ORIGINAL ARTICLE

Atopic dermatitis: disease characteristics and comorbidities in smoking and non-smoking patients from the TREATgermany registry

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Abstract

Background Atopic dermatitis (AD) is a chronic inflammatory skin disease with a multifactorial genesis including genetic predispositions and environmental risk and trigger factors. One of the latter possibly is smoking, indicated by an increased prevalence of AD in adults and children that are actively or passively exposed to cigarette smoke.

Objectives In this study, AD characteristics and its atopic comorbidities are compared in smoking and non-smoking AD patients.

Methods TREATgermany is a non-interventional clinical registry which includes patients with moderate to severe AD in Germany. Baseline data of patients included in TREATgermany from inception in June 2016 to April 2020 in 39 sites across Germany was analysed comparing AD disease characteristics and comorbidities in smokers vs. non-smokers.

Results Of 921 patients, 908 (male: 58.7%) with a mean age of 41.9 ± 14.4 reported their smoking status. The objective Scoring of Atopic Dermatitis (oSCORAD) did not differ between smokers ($n = 352$; 38.8%) and non-smokers, however, lesions' intensity of oozing/crusts and excoriations as well as patient global assessment scores (PGA) of AD severity were higher in smoking as opposed to non-smoking patients. Smokers reported a lower number of weeks with well-controlled AD and more severe pruritus than non-smokers. Total IgE levels were more elevated in smokers and they displayed a younger age at the initial diagnosis of bronchial asthma. After adjustment for potential confounders, the increased intensity of oozing/crusts, the reduced number of weeks with well-controlled AD and the greater pruritus remained different in smokers compared to non-smokers. In addition, smoking patients with adult-onset AD showed a 2.5 times higher chance of involvement of the feet.

Conclusions German registry data indicate that AD patients who smoke have a higher disease burden with a different distribution pattern of lesions in adult-onset AD.
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Conflict of interest

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Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease affecting approximately 1–3% of adults worldwide[1] with a 1-year prevalence of 4.9% in Europe ranging from 2.2% in Germany to 8.1% in Italy.[2,3]

In affected patients, AD leads to a significant reduction in quality of life,[4] with higher anxiety levels[5] and an increased risk of depression.[6] Furthermore, at population level AD presents a great socioeconomic burden. It ranks first among skin/subcutaneous diseases concerning disability-adjusted life-years, with an increase of 12.5% between 2007 and 2017 shown in the global report burden of disease study 2017.[7] Direct costs in Germany alone are estimated to amount to 1.2–3.5 billion annually.[8]

Clinical hallmarks of AD are intense pruritus and recurrent eczematous lesions[9] with an age-dependent distribution and morphology.[10] AD is associated with other atopic diseases, such as food allergies, bronchial asthma as well as allergic rhinitis[11] and displays a multifactorial genesis. Genetic predispositions, often related to the skin barrier function and/or the immune system, together with environmental factors lead to the manifestation of the disease.[12,13] Among known environmental risk factors are small family sizes, high levels of education,[9] living in urban areas and western diets.[14] Additionally, there is some evidence linking smoking and AD.[15,16] In 2016 in a meta-analysis of 86 studies, Kantor et al. showed that the diagnosis of AD is more prevalent in actively or passively smoking adults and children compared to non-smokers.[17] In 2017, another study including about 145,000 adolescents in Korea drew the same conclusions.[18] Concerning adult-onset AD, Lee et al. revealed current smoking and having ever smoked as risk factors and found that non-smoking adult-onset AD patients were more likely to have experienced passive smoking in their childhood than control patients.[19]

Furthermore, in the general population smokers display higher total IgE levels[20,21] as well as higher incidences of bronchial asthma[22] and lower rates of allergic sensitizations.[23]

The TREATgermany registry, which collects data from moderately to severely affected AD patients, was launched in 2016, following the TREATeczema registry.[24] Up to April 2020, 921 patients were included in 39 centres throughout Germany revealing valuable information from routine care.[25]

The aim of this analysis was to compare exploratory characteristics of AD and prevalences of the atopic comorbidities bronchial asthma and allergic rhinitis in smoking and non-smoking AD patients.

Materials and methods

Patients and methods

The TREATgermany registry is a Germany-wide registry for patients diagnosed with AD and has been approved by the Medical faculty of the Carl Gustav Carus University, Dresden, Germany (No. EK 118032016) as well as by ethics committees at all participating sites. Patients were included from 13 German states (all states except Brandenburg, Mecklenburg-Western Pomerania, and Saarland) with 21.0% of the patients being recruited in Lower Saxony, 17.5% in Saxony, and 12.8% in Bavaria. Inclusion criteria, the objective of the registry, data management details and the schedule of assessment as well as the measuring tools used are described in detail by Heratizadeh et al.[24] For the study presented here, the data acquired at the baseline visit of all patients included in the registry from June 2016 until April 2020 was analysed with regards to their smoking status. Smokers comprised 'current smokers' and 'ex-smokers for less than 10 years', non-smokers included 'never smokers' and 'ex-smokers for more than 10 years'. Tobacco consumption was not quantified. Items reported by the participants included year of birth, gender, height, weight, level of education, family status, time of onset of AD, patient's global assessment (PGA), number of weeks in which the AD was well controlled within the last 3 months and severity of pruritus within the last three days (on a scale of 1–10). Information was acquired by physicians on affected body areas, objective Scoring of Atopic Dermatitis (oSCORAD), Eczema Area and Severity Index (EASI), investigator's global assessment (IGA), applied therapies, IgE levels, presence of sensitizations, bronchial asthma, allergic rhinitis, diabetes, hypertension, heart failure, myocardial infarction and stroke as well as on age at initial diagnosis of bronchial asthma and allergic rhinitis. Since adult-onset AD has been linked to smoking and has been described to display a different distribution of lesions than early-onset AD,[19,26] analyses of affected body parts were additionally performed for patients with adult-onset AD only. Adult-onset AD was defined as AD 'since adulthood' opposed to 'since infancy', 'since before school enrolment' or 'since school/adolescence'.

Statistical analyses

Descriptive data were generated using mean and standard deviation (mean ± SD) as well as absolute numbers and proportions. Analyses of quantile-quantile plots, histograms as well as Shapiro–Wilk–Tests were conducted for each metrical variable. Significance was examined using unpaired t-tests for normally distributed variables and Mann–Whitney U tests for not normally distributed and ordinally scaled variables. Pearson's chi-squared test and Fisher's exact test were performed for nominally scaled variables. To adjust for potential confounders, multiple linear regression and binary regression models with subsequent addition of independent variables were fitted to the data of the AD-related outcomes/items that were primarily found to differ between smokers and non-smokers. Apart from smoking status, independent variables included gender, age, family status and level of education. Since 'total IgE' was not distributed normally, the natural logarithm of 'total IgE' was used in the regression models. Differences in means (MD) and odds ratios (OR) as well as corresponding 95% confidence intervals (CI) were calculated. Data analysis was performed using IBM SPSS Statistics (Version 26, IBM Corporation, Armonk, NY, USA) and graphics were generated with GraphPad Prism (Version 7, Graphpad Software, Inc., San Diego, CA, USA).

Results

Patient characteristics

A total of 921 participants were included in the registry across 39 sites from June 2016 to April 2020. Of these, 95.8% ($n = 908$; male 58.7%) with a mean age of 41.9 ± 14.1 years reported their smoking status. 352 (38.8%) were classified as smokers ('current smokers ($n = 226$)' and 'ex-smokers less than 10 years ($n = 126$)') and 556 (61.2%) as non-smokers ('never smokers ($n = 461$)' and 'ex-smokers more than 10 years ($n = 95$)'; Table 1). 64.8% of smokers and 54.9% of non-smokers were male ($P = 0.003$). Between smokers and non-smokers the mean age (41.6 ± 13.5 vs. 42.0 ± 15.0; $P = 0.643$) and mean body mass index (26.2 ± 5.5 vs. 25.6 ± 5.1; $P = 0.156$) did not differ. Regarding the level of education, smokers had reached a lower level than non-smokers ($P < 0.001$) with fewer participants having a general qualification for university entrance (22.5% vs. 26.6%) as well as a graduate degree (17.4% vs. 28.4%). Furthermore, the family status varied across the two groups ($P = 0.004$). Smokers were less often in a married or in a stable non-marital relationship (59.5% vs 68.6%).

Disease characteristics

The mean EASI was 16.7 ± 13.4 in smokers and 15.7 ± 12.3 ($P = 0.463$; Table 2) in non-smokers. The mean oSCORAD score amounted to 41.9 ± 15.9 and 40.1 ± 16.0 respectively ($P = 0.085$). Here, the mean attained area was comparable between the two analysed groups (35.0 ± 27.0 vs. 34.5 ± 24.2).

Table 1 General patient characteristics in smoking and non-smoking AD patients

Characteristic	Smoking status		*P*-value
	Current or <10y Ex	Never or >10y Ex	
Demographics, $n_s = 352$, $n_{ns} = 556$			
Male gender, *n* (%);	228 (64.8)	305 (54.9)	0.003†
Age in years, mean ± SD	41.6 ± 13.5	42.0 ± 15.0	0.643‡
Body mass index, mean ± SD, $n_s = 351$, $n_{ns} = 552$	26.2 ± 5.5	25.6 ± 5.1	0.156§
Level of education, $n_s = 351$, $n_{ns} = 556$			<0.001§
Without graduation, *n* (%)	4 (1.1)	3 (0.5)	
Certificate of secondary education	56 (16.0)	55 (9.9)	
General certificate of secondary education	151 (43.0)	192 (34.5)	
General qualification for university entrance	79 (22.5)	148 (26.6)	
Graduate degree	61 (17.4)	158 (28.4)	
Family status, $n_s = 351$, $n_{ns} = 554$			0.004†
Married/stable non-marital partner, *n* (%)	209 (59.5)	380 (68.6)	
Divorced, *n* (%)	12 (3.4)	24 (4.3)	
Widowed, *n* (%)	2 (0.6)	8 (1.4)	
Single, *n* (%)	128 (36.5)	142 (25.6)	

n, number; ns, non-smoker; s, smoker; SD, standard deviation; y, years.
† Pearson's chi-squared test for nominally scaled variables.
‡ Unpaired *t*-test for metrically scaled normally distributed variables.
§ Mann–Whitney *U* test for metrically scaled not normally distributed and ordinally scaled variables.

Concerning the six intensity items of the SCORAD, oozing/crusts (1.2 ± 0.9 vs. 0.9 ± 0.9; $P < 0.001$) and excoriation (1.6 ± 0.9 vs. 1.5 ± 0.9; $P = 0.022$) differed between smokers and non-smokers, whereas the level of erythema (2.0 ± 0.7 vs. 1.9 ± 0.7; $P = 0.124$), oedema/papulation (1.6 ± 0.8 vs. 1.5 ± 0.8; $P = 0.119$), lichenification (1.8 ± 0.9 vs. 1.8 ± 0.9; $P = 0.871$) and dryness (1.9 ± 0.9 vs. 1.9 ± 0.9; $P = 0.931$) did not differ. The mean IGA was reported to be 3.2 ± 1.1 in smokers and 3.1 ± 1.0 in non-smokers ($P = 0.055$) and the PGA was higher in smokers than non-smokers (3.2 ± 1.3 vs. 3.0 ± 1.2; $P = 0.036$).

Furthermore, smokers reported a lower number of weeks within the past 3 months of well-controlled AD (3.9 ± 3.8 vs. 4.7 ± 3.8; $P = 0.002$) than non-smokers. Pruritus in the past three days was experienced as more severe in smokers as opposed to non-smokers (5.9 ± 2.9 vs. 5.4 ± 2.6; $P = 0.004$).

Concerning the current treatment of analysed patients, no differences in the proportion of patients receiving systemic treatment, UV therapy, allergen immunotherapy or topical treatment with steroids or calcineurin inhibitors were detected (data not shown).

Looking at the distribution of lesions with regard to different body areas in smoking and non-smoking patients, the face (79.3% vs. 79.0%), hands (74.1% vs. 75.2%), flexures (74.3% vs. 76.3%) and the neck (78.3% vs. 79.0%) were affected in the large majority of participants in both groups (Fig. 1a; Table S1). About 16.2% of all participants reported involvement of the genital area (17.0% vs. 15.5%) and 44.2% of the feet. Here, smokers more often reported lesions on their feet than non-smokers (49.7% vs. 41.0%; $P = 0.010$). When analysing patients with adult-onset AD only (total: $n = 155$; smoking: $n = 57$; non-smoking: $n = 98$), a trend of a higher proportion of smokers with involvement of the hands (75.4% vs. 68.4%; $P = 0.350$) was observed. In addition, a higher proportion of smoking adult-onset AD patients had lesions on the feet (54.4% vs 31.6%; $P = 0.005$) and a lower proportion of this group exhibited involvement of the flexures as opposed to non-smoking patients (44.4% vs. 68.4%; $P = 0.017$; Fig. 1b; Table S1). Regarding the presence of diabetes or cardiovascular comorbidities such as hypertension, heart failure, myocardial infarction and stroke, no differences between smoking and non-smoking adult-onset AD patients were detected (data not shown).

Atopic comorbidities

Total IgE levels of smokers at 5654.7 ± 8483.7 kU/L were higher than those of non-smokers (4867.0 ± 8065.8 kU/L) (Table 3). However, when analysing the presence of specific sensitizations to pollen (72.8% vs. 72.4%), house dust mite (63.5% vs. 66.9%), mould (27.2% vs. 28.7%) and food (39.1% vs. 36.9%), no difference between the two groups was observed. Allergic rhinitis was present in 67.4% and 67.7% of patients respectively. The mean age at initial diagnosis of allergic rhinitis was reported to be 16.7 ± 14.6 and 15.5 ± 13.1 ($P = 0.681$). 46.2% of smokers and 43.8% of non-smokers ($P = 0.479$) had bronchial asthma, with a lower age at initial diagnosis in smokers (12.8 ± 14.5) than non-smokers (16.8 ± 15.2; $P = 0.010$). No difference in the percentage of patients receiving treatment for either allergic rhinitis or

Table 2 Disease severity in smoking and non-smoking AD patients assessed using objective and subjective measurement tools

Assessment	Smoking status†		*P*-value
	Current or <10 Ex	Never or >10y Ex	
oSCORAD, $n_s = 349$, $n_{ns} = 553$	41.9 ± 15.9	40.1 ± 16.0	0.085‡
Area (in %)	35.0 ± 27.0	34.5 ± 24.2	0.752‡
Erythema	2.0 ± 0.7	1.9 ± 0.7	0.124§
Oedema/papulation	1.6 ± 0.8	1.5 ± 0.8	0.119§
Oozing/crusts	1.2 ± 0.9	0.9 ± 0.9	<0.001§
Excoriation	1.6 ± 0.9	1.5 ± 0.9	0.022§
Lichenification	1.8 ± 0.9	1.8 ± 0.9	0.871§
Dryness	1.9 ± 0.9	1.9 ± 0.9	0.931§
EASI, $n_s = 349$, $n_{ns} = 550$	16.7 ± 13.4	15.7 ± 12.3	0.463§
IGA, $n_s = 349$, $n_{ns} = 551$	3.2 ± 1.1	3.1 ± 1.0	0.055§
PGA, $n_s = 350$, $n_{ns} = 555$	3.2 ± 1.3	3.0 ± 1.2	0.036§
Well-controlled AD, number of weeks, (last 3 months) $n_s = 350$, $n_{ns} = 555$	3.9 ± 3.8	4.7 ± 3.8	0.002‡
Pruritus (last 3 days; 0–10), $n_s = 350$, $n_{ns} = 555$	5.9 ± 2.9	5.4 ± 2.6	0.004‡

AD, Atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's global assessment; *n*, number; ns, non-smoker; s, smoker; oSCORAD, objective Scoring of Atopic Dermatitis; PGA, Patient's global assessment; y, years.
†For each variable mean and standard deviation is depicted.
‡Unpaired t-test for metrically scaled normally distributed variables.
§Mann–Whitney U test for metrically scaled not normally distributed variables and ordinally scaled variables.

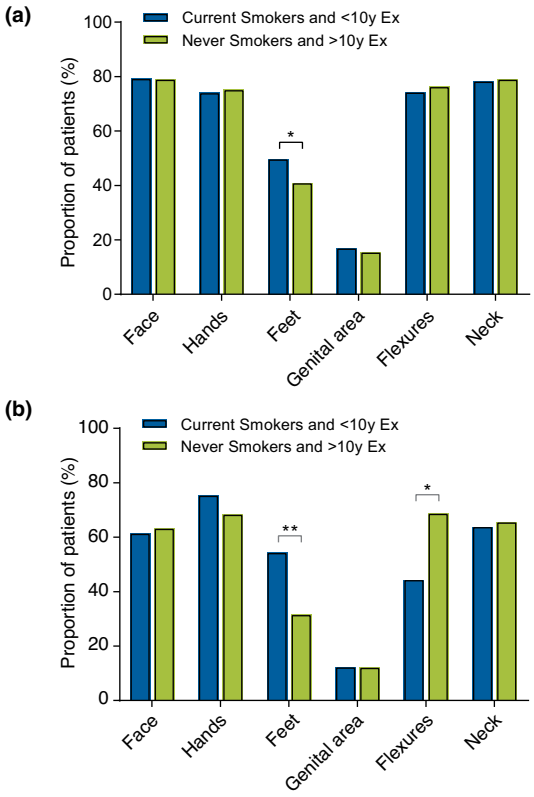

Figure 1 Body areas affected by AD in all AD patients (a) and in patients with adult-onset AD only (b); y, years; *$P < 0.05$; **$P < 0.01$.

bronchial asthma between smokers and non-smokers was seen (data not shown).

Adjusting for potential confounders

After adjustment for gender and age as well as after additional adjustment for level of education and family status, the differences observed above regarding the intensity of oozing/crusts (MD: 0.19; 95% CI: 0.07 to 0.32; $P = 0.003$) and pruritus (MD: 0.57; 95% CI: 0.20 to 0.94; $P = 0.003$) as well as the number of weeks during which the disease was well controlled remained between the two groups (Table 4). Thus, non-smokers had approximately 6 more days (=0.85 weeks; 95% CI: 1.38–0.33; $P = 0.001$) of well-controlled AD during a 12-week period than smokers. Furthermore, the differences between smokers and non-smokers in adult-onset AD with regard to lesions on feet and lesions on flexures were still present after the adjustment for potentially confounding factors. Smoking adult-onset AD patients showed an increased chance of having lesions on the feet (OR: 2.5; 95% CI: 1.16–5.25), as well as a decreased chance of having lesions on flexures (OR: 0.32; 95% CI: 0.12–0.88) compared to non-smoking adult-onset AD patients. When analysing only current smokers vs. those who have never smoked, thereby disregarding all ex-smokers, all the main differences and their robustness after confounding analyses were equally or even more profoundly observed (Table S2).

Discussion

The aim of the study presented here was to assess characteristics of AD and its associated comorbidities in smoking compared to non-smoking AD patients using data of the national TREATgermany registry. After adjustment for potential confounders, smokers showed greater pruritus, increased intensity of oozing/crusts and reduced number of weeks with well-controlled AD as opposed to non-smokers. In addition, adult-onset AD patients who smoked showed a 2.5 times higher chance of having the involvement of the feet and a 68% decreased chance of exhibiting involvement of flexures.

Overall, the demographic data in this study align with previous findings in the literature, which show that smokers are more likely to be male, less educated and single rather than married when compared with non-smokers.[27,28]

Table 3 Allergic sensitizations and comorbidities in smoking and non-smoking AD patients

Assessment	Smoking status		*P*-value
	Current or <10y Ex	Never or >10y Ex	
Total IgE (kU/L), mean ± SD, n_s = 195, n_{ns} = 305	5654.7 ± 8483.7	4867.0 ± 8065.8	0.046†
Allergic sensitizations, n_s = 345, n_{ns} = 544			
Pollen, *n* (%)	251 (72.8)	394 (72.4)	0.525‡
House dust mite, *n* (%)	219 (63.5)	364 (66.9)	0.351‡
Mould, *n* (%)	94 (27.2)	156 (28.7)	0.895‡
Food, *n* (%)	135 (39.1)	201 (36.9)	0.654‡
Atopic comorbidities			
Allergic rhinitis, *n* (%), n_s = 337, n_{ns} = 539	227 (67.4)	365 (67.7)	0.912‡
Age at initial diagnosis of allergic rhinitis (in years), mean ± SD, n_s = 152, n_{ns} = 251	16.7 ± 14.6	15.5 ± 13.1	0.681†
Bronchial asthma, *n* (%), n_s = 342, n_{ns} = 546	158 (46.2)	239 (43.8)	0.479‡
Age at initial diagnosis of bronchial asthma (in years), mean ± SD, n_s = 105, n_{ns} = 163	12.8 ± 14.5	16.8 ± 15.2	0.010†

n, number; ns, non-smoker; s, smoker; SD, standard deviation; y, years.
† Mann–Whitney *U* test for metrically scaled not normally distributed variables and ordinally scaled variables.
‡ Pearson's chi-squared test for nominally scaled variables.

Table 4 Adjusting for potential confounders in investigations of the effect of smoking on multiple AD-related outcomes

Assessment†	Differences of AD-related outcomes of 'Current or <10y Ex' smokers in reference to 'Never or >10y Ex' smokers	
	Adjusted for gender and age	Additionally adjusted for level of education and family status
Oozing/crusts, MD (95% CI)	0.21 (0.09 to 0.34; *P* = 0.001)	0.19 (0.07 to 0.32; *P* = 0.003)
Excoriation, MD (95% CI)	0.12 (0.02 to 0.24; *P* = 0.047)	0.11 (−0.13 to 0.23; *P* = 0.080)
PGA, MD (95% CI)	0.14 (−0.02 to 0.31; *P* = 0.082)	0.14 (−0.02 to 0.31; *P* = 0.092)
Well-controlled AD, number of weeks (last 3 months), MD (95% CI)	− 0.83 (−1.34 to −0.31; *P* = 0.002)	−0.85 (−1.38 to −0.33; *P* = 0.001)
Lesions on feet, OR (95% CI)	1.38 (1.05 to 1.81; *P* = 0.020)	1.29 (0.98 to 1.71; *P* = 0.074)
Lesions on feet‡, OR (95% CI)	2.86 (1.42 to 5.75; *P* = 0.003)	2.48 (1.16 to 5.25; *P* = 0.018)
Lesions on flexures‡, OR (95% CI)	0.37 (0.16 to 0.89; *P* = 0.026)	0.32 (0.12 to 0.88; *P* = 0.026)
Pruritus (last 3 days), MD (95% CI)	0.59 (0.23 to 0.96; *P* = 0.001)	0.57 (0.20 to 0.94; *P* = 0.003)
Total IgE§, MD (95% CI)	0.29 (−0.6 to 0.63; *P* = 0.103)	0.27 (−0.09 to 0.63; *P* = 0.135)
Age at initial diagnosis of bronchial asthma, MD (95% CI)	−2.70 (−6.18 to 0.77; *P* = 0.127)	−2.47 (−6.17 to 1.23; *P* = 0.190)

AD, Atopic dermatitis; CI, Confidence Interval; MD, Difference of group means (Smokers – Non-Smokers); OR, Odds Ratio (Smokers / Non-Smokers), PGA, Patient's global assessment, y, years.
†For all outcomes (except the ones regarding body areas affected) linear regression models were fitted to the data; for 'lesions on feet' and 'lesions on flexures' binary logistic regression was fitted to the data.
‡Only patients with late-onset AD included.
§The natural logarithm of 'total IgE' was applied.

Several studies have found an association between smoking and the prevalence of AD, but so far none have analysed smoking with regard to AD severity.[17,18] Here, the presented study identified a higher PGA in AD of smokers compared to non-smokers as well as higher intensities of oozing/crusts and excoriations. The IGA displayed a trend towards higher scores in smokers. Smokers also reported a smaller number of weeks, in which the disease was well controlled. Furthermore, increased pruritus in smoking AD patients was found. In haemodialysis patients, smoking is known to be associated with moderately to extremely distressing itching skin.[29] In addition, smoking is linked to the prevalence of chronic pruritus.[30] However, the influence of smoking on pruritus in AD has not yet been investigated in other studies. Therefore, one can only hypothesize with regard to a possible pathomechanism. Serum levels of interleukin (IL)-31, a pruritus-mediating cytokine, were described to be elevated in haemodialysis patients who suffer from uremic pruritus.[31] Furthermore, in those patients, heavy pruritus and smoking have been linked,[32] and a trend towards increased levels of IL-31 in smokers has been described.[33] Overall, the results of this study hint at a higher disease severity in smoking AD patients as opposed to non-smoking AD patients.

An association between smoking and active hand dermatitis has been shown.[34] The data shown here indicate more often involvement of the feet in smoking AD patients as opposed to non-smoking AD patients. Gupta et al. found that cigarette smoking in men with psoriasis was associated with a higher severity at the distal portions of the extremities, namely forearms, hands and feet.[35] Furthermore, in adult-onset AD, which is associated with smoking,[19] hands have been shown to be the most frequently affected body site.[26] Here, a subanalysis which only included adult-onset AD patients revealed that smokers presented a trend towards more involvement of the hands and a higher percentage of involvement of the feet as opposed to non-smokers. The proportion of non-smokers with lesions on the hands was a priori very high (68.4%), possibly concealing the effect of smoking on involvement of the hands. The observed association of smoking and lesions on feet remained after adjustment for gender, age, education and family status. This indicates that smoking may also serve as an independent risk factor for involvement of feet in adult-onset AD. Smoking has proinflammatory effects,[36] induces oxidative stress[37] and leads to cutaneous microvascular dysfunction.[38] In other chronic inflammatory diseases, such as inflammatory bowel diseases, altered microvascular structures and functions have been linked to maintenance of chronic inflammation.[39] Similarly, an increased inflammatory component in the hands and feet of smoking adult-onset AD patients seems possible.

Moreover, in this study, an initial association of total IgE levels and the smoking status was observed. In the general population, it is well known that IgE levels are elevated in smoking individuals.[40] The total IgE levels in currently smoking adults correlate to the number of cigarettes smoked daily.[20] However, total IgE levels are also age- and gender-dependent.[41] Men display higher total IgE levels than women across all smoking categories[40] and total IgE levels are inversely correlated with age.[42] In this study, the elevated total IgE levels could not be definitely attributed to smoking. Elevated IgE levels as a characteristic for AD could have simply outweighed the possible effect of smoking on total IgE levels. Concerning specific sensitizations and the prevalence of allergic rhinitis in the general population, smokers opposed to non-smokers display lower sensitization rates to aeroallergens and lower prevalence of allergic rhinitis.[23] Furthermore, no differences in the severity of allergic rhinitis were seen in smokers as opposed to non-smokers.[43] Therefore, the data presented here for AD patients depicting no difference between smokers and non-smokers concerning the prevalence of allergic rhinitis or the age at initial diagnosis is in accordance with the literature. However, smoking has long been identified as an independent, dose-dependent risk factor for the incidence of asthma in adults and adolescents, with smoking patients demonstrating a greater asthma severity.[22,44–46] Other independent risk factors for bronchial asthma include the presence of allergic rhinitis[22] and allergic sensitizations.[47] A study looking at the risk of asthma in children even found that those who smoked regularly, but had a history of allergy, had no increased risk of asthma opposed to non-smoking, allergic children.[48] In this study, only AD patients were analysed. They displayed to a large extent allergic rhinitis and allergic sensitizations, thus harbouring additional independent risk factors for asthma than smoking. Therefore, it makes sense that no increased prevalence of asthma in smoking AD patients compared to non-smoking AD patients could be found. Moreover, after adjustment for potential confounding factors, no association between smoking and a younger age of diagnosis of asthma was seen, emphasizing a non-causal role for smoking in the setting of asthma in AD.

Limitations of this study include the lack of information about the number of cigarettes smoked per day as well as the number of active smoking years. Therefore, no dose-dependent effects could be investigated. However, a study analysing the risks of developing coronary heart disease and stroke has shown that the effect of one cigarette a day may be much stronger than expected, rendering it possible that for basic analyses, the exact number may not be of such great importance.[49] Another limitation of the presented study is using the cut-off after 10 years of smoking cessation as the delineation between smokers and non-smokers. The risk decrease for smokers over time is a continuum rather than a clear cut-off and differs for various outcomes.[50,51] Nevertheless, important elevated risks, such as total mortality and cardiovascular diseases, are estimated to have decreased to the level of those who have never smoked after around 10–15 years.[52–54] In addition, all the main differences between smoking and non-smoking AD patients, including their robustness after confounding analyses, were also found when only current smokers vs. those who have never smoked were analysed. Additionally, the possible influence of passive smoking through other smoking members of the household was not taken into account. But since effects of active smoking are probably comparable to active plus passive smoking, this limitation is rather negligible. A methodological limitation concerns multiple testing so that significant findings on the 5%-level need to be interpreted with caution.

In summary, the study data identify smoking in AD patients as an independent risk factor for increased pruritus, fewer weeks of well-controlled AD and more intense oozing/crust lesions, hinting at a higher disease burden in smoking as opposed to non-smoking AD patients. In addition, smoking patients with adult-onset AD are more prone to have AD lesions on their feet and less often on flexures. These new findings serve to adapt treatment strategies in patient-centred routine care and may provide further arguments for giving up smoking.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1-S2