked in bold print. A blue background marks significantly decreased 95 % CI, and a red background highlights significantly increased 95 % CI.

Positive reaction to allergen	EAS ≥ 10	Past or present atopic dermatitis	Medical profession	Male sex	Age 40 +
Methylchloroisothiazolinone/Methylisothiazolinone (MCI/MI)	2.383 [1.631–3.500]	1.363 [0.956–1.955]	1.724 [1.166–2.512]	0.885 [0.639–1.218]	1.814 [1.284–2.616]
Potassium dichromate	2.089 [1.388–3.143]	1.036 [0.694–1.555]	0.732 [0.392–1.272]	1.442 [1.025–2.035]	1.311 [0.906–1.935]
Methylisothiazolinone	1.891 [1.269–2.832]	1.569 [1.075–2.308]	1.281 [0.826–1.941]	0.902 [0.644–1.260]	1.725 [1.204–2.523]
Cobalt (II)-chloride	1.683 [1.188–2.380]	0.894 [0.629–1.272]	1.031 [0.674–1.535]	0.580 [0.422–0.790]	0.948 [0.700–1.297]
Thiuram mix	1.614 [1.041–2.502]	1.095 [0.710–1.696]	1.667 [1.029–2.626]	0.849 [0.576–1.242]	1.292 [0.873–1.954]
Nickel (II)-sulphate	1.530 [1.210–1.933]	0.996 [0.785–1.264]	1.037 [0.796–1.342]	0.205 [0.159–0.262]	0.940 [0.765–1.157]
Fragrance-mix II	1.317 [0.906–1.905]	0.903 [0.615–1.324]	1.993 [1.325–2.943]	0.756 [0.539–1.053]	2.053 [1.407–3.083]
Colophony	1.292 [0.860–1.931]	1.209 [0.801–1.828]	0.583 [0.290–1.062]	1.400 [1.003–1.961]	1.361 [0.940–2.012]
Fragrance mix	1.193 [0.890–1.596]	1.381 [1.028–1.857]	1.021 [0.712–1.437]	0.650 [0.503–0.837]	1.923 [1.447–2.591]
Myroxylon pereiirae (Balsam of Peru)	0.919 [0.653–1.280]	0.620 [0.424–0.900]	0.920 [0.571–1.425]	0.672 [0.502–0.895]	2.453 [1.702–3.646]

disease from intrinsic skin diseases such as AD, it has never gained similar international recognition and application. Limited diagnostic performance of the EAS has been attributed to insufficient validation of the score in community versus hospital settings and investigator bias due to the presence or absence of flexural dermatitis [24, 25]. Thus, future research for improvement of the EAS or establishment of a superior method to assess atopic skin diathesis should be encouraged. Some studies reported a higher prevalence of ACD in AD [9, 26], while others did not identify relevant differences compared to individuals without AD [7, 10, 13, 27]. Gene expression studies even suggested an attenuated immune response to contact allergens in AD patients, although the authors did not present clinical data for their sampled patient cohort of ten AD patients [6]. Thus, existing data show a trend towards higher allergic sensitization rates in patients with AD, although these differences seem to be modest at best, without dissecting reactivity to specific allergens.

Impaired skin barrier function has been identified as one of the most important pathogenic factors in AD, with *filaggrin* expression, deficiency of antimicrobial peptides, modified microbiome, and altered composition of intercellular lipids being involved in formation of the deficient skin barrier [28]. A recent systematic review on 40 studies investigating skin penetration and absorption described an almost doubled skin absorption rate of different compounds penetrating the skin of AD patients, compared to healthy controls [29]. However, dinitrochlorobenzene (DNCB) penetration in human skin explants revealed no difference in skin penetration of controls vs. AD patients, independently of *filaggrin* mutation status [30]. Further, AD patients being sensitized to DNCB responded to a second DNCB challenge with a positive skin reaction in 100 % of patients with mild AD (40/40 patients), whereas only 33 % of patients with severe AD (8/24) displayed a positive challenge test [31].

Current research has tested the hypothesis that hapten-specific properties rather than general effects of immune polarization that favor or counter ACD development may be involved [32]. Thus, manifestation of ACD may depend on (1) hapten-specific properties influencing penetration of the skin barriers, (2) immunological features of the hapten and/or allergen facilitating immune activation in the skin after penetration, (3) status of the immune activation or non-activation condition in the skin/of the host before penetration or incorporation of the allergen. Our patient cohort with atopic skin diathesis showed significantly increased sensitization rates to the metal salts nickel, cobalt, and chromium. Earlier work suggested a functional relationship between nickel allergy and *filaggrin* mutation status [33]. Of note, no significant difference was found in our study for sensitization rates to the metal salts in correlation to past or present AD, as proposed earlier. Our findings are consistent with a

recent meta-analysis that failed to identify a relevant correlation between nickel sensitization and AD [27]. This may be explained by immunological and clinical considerations: (1) Human skin biopsies from positive nickel-patch tests demonstrated an attenuated Th1 and Th2-immune response with increased Th17/IL-23 skewing [6], (2) suitability of patch-testing patients with atopic skin diathesis and/or AD affects test results. Patients with AD are more often suspected to display more doubtful or weak positive reactions (particularly follicular reactions) to metal salts such as nickel sulphate, cobalt chloride, and potassium dichromate [34]. Doubtful irritant reactions are especially seen on Day 1 of patch test reading in patients with a predisposition towards AD (according to the criteria of Hanifin and Rajka), compared to patients without a history or present atopic dermatitis [35]. However, a generalization of this observation should be avoided in light of our recent publication demonstrating a lack of correlation of irritant contact dermatitis (induced by SLS in patch tests) in individuals with atopic skin diathesis or atopic diseases [36].

The frequent use of emollients in AD patients may entail a higher risk for acquisition of ACD towards these compounds. Frequency of contact allergy to MCI/MI was strongly elevated in patients with atopic skin diathesis, but again not in patients with past or current AD. The use of methylisothiazolinone as cosmetic preservative at higher concentrations than before resulted in a dramatic increase of sensitization to MI in the last decade [37]. Patients with atopic skin diathesis were significantly more often affected with occupational dermatitis and hand dermatitis in our study group. Subgroup analyses showed that especially medical professions with atopic skin diathesis have a significantly increased risk for MCI/MI and MI sensitization. These findings are in accordance with the results of a German analysis of ECT results in nurses as well as earlier studies on AD patients in the IVDK network [10, 38].

The higher incidence of sensitization to fragrances in patients with AD is in line with former study results identifying increased fragrance sensitization in AD patients [9, 10]. Interestingly, we confirmed a weak, but significant association of fragrance sensitization with AD, but no association with atopic skin diathesis. Fragrance mix was reported to primarily activate the Th2/Th22-axis [5, 32], which induces similar cytokines as found in acute AD [1]. In our study cohort, fragrance mix I was one of the few allergens increased in patients with AD. However, positive reactions to fragrance mix I are frequently false positives, since patch-testing with the eight individual fragrances from this mix are positive in 55–60 % of patients only. Fragrances are also known as potential substances responsible for irritant reactions in patients with AD [34]. Thus, classifying patients with and without atopic skin diathesis may allow a better discrimination in the assessment of patch test results to fragrances than being positive or negative

for past or present AD. Our association of sensitization to fragrances with higher age (40+) and medical profession is in line with earlier studies [39, 40].

In summary, we identified some relevant differences in the spectrum of allergic sensitizations in individuals with atopic skin diathesis. Consequently, individuals with atopic skin diathesis may profit from avoidance of a few specific compounds that convey an increased risk of ACD. The overall risk of ACD is largely similar to that of healthy individuals. Owing to this observation, we currently do not suggest the elimination of specific allergens in patients with atopic skin diathesis until more confirmatory studies become available. It seems plausible that epidermal barrier impairment may be a risk factor in acquisition of contact dermatitis; however, it is arguably not the sole explanation for these observations. Since recent findings on ACD have begun to elucidate the different immune-polarizing properties of haptens as well as the relevance of immune-polarizing and genetic or barrier factors of the individual, our data add important new aspects to the growing body of evidence for precision medicine in ACD.

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Table S1a Items of the Erlangen atopy score (EAS). Awarding partial points (0.5 points) is encouraged, if the symptom/item is weakly expressed or unclear.

Family history of atopy (first degree relatives)	
Eczema	max. 2 points
Family history of allergic rhinitis/asthma	max. 0.5 points
Personal history of atopic diseases	
Personal history of allergic rhinitis/ conjunctivitis	1 point
Personal history of allergic asthma	1 point
Cradle cap in the newborn period	1 point
Itch when sweating	3 points
Wool intolerance	3 points
Metal intolerance (e.g. nickel sensitivity)	1 point
Photophobia	1 point
Minimal forms of atopic dermatitis	
Xerosis	3 points
Ear rhagades	2 points
Dyshidrosis/ podopompholyx	2 points
Pityriasis alba	2 points
Atopic winter feet/ pulpitis sicca	2 points
Nipple eczema	2 points
Cheilitis sicca/ perleche	1 point
Atopic signs	
Hyperlinear palms	max. 2 points
Hertoghe sign	max. 2 points
“Dirty neck”	max. 2 points
Keratosis pilaris	max. 1 point
Dermal neurovegetative Symptoms	
White dermographism	max. 2 points
Acrocyanosis	1 point
Laboratory results	
Total serum IgE > 150 U/ml	1 point
Total serum IgE > 400 U/ml	2 points
Positive immunocap assay	1 point

Table S1b: Evaluation / Assessment of the total score of the EAS.

Erlangen Atopy Score [points]	Percentage of patients with atopic eczema	Assessment
0–3	0	No atopic skin diathesis
4–7	5	Improbable atopic skin diathesis
8–9	34	Indistinct atopic skin diathesis
10–14	78	Atopic skin diathesis
15–19	97	Atopic skin diathesis
> 20	100	Atopic skin diathesis

Table S2 Occupation of the individuals in the study group, in patients without atopic skin diathesis ($EAS \leq 7$) versus with atopic skin diathesis ($EAS \geq 10$).

Occupation	EAS ≤ 7		EAS ≥ 10		Significance
	(n = 2165)		(n = 1743)		
	n	%	n	%	Chi ² -test, p-value
Medical professions	148	6.8	320	18.4	< 0.0001
Undefined occupational exposure	616	28.5	279	16.0	< 0.0001
Mechanics and tool makers	194	9.0	181	10.4	0.1331
Office workers	209	9.7	118	6.8	0.0012
Hairdressers	44	2.0	81	4.6	< 0.0001
Housekeeping	120	5.5	71	4.1	0.0342
Metalworkers	76	3.5	55	3.2	0.5401
Cleaners	58	2.7	52	3.0	0.5674
Locksmiths and plumbers	55	2.5	51	2.9	0.4608
Teacher and pastoral workers	44	2.0	49	2.8	0.1123

Tabelle S1a Kriterien des Erlanger Atopie-Scores (EAS). Die Vergabe von halben Punkten (0,5 Punkte) ist dann vorgesehen, wenn das Symptom/Kriterium nur schwach ausgeprägt oder unklar ist.

Familienanamnese atopischer Erkrankungen (Verwandte ersten Grades)	
Ekzem	max. 2 Punkte
Familienanamnese allergische Rhinitis/Asthma	max. 0,5 Punkte
Eigenanamnese atopische Erkrankungen	
Eigenanamnese allergische Rhinitis/Konjunktivitis	1 Punkt
Eigenanamnese allergisches Asthma	1 Punkt
Milchschorf als Neugeborenes	1 Punkt
Juckreiz beim Schwitzen	3 Punkte
Unverträglichkeit auf Wolle	3 Punkte
Metallunverträglichkeit (e.g. Nickelunverträglichkeit)	1 Punkt
Photophobie	1 Punkt
Minimale Formen der atopischen Dermatitis	
Trockene Haut	3 Punkte
Ohr-Rhagaden	2 Punkte
Dyshidrose/ Podopompholyx	2 Punkte
Pityriasis alba	2 Punkte
Atopischer Winterfuß/ Pulpitis sicca	2 Punkte
Brustwarzenekzem	2 Punkte
Cheilitis sicca/ Perlèche	1 Punkt
Atopische Stigmata	
Hyperlineare Handflächen	max. 2 Punkte
Hertoghe-Zeichen	max. 2 Punkte
„Dirty neck“	max. 2 Punkte
Keratosis pilaris	max. 1 Punkt
Dermales Neurovegetativum	
Dermographismus albus	max. 2 Punkte
Akrozyanose	1 Punkt
Laborwerte	
Gesamt-IgE im Serum > 150 U/ml	1 Punkt
Gesamt-IgE im Serum > 400 U/ml	2 Punkte
Positiver Immunocap-Assay	1 Punkt

Tabelle S1b: Auswertung / Einschätzung des EAS-Gesamtscores

Erlanger Atopie-Score [Punkte]	Prozentsatz der Patienten mit atopischem Ekzem	Beurteilung
0–3	0	Keine atopische Hautdiathese
4–7	5	Atopische Hautdiathese unwahrscheinlich
8–9	34	Atopische Hautdiathese unklar
10–14	78	Atopische Hautdiathese

15–19	97	Atopische Hautdiathese
> 20	100	Atopische Hautdiathese

Tabelle S2 Beruf der Personen in der Studienkohorte, aufgeschlüsselt nach Personen ohne atopische Hautdiathese ($EAS \leq 7$) versus solche mit atopischer Hautdiathese ($EAS \geq 10$).

Beruf	EAS ≤ 7		EAS ≥ 10		Signifikanz
	(n = 2165)		(n = 1743)		
	n	%	n	%	Chi ² -test, p-Wert
Medizinischer Beruf	148	6,8	320	18,4	< 0,0001
Undefinierte berufliche Exposition	616	28,5	279	16,0	< 0,0001
Mechaniker und Werkzeugmacher	194	9,0	181	10,4	0,1331
Büroangestellte	209	9,7	118	6,8	0,0012
Friseure	44	2,0	81	4,6	< 0,0001
Hausangestellte	120	5,5	71	4,1	0,0342
Metallverarbeitender Beruf	76	3,5	55	3,2	0,5401
Reinigungskräfte	58	2,7	52	3,0	0,5674
Schlosser und Klempner	55	2,5	51	2,9	0,4608
Lehrer und Seelsorger	44	2,0	49	2,8	0,1123