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Atopic dermatitis shows significant cutaneous comorbidity: results from large-scale investigations in the working population

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Abstract

Background

Atopic dermatitis (AD) is one of the most common chronic inflammatory diseases of the skin. Rare large-scale data have been published on the prevalence of concomitant dermatoses.

Objective

To analyze the prevalence and cutaneous comorbidity of AD in Germany.

Methods

A cross-sectional study on voluntary whole-body skin checks by trained dermatologists in over 400 companies throughout Germany reflecting the adult working population was conducted. Prevalence ratios (PR) were calculated to compare dermatological comorbidity in employees with and without current AD. A logistic regression analysis controlling for age, sex and skin type revealed odds ratios (OR) of the occurrence of skin diseases in AD.

Results

A total of N = 118,939 people were examined between 2006 and 2017 (43.2 % female, mean age 43.2 ± 10.7 years, min. age 16 years, max. age 70 years). AD (point prevalence) was identified in 1.45 % (men: 1.50 %, women 1.39 %) and decreased significantly with age. Self-reported lifetime prevalence of AD was 4.95 % (men: 3.72 %, women: 6.55 %). The following skin diseases were significantly more frequent in people with current AD: Contact dermatitis (PR 3.38), hand eczema (PR 4.62), exsiccation dermatosis (PR 2.19), folliculitis (PR 1.95), and port wine stains (PR 1.49). Among those, folliculitis was the most frequent (prevalence in AD 16.42 %). Controlled for age, sex and skin type, AD was significantly associated with – among others - hand eczema (OR 3.96; 95 % CI 2.95-5.32), contact dermatitis (OR 2.97; 95 % CI 1.50-5.88) and exsiccation dermatosis (OR 1.78; 95 % CI 1.30-2.44). Psoriasis was significantly less frequent in people with AD (OR 0.61; 95 % CI 0.39-0.94).

Conclusion

In summary, cutaneous comorbidity is frequent and of great importance in people with AD, suggesting the need for comprehensive, dermatologically guided diagnostics in AD.

Background

Atopic dermatitis (AD) is one of the most common chronic inflammatory diseases of the skin. Worldwide, lifetime prevalence increased in the past decades and has reached a maximum prevalence threshold of 20 % in developed countries.^{1,2} However, trends in prevalence are quite heterogeneous between different age groups. In Germany, AD shows a point prevalence of 2-4 % in adults^{3,4} and 8-13 % in children.⁵⁻⁷ Lifetime prevalence rates of AD were reported to be 3.5 % for adults⁸ and 13.2 % for children.⁹ Symptoms of AD include itch, pain, erythema, lichenification, scaling, oozing/weeping, and prurigo nodules. The patients suffer from insomnia, social anxiety and the presence of visible skin changes. AD is known to significantly impact the quality of life of affected patients and their families.¹⁰⁻¹³

As with psoriasis vulgaris, comorbidities play an important role in AD. Data from German health insurance companies show a significantly increased rate of atopic diseases such as asthma and allergic rhinitis, skin infections as well as vitiligo and alopecia.⁴ Furthermore, patients with early onset of cholinergic urticaria have been found to have a significantly higher rate of concomitant atopic dermatitis (16.9 % vs 5.2 %; $p = 0.028$).¹⁴ Additionally, patients with AD suffer from increased frequencies of hand eczema and allergic contact dermatitis.¹⁵

AD has been shown to occur in association with allergic rhinitis and asthma, indicating that these diseases might share causal mechanisms.¹⁶ Some studies describe AD as the first step in the atopic march leading eventually to asthma and allergic rhinitis, while recent epidemiological studies rather refer to the epidermis and its barrier functions. Especially studies on a population based level indicate that there does not necessarily have to be a causal association between atopy and AD.^{17,18}

Up to now, there has been a lack of sufficiently large populations based cohorts with verified data on dermatological comorbidities of AD in Germany. Shortcomings of health insurance data might be the lack of verifiability of the findings and thus possible coding errors in comparison to direct dermatological examination. Against this background, the present study was conducted with the objective to determine robust data on the prevalence of dermatological comorbidity in people with AD in the adult population.

Methods

An observational study with cross sectional design was carried out between 2006 and 2017. The investigational procedure followed a standardized, quality-assured scheme as described in previous publications.^{19–21} The database was derived from company-based skin screenings, conducted in more than 400 German companies nationwide. There was a variety of different branches including producing, marketing, trading, banking and service providing entities. Trained dermatologists performed standardized full body examinations on all employees who were willing to participate, and documented all clinical findings and anamnestic data in an electronic database.

In the AD-specific documentation, a distinction was made between people with AD as the current diagnosis (clinical signs according to the criteria of Hanifin and Rajka at time of skin check²²), and those who reported a confirmed diagnosis of AD in anamnestic interviews. In this article, the former is referred to as ‘physician-reported point prevalence’, the latter as ‘patient-reported lifetime prevalence’. Equivalent to the assessment of AD at time of screening, dermatological comorbidity was obtained from the clinical examinations. Thus, all analyses in relation to comorbidity refer to point prevalence rates of AD and concomitant skin diseases solely.

In total, 22 inflammatory, viral, bacterial or fungal skin diseases as well as vascular lesions of the skin were assessed next to AD in the course of the examinations. Due to the explorative design of our analyses we considered all these as potential concomitant conditions of AD. Next to atopic dermatitis, history of allergic rhinoconjunctivitis and allergic asthma was assessed in the course of the interviews and reported as patient-reported lifetime prevalence.

Statistical analyses were performed using SPSS for Windows version 23. Prevalence rates were calculated as percentage values of the study population. Missing data on clinical signs and in anamnestic interviews of the diagnoses of interest were rated as ‘not prevalent’. Group differences according to age, gender or skin type were tested by Chi²-tests. 95 % confidence intervals (95% CI) of prevalence rates were computed based on an inverse-chi-squared distribution. The frequency of occurrence of concomitant skin conditions was compared between the groups “AD point prevalence (physician-reported)”, “AD lifetime prevalence (patient-reported)” and “Participants without AD at any time”. Due to the unequal gender distribution in these groups a direct standardization was performed based on the

gender distribution in the total sample for these comparisons. To explore the association of current AD and further dermatological conditions, crude prevalence ratios were calculated. Logistic regression analysis was performed to test whether there are associations between current AD (dependent variable) and the other skin conditions when controlling for age, gender and skin type. To account for multiple significance testing in the logistic regression using 27 possible predictors, Bonferroni correction of p-values was applied. Uncorrected p-values were reported and those, that remain significant after correction, were marked.

Results

During the 12-years period of data assessment, a total of 118,939 people was clinically examined and surveyed by dermatologists (Table 1). Of these, 43.2 % were female, mean age was 43.2 ($\pm$ 10.7) years.

Prevalence of atopic dermatitis

Point prevalence, i.e. AD diagnosed at clinical examination, was 1.45 % (n = 1,724; 1.50 % for men and 1.39 % for women) and decreased significantly with age (Table 1). Almost 5 % of the employees reported an anamnestic diagnosis of AD, i.e. lifetime prevalence. In contrast to the screening diagnoses, AD in medical history was stated significantly more often by women (6.6 %) than by men (3.7 %). Fitzpatrick skin type showed no constant trend for AD point prevalence. However, lifetime prevalence was highest and significantly elevated ($p \leq 0.001$) in people with skin type III.

Overall, 5.8 % of the study participants (n = 6,885) have had either an anamnestic or a current diagnosis of AD. Among those currently diagnosed at screenings, 41.9 % reported an anamnestic AD, too (Table 2).

Cutaneous Comorbidity

Prevalence of skin diseases, other than AD, corresponds to ranges as observed in occupational screenings from previous time periods.¹⁹ Significant differences in prevalence for people with current AD vs. no AD at any time were found for several skin diagnoses (Table 2, Fig. 1). For example, employees diagnosed with AD

suffered significantly more often from hand eczema (prevalence more than four times higher), contact dermatitis, and exsiccation dermatosis. Apart from pre-existing conditions (allergic rhinoconjunctivitis and allergic asthma), the most common and significantly elevated comorbidities in patients with AD were folliculitis (19.53 %; PR 1.95) and port wine stains (3.07 %; PR 1.49). Allergic asthma (PR 2.62) and allergic rhinoconjunctivitis (PR 1.58) obtained from anamnestic interviews were significantly more frequent when compared to people without AD.

The regression analysis (Table 3, Fig. 1), with the different skin conditions as well as age, gender and skin-type as possible predictors and current AD as dependent variable, revealed comparable findings. Hand eczema (OR 3.96), folliculitis (OR 2.03), allergic asthma (OR 2.03), exsiccation dermatosis (OR 1.78), allergic rhinoconjunctivitis (OR 1.56), and port wine stains (OR 1.45) were significantly and positively associated with AD. Psoriasis was a significant negative predictor (OR 0.61) for AD. Furthermore, the association of AD with contact dermatitis (OR 2.97) and tinea corporis (OR 2.00) reached statistical significance in the regression analysis.

Discussion

The objective of the present study was to determine dermatological comorbidity in patients with atopic dermatitis in the general working population. One background to this objective was an extensive analysis of German claims data, in which significantly increased prevalence rates of vitiligo, alopecia, skin infections and atopic diseases were found in people with atopic dermatitis.⁴ These findings in a clinically uncontrolled cohort of patients from secondary data analysis should now be investigated in large-scale clinical examinations conducted by well-trained dermatologists.

We report a point prevalence of physician-diagnosed AD of 1.45 % and a patient-reported lifetime prevalence of 4.95 %. Our data show that both patients with present flares of atopic dermatitis and patients with a history of atopic dermatitis have a significantly higher rate of comorbid diseases as also found in the health insurance data.⁴ In the current analysis hand eczema, contact dermatitis, exsiccation dermatosis, and folliculitis were significantly associated with AD. Furthermore, the

coexistence of AD with allergic asthma and allergic rhinoconjunctivitis was confirmed. This finding underlines the necessity to examine patients with atopic dermatitis for the presence of further skin diseases. In general, patients with atopic dermatitis as well as people with atopic disposition should also be advised about the risks of cutaneous co-morbid diseases.

The data largely correspond with previous publications on smaller and more focused patient groups. Hand eczema has been described before to be significantly associated with AD²³ and contact dermatitis has been found to be especially relevant among patients with adult-onset of AD.²⁴ *Malassezia* yeasts, which are known to cause folliculitis, also have already been discussed to be associated with atopic dermatitis.^{25,26} Furthermore, patients with AD have been shown to be at increased risk for skin infections with *Staphylococcus aureus*, eczema herpeticum, eczema vaccinatum, and eczema cocksi. ²⁷ Epidermal skin barrier defects in AD might be a reason for an increased transepidermal water loss, which explains the associated xerosis and allows greater penetration of allergens, irritants, and skin colonizing organisms that can result in a skin infection.^{18,28,29} Dysfunctional epidermal barrier in AD and associated pathophysiological changes of the epidermis as well as a pathological colonization of the microbiome could contribute to the increased risk of skin infections as well as the increased occurrence of stress and burden of disease.

The association of AD with further atopic conditions is well known from primary¹⁶ as well as secondary data.⁴ By contrast, the findings of an association of AD with port wine stains as well as the negative association with psoriasis are less well described. Nevertheless, due to the large cohort and the exclusive examinations by dermatologists, these findings seem reliable. However, there is need for further exploration on the negative correlation of atopic dermatitis and psoriasis. From the clinical point of view, the concurrent occurrence of these two entities in fact seems to be rare. A publication from Eyerich et al. supports the scarcity of such concordance but presents single cases with facets of both a Th2-related pattern of atopic dermatitis and a Th1- and Th17-driven psoriasis profile in the same patients at the same time but in different locations.³⁰ The positive association of atopic dermatitis and port wine stains has not yet been described in literature. However, more workup on this needs to be done before coming to a conclusive theory.

The cohort of more than 110,000 workers investigated represents a valid, sufficiently large data basis. However, the methodology of data collection implies a number of peculiarities and limitations that should be considered when interpreting the results. Such a large cohort allows for analysis of skin diseases in the general population even of those with low prevalence rates. However, in case absolute numbers in subgroups are rather small ($n < 10$), results should be discussed with caution. In our analysis, this was the case for participants with AD and contact dermatitis ($n = 9$), AD and verruca vulgaris hands ($n = 8$), and AD and pyoderma ($n = 9$). Furthermore, data were collected in the course of skin screenings in companies. This could lead to certain selection effects due to the different morbidity profile of the working population compared to unemployed people, also known as healthy worker effect.³¹ Additionally, the study population might be selected due to the voluntary nature of the screenings. However, there is no reason to assume that people with AD differ from those with other skin conditions in their willingness to participate. Thus, the analysis of comorbidity most probably shows a low level of bias. Methodology driven changes in prevalence rates over time can be excluded as the method of data assessment was constant over the years. Diagnoses were made by trained dermatologists exclusively based on clinical symptoms without further laboratory confirmation. Therefore, the point prevalence of atopic dermatitis diagnosed clinically according to the Hanifin and Rajka criteria was limited to patients with current flares while lifetime prevalence was based on patient-reported previous diagnosis of AD.

In summary, cutaneous comorbidity is frequent and of great importance in people with AD, suggesting the need for comprehensive, dermatologically guided diagnostics in AD.

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Tables

Table 1 Cohort of examined employees by gender, age, skin type and AD prevalence

	Sample description of the total cohort		Prevalence rates							
			AD point prevalence (physician-reported)		AD lifetime prevalence (patient-reported)		AD lifetime prevalence combined (physician or patient-reported)		no AD (at any time)	
	N	%	n	%	n	%	n	%	n	%
Total	118,939	100.00	1,724	1.45	5,883	4.95	6,885	5.79	112,054	94.21
Gender										
Female	51,411	43.22	714	1.39	3,369	6.55	3,723	7.24	47688	92.76
Male	67,528	56.78	1,010	1.50	2,514	3.72	3,162	4.68	64366	95.32
Age groups										
16-29	14,758	12.41	239	1.62	1,147	7.77	1,265	8.57	13493	91.43
30-39	29,127	24.49	444	1.52	1,769	6.07	1,996	6.85	27131	93.15
40-49	39,888	33.54	547	1.37	1,830	4.59	2,142	5.37	37746	94.63
50-59	29,233	24.58	409	1.40	993	3.40	1,274	4.36	27959	95.64
60-70	5,933	4.99	85	1.43	144	2.43	208	3.51	5725	96.49
Skin Type (Fitzpatrick)										
I	10,297	8.71	163	1.58	522	5.07	619	6.01	9,678	93.99
II	71,796	60.76	1,028	1.43	3,434	4.78	4,042	5.63	67,754	94.37
III	33,927	28.71	491	1.45	1,786	5.26	2,061	6.07	31,866	93.93
IV	2,151	1.82	31	1.44	109	5.07	124	5.76	2,027	94.24

Table 2 Cutaneous comorbidity in people with current AD, lifetime AD and without AD at any time

	Participants with AD at screening (n=1,724)		Participants with AD in medical history (n=5,883)		Participants without AD at any time (n=112,054)		Prevalence ratio
	%	95% CI	%	95% CI	%	95% CI	current/no AD at all
Inflammatory skin diseases							
Acne	2.96	2.20-3.89	3.91	3.42-4.45	2.84	2.74-2.94	1.04
Hand eczema	2.90	2.15-3.82	1.80	1.48-2.18	0.63	0.58-0.68	4.62*
Seborrhoeic dermatitis	2.78	2.05-3.69	4.08	3.58-4.63	3.07	2.97-3.18	0.91
Exsiccation dermatosis	2.49	1.81-3.36	1.80	1.48-2.18	1.14	1.08-1.20	2.19*
Rosacea	2.09	1.46-2.89	1.50	1.20-1.84	2.08	1.99-2.16	1.00
Psoriasis	1.22	0.75-1.86	3.03	2.60-3.50	2.01	1.92-2.09	0.61*
Intertriginous dermatitis	1.22	0.75-1.86	0.90	0.67-1.18	0.72	0.67-0.77	1.70
Contact dermatitis	0.52**	0.24-0.99	0.22	0.12-0.38	0.15	0.13-0.18	3.38*
Viral skin diseases							
Verruca vulgaris feet	2.32	1.66-3.16	2.33	1.96-2.75	2.24	2.15-2.33	1.04
Verruca vulgaris hands	0.46**	0.20-0.91	0.49	0.33-0.71	0.62	0.57-0.67	0.75
Fungal skin diseases							
Onychomycosis	5.74	4.67-6.99	4.64	4.11-5.22	6.04	5.89-6.18	0.95
Tinea pedis	3.83	2.96-4.87	3.09	2.66-3.58	4.07	3.96-4.19	0.94
Pityriasis versicolor	0.93	0.53-1.51	0.76	0.56-1.02	1.06	1.00-1.12	0.87
Tinea corporis	0.81	0.44-1.36	0.46	0.30-0.67	0.41	0.38-0.45	1.97
Bacterial skin diseases							
Folliculitis	16.42	14.56-18.44	10.40	9.59-11.26	8.43	8.26-8.60	1.95*
Pyoderma	0.52**	0.24-0.99	0.36	0.22-0.55	0.4	0.36-0.44	1.31
Vascular lesions of the skin							
Haemangioma	39.5	36.59-42.58	33.03	31.57-34.53	40.15	39.78-40.52	0.98
Spider veins	16.53	14.67-18.57	13.79	12.85-14.77	17.4	17.15-17.64	0.95
Side branch varicosis	7.02	5.82-8.39	5.15	4.59-5.76	7.65	7.49-7.82	0.92
Teleangiectasia	5.22	4.20-6.42	4.18	3.68-4.74	4.62	4.49-4.74	1.13
Port wine stains	3.07	2.30-4.02	2.26	1.89-2.68	2.07	1.98-2.15	1.49*
Varicosis of saphenous veins	2.67	1.95-3.56	2.7	2.30-3.16	3.54	3.43-3.65	0.75
Pre-existing conditions (from anamnestic interviews)							
Atopic dermatitis	42.17	39.16-45.35	100	97.46-102.59	-	-	-
Allergic rhinoconjunctivitis	33.76	31.07-36.62	41.99	40.35-43.67	21.43	21.16-21.71	1.58*
Allergic asthma	12.18	10.59-13.94	17.22	16.17-18.31	4.64	4.51-4.77	2.63*

* significant difference in prevalence rate between “current AD” and “without AD”

** n < 10

Table 3 Odds ratio (OR) from the regression analysis of the occurrence of different skin conditions among people with AD, controlling for age, gender and skin type (n = 1,724)

Skin disease	OR	95% CI	P ≤
Inflammatory skin diseases			
Hand eczema	3.96	2.95 – 5.32	0.001*
Contact dermatitis	2.97	1.50 – 5.88	0.002*
Exsiccation dermatosis	1.78	1.30 – 2.44	0.001*
Intertriginous dermatitis	1.12	0.72 - 1.75	0.618
Rosacea	0.96	0.68 – 1.36	0.827
Acne	0.90	0.68 – 1.20	0.479
Seborrhoeic dermatitis	0.82	0.61 – 1.09	0.167
Psoriasis	0.61	0.39 – 0.94	0.024
Viral skin diseases			
Verruca vulgaris feet	1.03	0.75 – 1.41	0.879
Verruca vulgaris hands	0.73	0.36 – 1.48	0.387
Fungal skin diseases			
Tinea corporis	2.00	1.17 – 3.43	0.011
Onychomycosis	0.99	0.80 – 1.22	0.920
Tinea pedis	0.96	0.74 – 1.23	0.729
Pityriasis versicolor	0.91	0.55 – 1.49	0.693
Bacterial skin diseases			
Folliculitis	2.03	1.77 – 2.32	0.001*
Pyoderma	0.85	0.43 – 1.67	0.642
Vascular lesions of the skin			
Port wine stains	1.45	1.10 – 1.92	0.008
Teleangiectasia	1.13	0.91 – 1.41	0.263
Haemangioma	0.95	0.86 – 1.05	0.311
Spider veins	0.95	0.83 – 1.10	0.492
Side branch varicosis	0.94	0.78 – 1.14	0.545
Varicosis of saphenous veins	0.79	0.59 – 1.07	0.122
Pre-existing conditions (from anamnestic interviews)			
Allergic asthma	2.03	1.73 – 2.37	0.001*
Allergic rhinoconjunctivitis	1.56	1.40 – 1.73	0.001*

* remains significant at nominal $\alpha \leq .05$ level after Bonferroni correction for 27 significance tests

Legends

Figure 1 Odds ratios (OR) of the occurrence of further skin diseases in people with AD (crude and adjusted).

