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ORIGINAL ARTICLE

Lifetime prevalence and determinants of hand eczema in an adolescent population in Germany: 15-year follow-up of the LISA cohort study

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Abstract

Background Hand eczema is a common inflammatory skin disorder in both adolescence and adulthood.

Objectives We sought to assess the lifetime prevalence of hand eczema and associated exogenous and endogenous risk factors among adolescents in Germany.

Methods This was a cross-sectional study embedded into a prospective population-based birth cohort in four regions of Germany, which recruited healthy neonates born between November 1997 and January 1999. We included 1736 participants who had completed the 15-year follow-up from birth cohort and 84.6% (1468/1736) had clearly reported whether they have ever had hand eczema. All the data were based on questionnaires and blood tests (immunoglobulin E). Multivariable logistic regression analysis was used to examine endogenous and exogenous factors in relation to the lifetime prevalence of hand eczema among adolescents.

Results One thousand four hundred and sixty-eight adolescents (715 girls, 48.7%) were included in the final analysis. The lifetime prevalence of hand eczema among adolescents at the age of 15 was 10.4% (95% confidence interval [CI]: 8.9%–12.1%), with a significantly higher lifetime prevalence among girls than boys (12.7% vs. 8.2%, $P = 0.005$). Multivariable logistic regression analysis indicated statistically significant associations between the lifetime prevalence of hand eczema and having ever been diagnosed with atopic dermatitis (aOR = 1.8, 95% CI: 1.1–2.8) or having ever had dry skin (aOR = 1.9, 95% CI: 1.1–3.1), respectively. No statistically significant independent associations were found between asthma, hay fever, allergy-related clinical symptoms, immunoglobulin E positivity and other exogenous factors in relation to hand eczema.

Conclusion Our study fills a research gap on the epidemiological burden of hand eczema among adolescents. One out of ten ever suffered from hand eczema until age 15 years indicating that hand eczema constitutes a significant burden in paediatric populations. The role of atopic dermatitis in hand eczema reinforces previous findings. Exogenous risk factors warrant further investigation.

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Conflicts of interest

Dr Christian Apfelbacher has received institutional funding from the Dr Wolff Group, and consultancy fees from the Dr Wolff Group, Sanofi Genzyme, Sanofi-Aventis Deutschland and LeoPharma. He is co-chairing the Harmonising

Outcome Measures for Eczema (HOME) and Hand Eczema Core Outcome Set (HECOS) initiatives. Dr Stephan Weidinger is a co-principal investigator of the German Atopic Dermatitis Registry TREATGermany; has received institutional research grants from Sanofi Deutschland GmbH, LEO Pharma and La Roche-Posay; has provided consultancies and lectures for Pfizer Inc., Sanofi-Genzyme, Regeneron, LEO Pharma, AbbVie, Eli Lilly, GlaxoSmithKline, Kymab and Almirall. Dr Jochen Schmitt has received institutional grants from Novartis, ALK, Pfizer, Sanofi for the investigator-initiated research and consultancy fees from Novartis, ALK, Lilly, Sanofi. Dr Jiancong Wang, Dr Christina Tischer, Dr Marie Standl, Dr Andrea von Berg, Dr Gunda Herberth, Dr Yik Weng Yew and Dr Joachim Heinrich declare that they have no conflict of interest relevant to this study.

Funding sources

The LISA study was mainly supported by grants from the Federal Ministry for Education, Science, Research and Technology and in addition from Helmholtz Zentrum München (former GSF), Helmholtz Centre for Environmental Research – UFZ, Leipzig, Research Institute at Marien- Hospital Wesel, Pediatric Practice, Bad Honnef for the first 2 years. The 4-year, 6-year, 10-year and 15-year follow-up examinations of the LISA study were covered from the respective budgets of the involved partners (Helmholtz Zentrum München [former GSF], Helmholtz Centre for Environmental Research – UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef, IUF – Leibniz-Research Institute for Environmental Medicine at the University of Düsseldorf) and in addition by a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296). Further, the 15-year follow-up examination of the LISA study was supported by the Commission of the European Communities, the 7th Framework Program: MeDALL project.

Introduction

Hand eczema, an inflammatory skin disorder visible on the hands, may occur in adolescence through to adulthood and is considered a global public health problem that affects quality of life.[1–4] Significant risk factors for hand eczema in adulthood are often associated with (i) occupation-related exposures, (ii) parental history and genetic factors and (iii) diagnosis of persistent and severe atopic dermatitis.[5–11]

Globally, the point prevalence of hand eczema in the general population has been estimated at 4.0%, with a 1-year prevalence of 9.1% and a lifetime prevalence of 14.5%.[4] The incidence of hand eczema is 7.3 cases per 1000 person-years,[4] with certain occupations having higher incidence rates, including nursing, hairdressing and others that involve exposure to moisture.[1,11–13] In Germany, the epidemiological burden of hand eczema among the general population shows a large variation. The 1-year prevalence of hand eczema varied from 0.2% to 9.2%, with the lifetime prevalence estimation of 2.6–16.0%.[14]

The population-based prevalence of hand eczema in adolescence remains largely understudied, despite its frequency. In the Swedish Children, Allergy, Milieu, Stockholm, Epidemiological Survey (BAMSE), Grönhagen *et al.*[3] estimated the self-reported lifetime prevalence of hand eczema at the age of 16 to be 9.7% and the incidence to be 5.7 per 1000 person-years. As compared to this, Mortz *et al.*[15] estimated an even higher lifetime prevalence of hand eczema (lifetime 0–29 years) of 23.0% and the incidence of 8.8 per 1,000 person-years in the Danish Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS). Both studies found significant gender heterogeneity, with a higher incidence among females than males. Nevertheless, information on endogenous and exogenous risk factors for the occurrence of hand eczema in adolescence remains scarce. The Swedish and Danish birth cohorts reported a positive association between a history of atopic dermatitis during childhood and later development of hand eczema in adolescence or young adulthood, particularly among children with persistent or more severe atopic dermatitis.[7,15] However, there are no studies in the adolescent dermatology literature that comprehensively examine the impacts of endogenous and exogenous factors on the lifetime prevalence of hand eczema.[7,9,15] The identification of such factors is particularly important for helping clinicians and parents to be aware of early hand eczema and to prevent it by providing early interventions or treatments for the impacting factors, thus improving quality of life.[16]

In this study, we used data from an ongoing German population-based birth cohort. The specific aims were (i) to assess the lifetime prevalence of hand eczema among 15-year-old adolescents in Germany, and (ii) to identify associations between potential endogenous and exogenous factors and the lifetime prevalence of hand eczema among adolescents.

Materials and methods

Study population

Influence of life-style factors on the development of the immune system and allergies in East and West Germany (LISA)[17] is an ongoing population-based birth cohort study in four regions of Germany (e.g. Munich, Leipzig, Wesel and Bad Honnef). This study recruited 3,097 healthy, full-term, normal-weight neonates born between November 1997 and January 1999. After delivery, the parents or legal guardians were asked to complete questionnaires every year until the children were 14 years old and to

report whether the children had been diagnosed with an allergy-related disease or its relevant clinical symptoms or had been exposed to environmental factors in the previous 12 months. At the 15-year follow-up, the adolescents themselves were asked to complete the self-report questionnaire (Table S1).

Study design

This study was a cross-sectional study that is embedded into the prospective population-based LISA birth cohort. Analyses were restricted to those adolescents who had completed the 15-year follow-ups.

Inclusion and exclusion criteria

We included adolescents who replied to '*Have you ever had hand eczema (i.e. rash, itchy rash or blisters on your hands)*?' with a clear answer either '*yes, having ever had hand eczema*' or '*no, having never had hand eczema*'. This question was only asked at the age of 15 (Table S1). Further, '*If yes, at what age did the hand eczema occur for the first time?*' Responses in which the adolescents did not clearly report whether they had experienced hand eczema (as missing values) were excluded.

Health outcome

The outcome was to measure the self-reported lifetime prevalence of hand eczema among adolescents at the age of 15.

Endogenous and exogenous factors

The potential endogenous and exogenous factors examined were chosen with reference to the Swedish BAMSE and the Danish TOACS cohorts, which reported factors that increased the likelihood of developing hand eczema.[7,9,15] The following endogenous factors were selected, including atopic diseases (i.e. having ever had a doctor's diagnosis of atopic dermatitis, asthma or hay fever) and relevant clinical symptoms (i.e. having ever had whistling or wheezing noises in the chest while breathing; itchy or watery eyes with nasal problems; or dry skin). We assessed endogenous positive immunoglobulin E (IgE) levels – specifically, inhalant allergens (>0.35 kUa/L) and mixed common food allergens (>0.35 kUa/L) – from serum samples, based on UK allergic sensitization criteria, as measured by the Radio-Allergo-Sorbent-Test.[18–20] For exogenous factors, we assessed whether adolescents had ever been exposed to residential visible mould, ever been in contact with pets at home or ever been exposed to familial cigarette smoking indoor. For lifestyle factors, we only assessed 15 year-olds' life behaviours in the previous 12 months, including frequency of showering, frequency of facial or body creams use. Table S1 details the definitions of endogenous and exogenous indicators.

Statistical analysis

The lifetime prevalence of hand eczema among adolescents at the age of 15 was analysed, and stratified by gender and different German geographical locations, with corresponding 95% confidence intervals (95% *CIs*). We graphed Kaplan–Meier curves to estimate the cumulative incidence of first onset of hand eczema among adolescents diagnosed with atopic dermatitis, asthma, hay fever and IgE positivity for food and inhalation allergens over the 15-year study period, obtaining hazard ratios with 95% *CIs*. Univariate logistic regression analysis was used to examine the endogenous and exogenous factors associated with the lifetime prevalence of hand eczema. Statistical significance was defined as a two-tailed *P*-value of 0.05 or less; variables associated with hand eczema with significant *P*-values in the univariate analysis were then examined in a multivariable regression analysis to identify independent risk factors. Results from the logistic regression analyses are presented as crude and adjusted odds ratios (*ORs*) with corresponding 95% *CIs*. All statistical analyses and graphs were performed using STATA 15.1 (STATA Corporation, College Station, Texas, US).

Ethics

The LISA study was approved by the relevant local ethics committees (i.e. Bavarian Board of Physicians [12067], Board of Physicians of Saxony [EK-BR-02/13-1] and Board of Physicians of North-Rhine-Westphalia [2012446]). Written consent was received before birth, when the parents and legal guardians of the participants agreed to recruitment into this birth cohort.[21] Another written consent was signed by adolescents at the age of 15 with the agreement by parents and legal guardians, when adolescents answered the self-reported questionnaires. During the ongoing follow-up period, all participating families and adolescents had the right to withdraw at any time. All data was pseudonymized and stored confidentially and appropriately for the analytic purposes of the research project.

Results

Study population

Of the 3,097 healthy, full-term, normal-weight neonates, 56.1% (1,736) of the parents or families completed the follow-ups from birth until adolescence. Of those 1,736 15-year-old adolescents, 84.6% (1,468) clearly reported whether they had ever had hand eczema, with 48.7% (715/1,468) girls. Most of the study population were located from Munich region (51.8%, 761/1,468) (Table 1A). The median age reported for the first occurrence of hand eczema was 12 years (interquartile range: 7–14). Figure 1 shows the distribution of the first occurrence of hand eczema over the 15-year study period. The likelihood of a first occurrence of hand eczema gradually increases with age.

The lifetime prevalence of hand eczema among adolescents at the age of 15 was 10.4% (n = 153, 95% CI: 8.9%–12.1%). The lifetime prevalence among girls was significantly higher than among boys (12.7% vs. 8.2%, P = 0.005). Munich had a higher lifetime prevalence (11.2%, 95% CI: 9.0–13.6%) than that

Table 1 Endogenous and exogenous factors associated with the lifetime prevalence of hand eczema among adolescents – Germany LISA birth cohort

A. Univariate logistic regression analysis					
Variable	**Study population, n (%)**	**Hand eczema, n (%)**	**No hand eczema, n (%)**	**Crude odds ratio (95%CI)**	***P*-value**
Total	1468	153	1315	–	–
Gender (*n* = 1468)					
Male	753 (51.3%)	62 (40.5%)	691 (52.6%)	Ref.	–
Female	715 (48.7%)	91 (59.5%)	624 (47.4%)	**1.6 (1.2–2.3)**†	**0.005**
Geographical location (*n* = 1468)					
Munich	761 (51.8%)	85 (55.6%)	676 (51.4%)	1.5 (0.8–2.8)	0.234
Leipzig	395 (26.9%)	42 (27.4%)	353 (26.8%)	1.4 (0.7–2.7)	0.338
Bad Honnef	160 (10.9%)	14 (9.2%)	146 (11.1%)	1.1 (0.5–2.5)	0.785
Wesel	152 (10.4%)	12 (7.8%)	140 (10.7%)	Ref.	–
Having ever had doctor's diagnosis of atopic dermatitis (0–15 years) (*n* = 1205)‡					
Yes	391 (32.4%)	57 (46.0%)	334 (30.9%)	**1.9 (1.3–2.8)**†	**0.001**
No	814 (67.6%)	67 (54.0%)	747 (69.1%)	Ref.	–
Having ever had doctor's diagnosis of asthma (0–15 years) (*n* = 1134)‡					
Yes	118 (10.4%)	13 (11.8%)	105 (10.2%)	1.2 (0.6–2.2)	0.610
No	1,016 (89.6%)	97 (88.2%)	919 (89.8%)	Ref.	–
Having ever had doctor's diagnosis of hay fever (0–15 years) (*n* = 1164)‡					
Yes	304 (26.1%)	44 (36.7%)	260 (24.9%)	**1.7 (1.2–2.6)**†	**0.006**
No	860 (73.9%)	76 (63.3%)	784 (75.1%)	Ref.	–
Having ever had whistling or wheezing breath noises in the chest (0–15 years) (*n* = 1290)‡					
Yes	675 (52.3%)	73 (55.3%)	602 (52.0%)	1.1 (0.8–1.6)	0.470
No	615 (47.7%)	59 (44.7%)	556 (48.0%)	Ref.	–
Having ever had itchy or watery eyes at the same time as nasal problems (0–15 years) (*n* = 1222)‡					
Yes	463 (37.9%)	58 (46.0%)	405 (37.0%)	**1.5 (1.0–2.1)**†	**0.048**
No	759 (62.1%)	68 (54.0%)	691 (63.0%)	Ref.	
Having ever had dry skin (in the past 12 months) (*n* = 1460)‡					
Yes	800 (54.8%)	109 (72.2%)	691 (52.8%)	**2.3 (1.6–3.4)**†	**<0.001**
No	660 (45.2%)	42 (27.8%)	618 (47.2%)	Ref.	
IgE levels for food allergens (0–15 years) (*n* = 672)‡					
Ever positive (>0.35 ku/l)	248 (36.9%)	27 (38.6%)	221 (36.7%)	1.1 (0.7–1.8)	0.760
Always negative	424 (63.1%)	43 (61.4%)	381 (63.3%)	Ref.	–
IgE levels for inhalant allergens (0–15 years) (*n* = 824)‡					
Ever positive (>0.35ku/l)	542 (65.8%)	56 (66.7%)	486 (65.7%)	1.0 (0.6–1.7)	0.856
Always negative	282 (34.2%)	28 (33.3%)	254 (34.3%)	Ref.	–
Having ever been exposed to residential visible mould (0–15 years) (*n* = 1237)‡					
Yes	858 (69.4%)	106 (77.9%)	752 (68.3%)	**1.6 (1.1–2.5)**†	**0.022**
No	379 (30.6%)	30 (22.1%)	349 (31.7%)	Ref.	–
Having ever had in contact with pets indoors (0–15 years) (*n* = 1405)‡					
Yes	1,042 (74.2%)	119 (81.5%)	923 (73.3%)	**1.6 (1.0–2.5)**†	**0.034**
No	363 (25.8%)	27 (18.5%)	336 (26.7%)	Ref.	–
Showering frequency (in the past 12 months) (*n* = 1462)‡					
<=1 time a week	70 (4.8%)	8 (5.2%)	62 (4.7%)	Ref.	–
2–6 times a week	810 (55.4%)	81 (53.3%)	729 (55.7%)	0.9 (0.4–1.9)	0.704
Daily	582 (39.8%)	63 (41.5%)	519 (39.6%)	0.9 (0.4–2.1)	0.878
Frequency of using nourishing creams for the face (in the past 12 months) (*n* = 1455)‡					
Never	384 (26.4%)	32 (21.2%)	352 (27.0%)	Ref.	–
Occasionally	648 (44.5%)	62 (41.1%)	586 (44.9%)	1.2 (0.7–1.8)	0.506
Daily	423 (29.1%)	57 (37.7%)	366 (28.1%)	**1.7 (1.1–2.7)**†	**0.021**
Frequency of using nourishing creams for the body (in the past 12 months) (*n* = 1463)‡					
Never	570 (39.0%)	50 (32.9%)	520 (39.7%)	Ref.	–

Table 1 *Continued*

A. Univariate logistic regression analysis					
Variable	**Study population, n (%)**	**Hand eczema, n (%)**	**No hand eczema, n (%)**	**Crude odds ratio (95%CI)**	***P*-value**
Occasionally	760 (51.9%)	84 (55.3%)	676 (51.5%)	1.3 (0.9–1.9)	0.172
Daily	133 (9.1%)	18 (11.8%)	115 (8.8%)	1.6 (0.9–2.9)	0.097
Frequency of exposure to familial cigarette smoke at home (0–15 years) (*n* = 1301)‡					
Never	941 (72.3%)	90 (71.4%)	851 (72.4%)	Ref.	–
Daily	107 (8.2%)	11 (8.7%)	96 (8.2%)	1.1 (0.6–2.1)	0.812
Occasionally	253 (19.5%)	25 (19.8%)	228 (19.4%)	1.0 (0.7–1.7)	0.879
B. Multivariable logistic regression analysis					
Variable	**Adjusted odds ratio (95%CI) (*n* = 887)§**				***P*-value**
Gender					
Male	Ref.				–
Female	1.5 (0.9–2.6)				0.090
Having ever had doctor's diagnosis of atopic dermatitis (0–15 years)					
Yes	**1.8 (1.1–2.8)**				**0.019**
No	Ref.				–
Having ever had doctor's diagnosis of hay fever (0–15 years)					
Yes	1.4 (0.8–2.5)				0.250
No	Ref.				–
Having ever had itchy or watery eyes at the same time as nasal problems (0–15 years)					
Yes	1.1 (0.6–1.9)				0.758
No	Ref.				–
Having ever had dry skin (in the past 12 months)					
Yes	**1.9 (1.1–3.1)**				**0.012**
No	Ref.				–
Having ever exposed to residential visible mould (0–15 years)					
Yes	1.6 (0.98–2.7)				0.058
No	Ref.				–
Having ever in contact with pets indoors (0–15 years)					
Yes	1.3 (0.8–2.3)				0.270
No	Ref.				–
Frequency of using nourishing creams for the face (in the past 12 months)					
Never	Ref.				–
Occasionally	0.9 (0.5–1.7)				0.806
Daily	1.2 (0.6–2.3)				0.569

Ref.: reference group; 95%CI: 95% confidence interval. Bold values represent significant associations in both the univariate and multivariable regression analysis.

†The variables (including gender, having ever been diagnosed with atopic dermatitis and hay fever, clinical symptoms of having ever had watery eyes with nasal problems and dry skin, having ever been exposed to residential visible mould, having ever had in contact with pets indoors, and daily use of facial creams) were included in the multivariable regression analysis.

‡Participants had one or more missing values when the models assessed the risk factors, and all the participants with missing values were therefore excluded from the analysis, as we were not sure in which categories to put them. The numbers in brackets represent the complete datasets for analysis.[7]

§A completed dataset was included for multivariable logistic regression analysis. All the participants with missing values within variables were therefore excluded from the analysis. The numbers in brackets represent the complete datasets for analysis.[7]

reported by other German regions, but there were no statistically significant differences between the four regions (Figure 2). Furthermore, at the age of 15, the cumulative incidence of first onset of hand eczema among the adolescents was statistically significantly higher for those who had ever been diagnosed with atopic dermatitis than for those who had not (14.6% vs. 8.2%, $P = 0.001$), with a high estimated sub-distribution hazard ratio (SHR) of 1.8 (95% CI: 1.3–2.6) (Figure 3). Similar to atopic dermatitis, adolescents with hand eczema who had ever been diagnosed with hay fever significantly contributed to higher hazard ratio than those who had not (SHR = 1.7, 95% CI: 1.2–2.4). However, the cumulative incidence of hand eczema did not

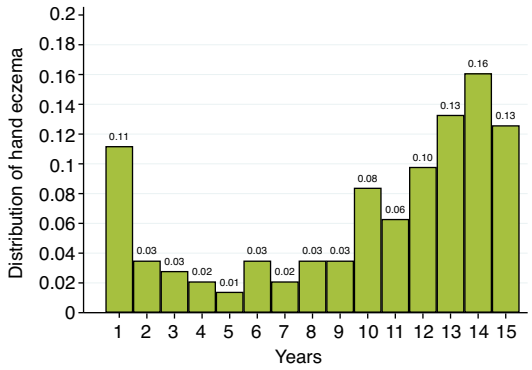

Figure 1 The distribution of the reports of hand eczema over the 15-year study period – German LISA birth cohort. Note: The distribution of the reports of hand eczema was calculated according to the first onset of hand eczema in each individual year (as numerator) divided by the total number of hand eczema cases over the 15-year study period (as denominator).

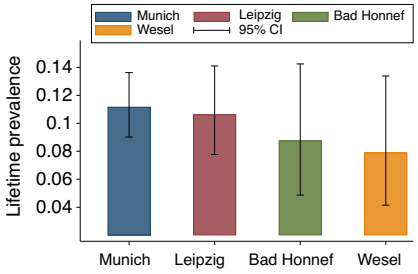

Figure 2 The lifetime prevalence of hand eczema at 15 years of age in four German regions – German LISA birth cohort.95%CI, 95% confidence interval. Note: The lifetime prevalence was presented by percentage.

show any significant difference between those who had ever been either diagnosed with asthma or found IgE positivity and those who had not (Figure 3).

Univariate logistic regression analysis

Table 1A summarizes the information on the endogenous and exogenous factors. In the univariate analysis, the following factors, including gender, reports of having ever been diagnosed with atopic dermatitis or hay fever, ever had itchy or watery eyes with nasal problems, ever had dry skin, ever been exposed to residential visible mould, ever had been in contact with pets indoor and daily use of facial cream, were significantly associated with hand eczema (Table 1A). However, asthma, IgE positivity for food and inhalant allergens and other lifestyle factors (e.g. reports of daily showering, daily use of body cream and daily exposed to familial cigarette smoking indoor) were not associated with hand eczema.

Multivariable logistic regression analysis

The endogenous factors of having ever been diagnosed with atopic dermatitis (aOR = 1.8, 95% CI: 1.1–2.8) or ever having had dry skin (aOR = 1.9, 95% CI: 1.1–3.1) were found to be significant independent risk factors for hand eczema. No statistically significant associations were found between exogenous factors and hand eczema (Table 1B).

Discussion

This is the largest population-based cohort study in Germany having assessed the relationship between risk factors and the lifetime prevalence of self-reported hand eczema among adolescents at the age of 15 years. The novelty of this study not only fills a research gap in the adolescent dermatology research community in Germany, but also provides a detailed depiction of the role of endogenous and exogenous factors (e.g. allergy-related diseases and relevant clinical symptoms, environmental and lifestyle factors) for hand eczema, which were not comprehensively considered by the Swedish BAMSE and the Danish TOACS birth cohorts (Table 2).[7,15] The lifetime prevalence in the German LISA birth cohort was 10.4%, which is similar to the Swedish BAMSE birth cohort[7] but significantly lower than the Danish TOACS cohort (Figure 4).[15] We observed that the lifetime prevalence of hand eczema among girls was statistically significant higher than among boys, which is consistent with the Swedish BAMSE and the Danish TOACS birth cohorts and other studies.[7,15,22]

In this study, we observed that a report of having ever been diagnosed with atopic dermatitis was an independent risk factor and strongly associated with the development of hand eczema. This is consistent with findings from the Swedish BAMSE and the Danish TOACS cohorts, and other studies.[6,7,15,23] Both this study and the Swedish BAMSE cohort show that by adjusting for similar confounders, the early age onset of atopic dermatitis was an additional risk factor (independent of the diagnosis itself) for the later development of hand eczema (Figure 5). It implies that early childhood prevention and treatment of atopic dermatitis is of great importance in clinical practice. On the other hand, we did not observe late-onset atopic dermatitis having the similar impact and the existing adolescent dermatology literature remains unclear whether the age onset of atopic dermatitis is associated with the risk of developing hand eczema in adolescence.[7,24,25] Furthermore, dry skin, as an important component of atopic dermatitis, was not researched by the Swedish BAMSE and the Danish TOACS cohorts; and our finding suggests, to some extent, an association with hand eczema. The high prevalence (72.2%) of dry skin in the past 12 months was reported only as a current exposure indicator for the lifetime prevalence of hand eczema among 15-year-olds, so the results should be interpreted with caution, and further evidence is needed before a causal relationship can be determined.

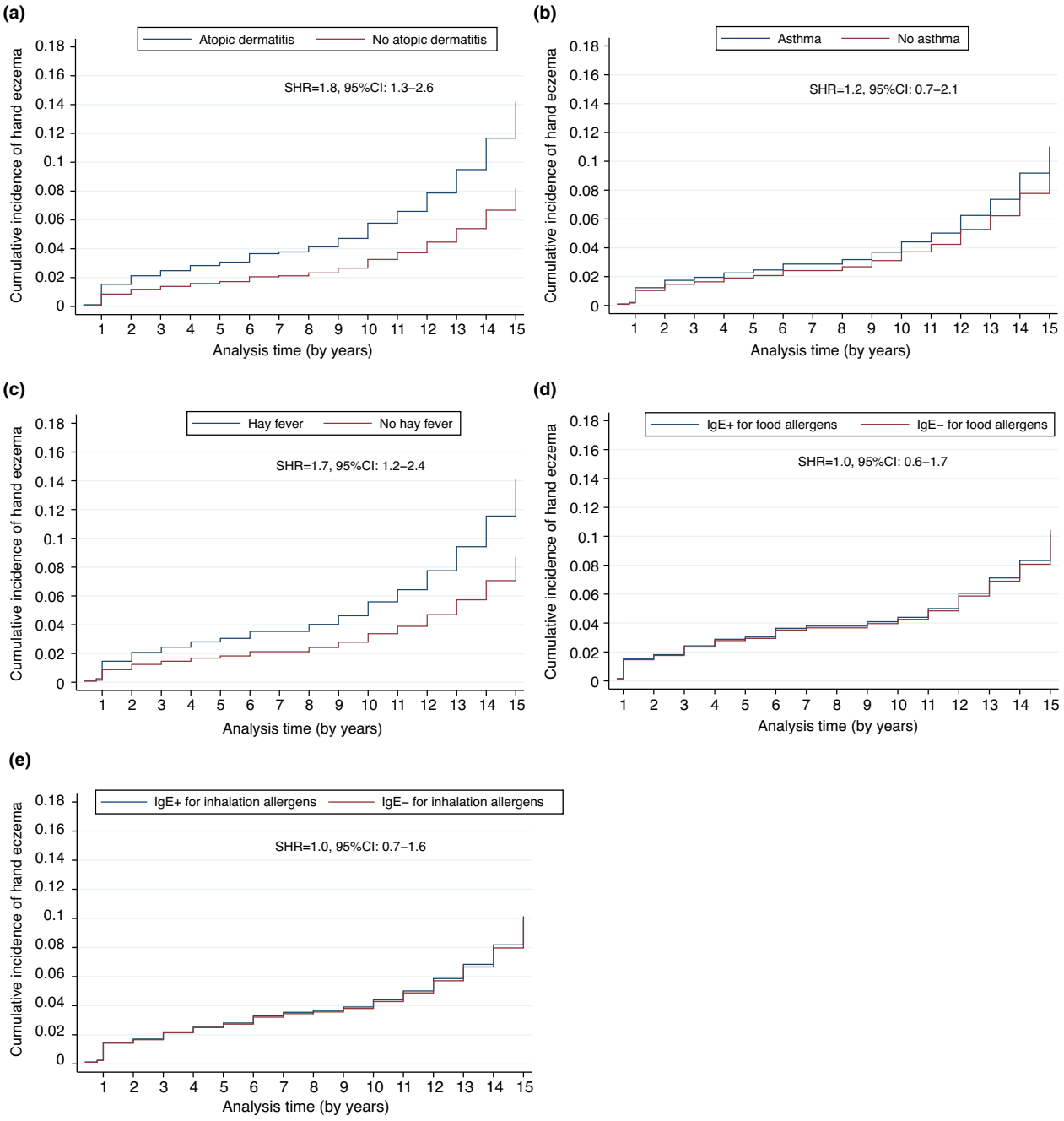

Figure 3 The cumulative lifetime incidences of first onset of hand eczema among adolescents diagnosed with atopic dermatitis, asthma, hay fever and IgE positivity for food and inhalation allergens over the 15-year study period – German LISA birth cohort. SHR, sub-distribution hazard ratio. Note: The cumulative lifetime incidences were presented by percentage.

Similar to atopic dermatitis, we observed a higher cumulative incidence of hand eczema among the adolescents who had ever been diagnosed with hay fever than for those who had not (14.5% vs. 8.8%, $P = 0.005$); but no association between the two disorders was found in the multivariable analysis (aOR = 1.4, 95% CI: 0.8–2.5). By contrast, Meding *et al.*,[26] reported that a history of hay fever suggested an increased risk in the development of hand eczema among adolescents and young adults

Table 2 Endogenous and exogenous factors hypothesized as being associated with hand eczema – Germany LISA birth cohort

	Indicators	German LISA cohort	Swedish BAMSE cohort[7]	Danish TOACS cohort[15]
Endogenous	Gender	✓	✓	✓
	Atopic dermatitis	✓	✓	✓
	Early onset of atopic dermatitis	✓	✓	N/A
	Asthma	✓	✓	N/A
	Hay fever or allergic rhinitis	✓	✓	N/A
	Rhinoconjunctivitis (e.g. itchy and watery eyes with nasal problems)	✓	✓	N/A
	Sensitization to food allergens	✓	✓	N/A
	Sensitization to inhalant allergens	✓	✓	N/A
	Dry skin	✓	N/A	N/A
Exogenous	Exposure to residential visible mould	✓	N/A	N/A
	Contact with pets indoors	✓	N/A	N/A
	Exposure to wet work	N/A	N/A	✓
	Hand washing and use of hand disinfectant	N/A	N/A	✓
	Use of moisturizer (e.g. nourishing creams)	✓	N/A	✓
	Showering	✓	N/A	N/A
	Exposure to familial cigarette smoke indoors	✓	N/A	✓

N/A, Not available information was reported.
In the German LISA birth cohort, the endogenous and exogenous factors were hypothesized as being associated with hand eczema.

between 10 and 19 years (adjusted risk ratio = 1.9; 95% CI: 1.2–2.8). The heterogeneous results might be attributable to the different age groups of the research population. Furthermore, half of adolescents with hand eczema reported whistling or wheezing breath noises, and itchy or watery eyes with nasal problems, respectively; but no association was found in the multivariable analysis. Neither this study nor the Swedish BAMSE cohort found any association between IgE tests for sensitization to food or inhalant allergens and hand eczema. The possible explanations for this finding are that: (i) the analytical sample used for analysing the role of IgE positivity was smaller than that was used for other endogenous and exogenous factors (Table 1A); (ii) hand eczema may not be directly driven by allergic sensitization.[7]

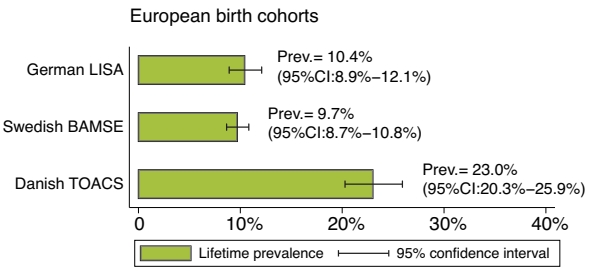

Figure 4 Comparison of the lifetime prevalence of hand eczema between the German LISA, the Swedish BAMSE and the Danish TOACS birth cohorts. Prev, Lifetime prevalence. Note: The lifetime prevalence of hand eczema in the German LISA cohort was similar to the Swedish BAMSE cohort but statistically significantly lower than the Danish TOACS.

In the latest adolescent dermatological literature, there are few studies that have directly analysed the association between environmental factors and the lifetime prevalence of hand eczema. We observed no direct associations between hand eczema and the factors of having ever been exposed to residential visible mould or having ever been in contact with pets indoor in the multivariable analysis. Furthermore, lifestyle factors (e.g. frequency of showering, use of facial or body creams and familial smoking exposure) were hypothesized as being associated with hand eczema; however, daily use of facial creams was the only one associated with hand eczema in the univariate analysis, but not in the multivariable analysis. This may be because, of the adolescents with hand eczema, a low proportion (15.7%, 24/153) reported both daily showers (e.g. exposure to moisture) and daily use of facial creams together, implying that the use of facial creams is correlative rather than causal; alternatively, it may be because lifestyle factors in the past 12 months were reported as current exposure indicators, rather than lifetime reported indicators. It therefore remains difficult to interpret causal relationships for lifestyle factors associated with the lifetime prevalence of hand eczema. Previous studies[27,28] also reported that exposed to cigarette smoking is a risk factor for hand eczema, but neither this study nor the Danish TOACS cohort[15] could confirm that relationship, and this inconsistency may differentiate between active and passive smoking. Passive smoking was the main exposure in this cohort. This could be another reason for a missing association among the adolescents.[29]

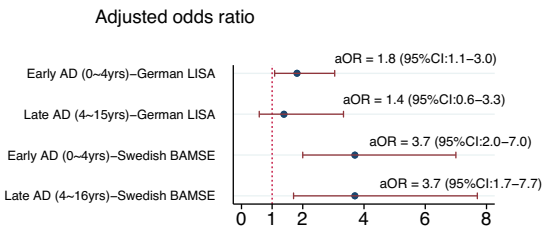

Figure 5 Results of the multivariable regression analysis for associations between early- or late-diagnosed atopic dermatitis and the lifetime prevalence of hand eczema among adolescents in the German LISA and the Swedish BAMSE birth cohorts. AD, Atopic dermatitis. •, Adjusted odds ratios with 95% confidence intervals. Note: In the multivariable analysis, early-diagnosed atopic dermatitis was associated with the lifetime prevalence of hand eczema among adolescents, by adjusting for the factors (including gender, having ever been diagnosed with hay fever, clinical symptoms of having ever had watery eyes with nasal problems and ever had dry skin, having ever been exposed to residential mould and ever been in contact with pets and daily use of facial creams) in the German LISA birth cohort.In the multivariable analysis, early-diagnosed atopic dermatitis was associated with the 1-year period prevalence of hand eczema among adolescents, by adjusting for the factors (including age at onset of asthma and/or rhinoconjunctivitis, any allergy-related disease, sensitization to airborne or food allergens, and parental allergy-related disease) in the Swedish BAMSE birth cohort. The Danish TOACS cohort did not apply multivariable analysis to adjust the factors, and did not look at the effect of early-diagnosed atopic dermatitis neither.

The main strengths of this study include its multi-city prospective design, its large sample size, the comprehensive assessment of endogenous and exogenous factors, which allow our study to fill some of the research gaps in the adolescent dermatology field, not only in Germany but also globally. However, this study has limitations. First, information (particularly self-reported hand eczema) is based on retrospective questionnaires; recall bias could therefore be present, and it is difficult to validate the answers given either by the adolescents or by their parents/families. Second, only 56.1% (1,736/3,097) of the parents or families have completed the 15-year follow-up. However, in the drop-out analysis (using baseline data), there was no statistically significant difference between the study population and the drop-out population in terms of demographic variables. We assumed that the drop-out population would not have a significant impact on the study population in the main analysis (Table S2). Third, our study only reported lifetime prevalence data, rather than prospective incidence data, whereas the Swedish BAMSE and the Danish TOACS cohorts presented both.[3,15]

In conclusion, we found that the lifetime prevalence of hand eczema among adolescents at the age of 15 was similar to the Swedish BAMSE birth cohort but lower than the Danish TOACS cohort. Similar to the Swedish birth cohort, a report of having ever been diagnosed with atopic dermatitis (particularly the early age onset of atopic dermatitis), was an independent risk factor for the lifetime prevalence of hand eczema. No statistically significant independent associations were found between asthma, hay fever, allergy-related clinical symptoms, IgE positivity and exogenous factors and hand eczema. Our results provide a benchmark and reference for future research on the lifetime prevalence of hand eczema in adolescents.

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Author contributions

Conception and study design: JW, CT, MS and CA. Acquisition of data: AB, GH, JH, MS. Data management: JW, CT and MS. Analysis and interpretation of data: JW, CT and CA. Drafting the manuscript: JW, CT and CA. Critical revision for important intellectual content and approval for submission: JW, CT, MS, SW, AB, GH, YWY, JH, JS and CA. All authors had full access to the study dataset and take responsibility for the integrity of the data presented.

Data availability statement

Due to data protection reasons, the datasets generated and/or analysed during the current study cannot be made publicly available. The datasets are available to interested researchers from the corresponding author on reasonable request, provided the release is consistent with the consent given by the LISA study participants. Ethical approval might be obtained for the release and a data transfer agreement from the legal department of the Helmholtz Zentrum München must be accepted.

References

1 Coenraads PJ. Hand eczema. *N Engl J Med* 2012; **367**: 1829–1837.

2 Apfelbacher C. Epidemiology of hand eczema from adolescence to adulthood. *Br J Dermatol* 2014; **171**: 210–211.
3 Grönhagen CM, Lidén C, Bergström A, Kull I, Wahlgren CF, Meding B. Prevalence and incidence of hand eczema in adolescence: report from BAMSE–a population-based birth cohort. *Br J Dermatol* 2014; **171**: 609–614.
4 Quaade AS, Simonsen AB, Halling AS, Thyssen JP, Johansen JD. Prevalence, incidence, and severity of hand eczema in the general population - A systematic review and meta-analysis. *Contact Dermatitis* 2021; **84**: 361–374.
5 Apfelbacher CJ, Funke U, Radulescu M, Diepgen TL. Determinants of current hand eczema: results from case-control studies nested in the PACO follow-up study (PACO II). *Contact Dermatitis* 2010; **62**: 363–370.
6 Heede NG, Thyssen JP, Thuesen BH, Linneberg A, Johansen JD. Predictive factors of self-reported hand eczema in adult Danes: a population-based cohort study with 5-year follow-up. *Br J Dermatol* 2016; **175**: 287–295.
7 Grönhagen C, Lidén C, Wahlgren CF *et al*. Hand eczema and atopic dermatitis in adolescents: a prospective cohort study from the BAMSE project. *Br J Dermatol* 2015; **173**: 1175–1182.
8 Thyssen JP, Johansen JD, Linneberg A, Menné T. The epidemiology of hand eczema in the general population–prevalence and main findings. *Contact Dermatitis* 2010; **62**: 75–87.
9 Ruff SMD, Engebretsen KA, Zachariae C *et al*. The association between atopic dermatitis and hand eczema: a systematic review and meta-analysis. *Br J Dermatol* 2018; **178**: 879–888.
10 Hamnerius N, Svedman C, Bergendorff O, Björk J, Bruze M, Pontén A. Wet work exposure and hand eczema among healthcare workers: a cross-sectional study. *Br J Dermatol* 2018; **178**: 452–461.
11 Zhang D, Zhang J, Sun S, Gao M, Tong A. Prevalence and risk factors of hand eczema in hospital-based nurses in northern China. *Australas J Dermatol* 2018; **59**: e194–e197.
12 Apfelbacher CJ, Ofenloch RF, Weisshaar E *et al*. Chronic hand eczema in Germany: 5-year follow-up data from the CARPE registry. *Contact Dermatitis* 2019; **80**: 45–53.
13 Gupta SB, Gupta A, Shah B *et al*. Hand eczema in nurses, nursing auxiliaries and cleaners-A cross-sectional study from a tertiary hospital in western India. *Contact Dermatitis* 2018; **79**: 20–25.
14 Ofenloch RF, Weisshaar E. Epidemiology of hand eczema in Germany: A retrospective view of the past 10 years of hand eczema research in Germany. *Hautarzt* 2019; **70**: 766–772.
15 Mortz CG, Bindslev-Jensen C, Andersen KE. Hand eczema in The Odense Adolescence Cohort Study on Atopic Diseases and Dermatitis (TOACS): prevalence, incidence and risk factors from adolescence to adulthood. *Br J Dermatol* 2014; **171**: 313–323.
16 Diepgen TL, Andersen KE, Chosidow O *et al*. Guidelines for diagnosis, prevention and treatment of hand eczema–short version. *J Dtsch Dermatol Ges* 2015; **13**: 77–85.
17 Helmholtz Zentrum München–German Research Centre for Environmental Health. Influence of life-style factors on the development of the immune system and allergies in East and West Germany (LISA). Available at: https://www.helmholtz-muenchen.de/epi/research/research-groups/allergic-disease-epidemiology/projects/lisa/index.html [Last accessed 12 August 2021].
18 South Tees Hospitals (NHS Foundation Trust). Serological tests for allergy. Available at: https://www.southtees.nhs.uk/services/pathology/tests/serological-tests-for-allergy/ [Last accessed 12 August 2021].
19 Ansotegui IJ, Melioli G, Canonica GW *et al*. IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper. *World Allergy Organ J* 2020; **13**: 100080.
20 East Kent Hospitals University (NHS Foundation Trust). Allergy diagnosis reference guide. Available at: https://www.mtw.nhs.uk/wp-content/uploads/2015/08/Allergy_diagnosis_reference_guide.pdf [Last accessed 12 August 2021].
21 Markevych I, Smith MP, Jochner S *et al*. Neighbourhood and physical activity in German adolescents: GINIplus and LISAplus. *Environ Res* 2016; **147**: 284–293.
22 Johannisson A, Pontén A, Svensson Å. Prevalence, incidence and predictive factors for hand eczema in young adults - a follow-up study. *BMC Dermatol* 2013; **13**: 14.
23 Rystedt I. Factors influencing the occurrence of hand eczema in adults with a history of atopic dermatitis in childhood. *Contact Dermatitis* 1985; **12**: 185–191.
24 Bantz SK, Zhu Z, Zheng T. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *J Clin Cell Immunol* 2014; **5**: 202.
25 Agner T, Elsner P. Hand eczema: epidemiology, prognosis and prevention. *J Eur Acad Dermatol Venereol* 2020; **34**(Suppl 1): 4–12.
26 Meding B, Järvholm B. Incidence of hand eczema-a population-based retrospective study. *J Invest Dermatol* 2004; **122**: 873–877.
27 Edman B. Palmar eczema: a pathogenetic role for acetylsalicylic acid, contraceptives and smoking? *Acta Derm Venereol* 1988; **68**: 402–407.
28 Zimmer KA, Armbrecht ES, Burkemper NM. The association of smoking with contact dermatitis and hand eczema - a review. *Int J Dermatol* 2018; **57**: 375–387.
29 Lerbaek A, Kyvik KO, Ravn H, Menné T, Agner T. Incidence of hand eczema in a population-based twin cohort: genetic and environmental risk factors. *Br J Dermatol* 2007; **157**: 552–557.

Supporting information

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

Table S1 Definitions of the endogenous and exogenous variables – German LISA birth cohort

Table S2 Drop-out analysis comparing the study population with the drop-out population – German LISA birth cohort