Atopic dermatitis: correlation of distinct risk factors with age of onset in adulthood compared to childhood

Laura Maintz, Marie-Therese Schmitz, Nadine Herrmann, Svenja Müller, Regina Havenith, Juliette Brauer, Claudio Rhyner, Anita Dreher, Eugen Bersuch, Danielle Fehr, Gertrud Hammel, Matthias Reiger, Daria Luschkova, Avidan Neumann, Claudia C. V. Lang, Ellen Renner, Peter Schmid-Grendelmeier, Claudia Traidl-Hoffmann, Cezmi A. Akdis, Roger Lauener, Marie-Charlotte Brüggen, Matthias Schmid, Thomas Bieber

Angaben zur Veröffentlichung / Publication details:

Maintz, Laura, Marie-Therese Schmitz, Nadine Herrmann, Svenja Müller, Regina Havenith, Juliette Brauer, Claudio Rhyner, et al. 2023. "Atopic dermatitis: correlation of distinct risk factors with age of onset in adulthood compared to childhood." Allergy 78 (8): 2181–201. https://doi.org/10.1111/all.15721.

Received: 10 October 2022 | Revised: 11 January 2023 | Accepted: 5 February 2023

DOI: 10.1111/all.15721

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

Atopic dermatitis: Correlation of distinct risk factors with age of onset in adulthood compared to childhood

Laura Maintz[1,2] | Marie-Therese Schmitz[2,3] | Nadine Herrmann[1,2] | Svenja Müller[1,2] | Regina Havenith[1,2] | Juliette Brauer[1,2] | Claudio Rhyner[2,4,5] | Anita Dreher[2,5] | Eugen Bersuch[2,6] | Danielle Fehr[2,6,7] | Gertrud Hammel[2,8,9] | Matthias Reiger[2,8,9] | Daria Luschkova[2,8,9] | Avidan Neumann[2,8,9] | Claudia C. V. Lang[2,6] | Ellen D. Renner[10,11] | Peter Schmid-Grendelmeier[2,6] | Claudia Traidl-Hoffmann[2,8,9] | Cezmi A. Akdis[2,4] | Roger Lauener[2,12] | Marie-Charlotte Brüggen[2,6,7,13] | Matthias Schmid[3] | Thomas Bieber[1,2,5]

[1]Department of Dermatology and Allergy, University Hospital Bonn, Bonn, Germany

[2]Christine Kühne-Center for Allergy Research and Education (CK-CARE), Davos, Switzerland

[3]Department of Medical Biometry, Informatics and Epidemiology, University Hospital Bonn, Bonn, Germany

[4]Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland

[5]DavosBioSciences, Davos, Switzerland

[6]Allergy Unit, Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland

[7]Faculty of Medicine, University of Zurich, Zurich, Switzerland

[8]Environmental Medicine, Faculty of Medicine, University of Augsburg, Augsburg, Germany

[9]Institute of Environmental Medicine Helmholtz Zentrum München, German Research Center for Environmental Health, Augsburg, Germany

[10]Translational Immunology of Environmental Medicine, School of Medicine, Technical University of Munich, Munich, Germany

[11]Department of Pediatrics, Klinikum Rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany

[12]Children's Hospital of Eastern Switzerland, St. Gallen, Switzerland

[13]Hochgebirgsklinik Davos, Davos, Switzerland

Correspondence
Laura Maintz, Department of Dermatology and Allergy, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany.
Email: laura.maintz@ukbonn.de

Funding information
Christine Kühne – Center for Allergy Research and Education

Abstract

Background: Atopic dermatitis (AD) has long been regarded as a primarily pediatric disease. However, there is growing evidence for a high rate of adult-onset AD. We aimed to characterize factors associated with adult-onset versus childhood-onset AD and controls.

Methods: We analyzed cross-sectional data of the CK-CARE-ProRaD cohorts Bonn, Augsburg, Davos, Zürich of 736 adult patients stratified by age of AD onset (childhood-onset <18 years: 76.4% (subsets: 0 to 2; ≥2 to 6; ≥7 to 11; ≥12 to 18); adult-onset

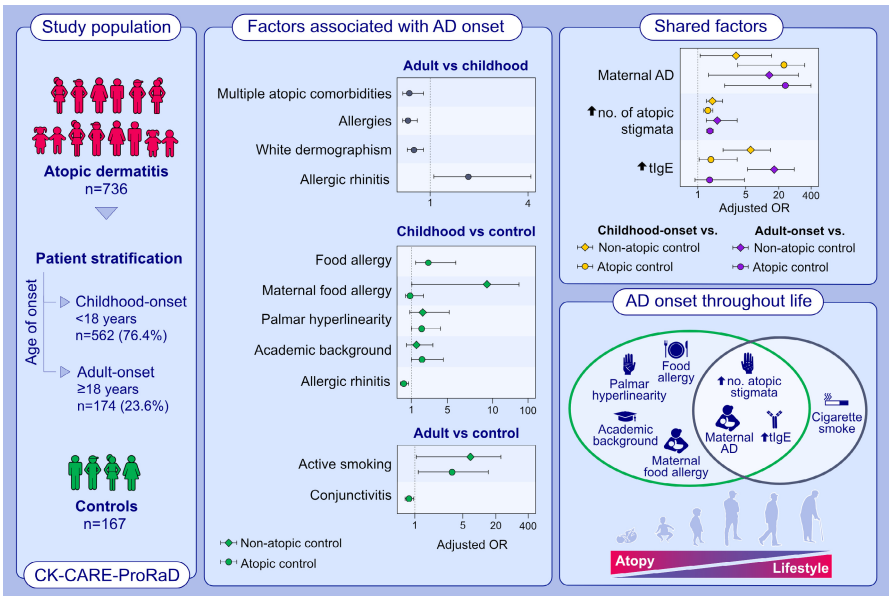
Abbreviations: AC, allergic conjunctivitis; AD, atopic dermatitis; AR, allergic rhinitis; BCS, British birth cohort studies; BMI, body mass index; BSA, body surface area; cAIC, corrected Akaike information criterion; DD, differential diagnosis; DLQI, dermatology life quality index; EASI, eczema area and severity index; EH, eczema herpeticum; ETS, environmental tobacco smoke; FA, food allergy; FAMD, factor analysis of mixed data; HSV, herpes simplex virus; LR, logistic regression; MLGB, machine-learning gradient boosting; MLR, multinomial logistic regression; OR, odds ratio; PA, physical activity; ProRaD, prospective longitudinal study investigating the remission phase in patients with atopic dermatitis and other allergy-associated diseases; SCORAD, scoring atopic dermatitis; T2, type 2; tIgE, total serum immunoglobulin E.

≥18 years: 23.6% (subsets: ≥18 to 40; ≥41 to 60; ≥61) and 167 controls (91 atopic, 76 non-atopic)).

Results: We identified active smoking to be associated with adult-onset AD versus controls (adjusted Odds Ratio (aOR) = 5.54 [95% Confidence Interval: 1.06–29.01] vs. controls$^{non\text{-}atopic}$, aOR = 4.03 [1.20–13.45] vs. controls^{atopic}). Conjunctivitis showed a negative association versus controls^{atopic} (aOR = 0.36 [0.14–0.91]). Food allergy (aOR = 2.93 [1.44–5.96]), maternal food allergy (aOR = 9.43 [1.10–80.95]), palmar hyperlinearity (aOR = 2.11 [1.05–4.25]), and academic background (aOR = 2.14 [1.00–4.54]) increased the odds of childhood-onset AD versus controls^{atopic}. Shared AD-associated factors were maternal AD (4-34x), increased IgE (2-20x), atopic stigmata (2-3x) with varying effect sizes depending on AD onset and control group. Patients with adult-compared to childhood-onset had doubled odds of allergic rhinitis (aOR = 2.15 [1.12–4.13]), but reduced odds to feature multiple (3–4) atopic comorbidities (aOR = 0.34 [0.14–0.84]). Adult-onset AD, particularly onset ≥61 years, grouped mainly in clusters with low contributions of personal and familial atopy and high frequencies of physical inactivity, childhood-onset AD, particularly infant-onset, mainly in "high-atopic"-clusters.

Conclusions: The identified associated factors suggest partly varying endo- and exogeneous mechanisms underlying adult-onset versus childhood-onset AD. Our findings might contribute to better assessment of the individual risk to develop AD throughout life and encourage prevention by non-smoking and physical activity as modifiable lifestyle factors.

KEYWORDS
adult-onset, associated factor, atopic dermatitis, childhood-onset, phenotype



GRAPHICAL ABSTRACT

Adult compared to childhood-onset AD was associated with allergic rhinitis, but reduced odds of multiple atopic comorbidities, allergies, and white dermographism. Compared to controls, adult-onset was associated with active smoking, childhood-onset with food allergy, maternal food allergy, palmar hyperlinearity and both with maternal AD, increased tIgE, higher number of atopic stigmata. Our data point towards partly varying endo- and exogeneous mechanisms underlying adult- and childhood-onset with the highest impact of atopy on onset in early life while lifestyle factors gain importance within adult-onset.

Abbreviations: AD, atopic dermatitis; Ig, immunoglobulin; no., number; OR, odds ratio; tIgE, total serum IgE

1 | INTRODUCTION

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease with a high impact on patients' and relatives' quality of life, productivity at work and burden on the healthcare system with an increasing cumulative lifetime prevalence of 15%–28% in developed countries.[1,2] Main factors of the complex pathophysiology are an altered skin barrier, modified immune system, skin microbiome dysbiosis, all influenced by gene–gene and gene–environment interactions.[1,3–7]

There is a wide range of (endo) phenotypes and disease trajectories.[1,4,6,8–30] While early birth cohort studies have suggested a clearance of AD in >50% of affected children, there is growing evidence for AD being a lifelong disease with variable phenotypic expression, high rate of adult-onset or relapsing AD after long asymptomatic intervals with different influencing factors such as age, disease-onset, ethnicity, and others.[1,2,4,9,12–15,18,19,23,24,30–32]

A meta-analysis conducted in 2018 reported a pooled proportion of 26.1% of patients with AD onset ≥16 years across different countries in Europe (24.0%), Asia (21.4%), the United States (53.0%), and other regions (24.3%),[12] a recent longitudinal study of two British birth cohort studies (BCS) adult-onset ≥23 years in 40%–43%.[2] A higher frequency of hand and/or head–neck-dermatitis[12,15] and atopic stigmata[9,15] in adult-compared to childhood-onset AD has been reported by some, but not all[33] studies. Overall, there is growing, but varying and still limited information on adult-onset AD, especially in late adulthood.[15]

Therefore, we sought to characterize factors associated with adult-onset versus childhood-onset AD and controls.

2 | METHODS

2.1 | Study design and participants

We analyzed cross-sectional baseline data of 903 adults enrolled in the ProRAD[8,34] study at Bonn, Augsburg, Davos, Zürich between 11/2016 and 01/2021 after written informed consent: 736 AD patients according to Hanifin and Rajka and 167 controls without AD (76 non-atopic and 91 atopic controls (no AD, but allergic rhinitis (AR) and/or asthma and/or food allergy (FA), and/or allergic conjunctivitis (AC) and/or allergies (self-reported)). AD patients were stratified by age of AD onset in adulthood ≥18 years (n = 174) and childhood <18 years (n = 562) with further stratification in onset at (i) 0 to <2 years (infancy), (ii) ≥2 to <7, (iii) ≥7 to <12, (iv) ≥12 to <18 years (adolescence), (v) early- (≥18 and <41 years), (vi) middle- (≥41 and <61 years), and (vii) late- (≥61 years) adulthood. Participants' characteristics are presented in Table 1 and Table S1. All study methods followed the Declaration of Helsinki and were approved by the respective local ethics committees. Further details are outlined in Methods S1.

2.2 | Statistical analysis

The associations of AD onset with clinical and epidemiological factors were analyzed using binary logistic regression (LR) with outcomes (1) adult-versus childhood-onset AD (2); adult-onset AD versus (2.1) controls$^{non\text{-}atopic}$; (2.2) controls^{atopic} (3); childhood-onset AD versus (3.1) controls$^{non\text{-}atopic}$; (3.2) controls^{atopic}; and multinomial LR (MLR) with outcomes (4) strata of childhood- and adult-onset AD versus (4.1) controls$^{non\text{-}atopic}$; (4.2) controls^{atopic} (5); strata of adult-onset versus childhood-onset AD (6); strata of childhood-onset AD versus adult-onset AD (7); adolescence versus early-adulthood; and (8) strata of onset at age (i) ≥2 to <7, (ii) ≥7 to <12; (iii) ≥12 to <18; (iv) ≥18 to <41; (v) ≥41 to <61; and (vi) ≥61 years versus onset in infancy (covariates see Figures 1–3, Tables 1–3 and Table S1). MLR models of the AD subgroups were adjusted for sex and age, localization of eczema additionally for severity, binary LR models for all covariates. Effect sizes are given in terms of univariate and adjusted odds ratios ((a)OR) with 95% confidence intervals (CI). Additionally, we performed factor analyses of mixed data (FAMD) of (i) all subjects: AD and controls and (ii) only AD patients, followed by hierarchical clustering using Ward's criterion.[35,36] All p-values are two-sided with a significance level of 5%. Statistical analysis was conducted using R version 3.5.3[37] and SPSS version 27.0. Further details such as add-on packages,[35,38–47] data pre-processing,[8,48,49] and variable selection[8,50,51] are provided in Methods S2.

3 | RESULTS

3.1 | Distribution of age of AD onset

Disease onset in adulthood ≥18 years was reported by 23.6% of our patients (n = 174) with 12.8% in early- (≥18 and <41 years), 6.2% middle- (≥41 and <61 years) and 4.6% late adulthood (≥61 years). Childhood-onset was reported in 76.4% (n = 562), with 44.2% in infancy (0 to <2 years), mainly in the first 6 months of life (32.6%) and 11.6% between 7 and 24 months, 19.3% between age 2 and 6 years, 6.2% between age 7 and 11 years, and 6.7% in adolescence (≥12 to <18 years; Table 1, Figure 1 and Figure S1).

3.2 | Family history

Familial atopy is a known risk factor (RF) for AD[1,6] but the impact on AD onset in diverse life periods less clear. In our cohort, maternal AD was the most important associated factor for both childhood- and adult-onset AD compared to controls without AD and increased the odds of AD up to 34-fold (childhood-onset: aOR = 4.36, 95% CI [1.18–16.17] vs. controls$^{non\text{-}atopic}$, aOR = 32.97 [4.03–269.68] vs. controls^{atopic}; Figure 2), adult-onset AD: aOR = 15.79 [1.81–137.74] versus controls$^{non\text{-}atopic}$, aOR = 34.15

TABLE 1 Characteristics of patients with atopic dermatitis stratified by age at AD onset.

	Age at onset of AD (years)																	
Factor	**0 to 18**		**≥18**		**0 to <2**		**≥2 to <7**		**≥7 to <12**		**≥12 to <18**		**≥18 to <41**		**≥41 to <61**		**≥61**	
Biomarkers	***n* = 562/736**	**76.4%**	***n* = 174**	**23.6%**	***n* = 325**	**44.17%**	***n* = 142**	**19.3%**	***n* = 46**	**11.5%**	***n* = 49**	**6.2%**	***n* = 94**	**12.8%**	***n* = 46**	**6.2%**	***n* = 34**	**4.6%**
tIgE [IU/mL], [Median, Q1–Q3]	544.1	177.5–2499.2	477.5	95.2–1777.2	749.0	131.0–3103.0	280.5	84.0–1288.5	406.3	120.5–1387.8	764.8	154.0–2391.0	477.5	106.2–1409.2	769.5	72.6–2843.5	443.5	73.1–1418.2
Increased tIgE [*n*, %]	436	77.6	128	73.6	257	79.1	104	73.2	38	82.6	37	75.5	72	76.6	32	69.6	24	70.6
Eosinophils [G/L], [Median, Q1–Q3]	0.2	0.1–0.4	0.2	0.1–0.3	0.2	0.1–0.4	0.2	0.1–0.3	0.2	0.1–0.3	0.3	0.2–0.4	0.2	0.1–0.3	0.2	0.1–0.3	0.3	0.2–0.6
Eosinophilia > 0.5 G/L [*n*, %]	86	15.3	28	16.1	53	16.3	18	12.7	7	15.2	8	16.3	9	9.6	9	19.6	10	29.4
Comorbidities	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Asthma	287	51.1	47	27.0	184	56.6	60	42.3	17	37.0	26	53.1	29	30.9	13	28.3	5	14.7
Allergic rhinitis	428	76.2	100	57.5	262	80.6	102	71.8	29	63.0	35	71.4	69	73.4	22	47.8	9	26.5
Food allergy	330	58.7	56	32.2	227	69.8	67	47.2	14	30.4	22	44.9	38	40.4	12	26.1	6	17.6
Conjunctivitis	350	62.3	79	45.4	212	65.2	86	60.6	24	52.2	28	57.1	55	58.5	16	34.8	8	23.5
No. of atopic com.																		
0	68	12.1	48	27.6	30	9.2	19	13.4	12	26.1	7	14.3	14	14.9	17	37.0	17	50.0
1	70	12.5	34	19.5	30	9.2	25	17.6	7	15.2	8	16.3	17	18.1	7	15.2	10	29.4
2	98	17.4	44	25.3	50	15.4	31	21.8	7	15.2	10	20.4	28	29.8	13	28.3	3	8.8
3	175	31.1	32	18.4	105	32.3	40	28.2	17	37.0	13	26.5	22	23.4	6	13.0	4	11.8
4	151	26.9	16	9.2	110	33.8	27	19.0	3	6.5	11	22.4	13	13.8	3	6.5	0	0.0
3–4	326	58.0	48	27.6	215	66.2	67	47.2	20	43.5	24	49.0	35	37.2	67	47.2	20	43.5
Self-reported allergies	487	86.7	106	60.9	295	90.8	120	84.5	36	78.3	36	73.5	68	72.3	28	60.9	10	29.4
Cardiovascular diseases	59	10.5	42	24.1	37	11.4	10	7.0	5	10.9	7	14.3	9	9.6	12	26.1	21	61.8
Alopecia areata	35	6.2	15	8.6	23	7.4	6	4.4	2	4.3	4	8.2	11	11.7	3	6.5	1	2.9
Atopic stigmata	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
No. of atopic stigmata (Median, Q1–Q3)	7	5–9	5	3–8	7.0	5.0–9.0	6.0	3.2–8.0	5.0	3.0–7.8	6.0	5.0–8.0	6.0	3.2–8.0	5.0	4.0–7.8	4.5	3.0–7.0
Hertoghe´s sign	244	43.4	78	44.8	149	45.8	56	39.4	19	41.3	20	40.8	44	46.8	19	41.3	15	44.1
Facial pallor/ erythema	302	53.7	95	54.6	194	59.7	64	45.1	21	45.7	23	46.9	56	59.6	21	45.7	18	52.9

TABLE 1 (Continued)

	Age at onset of AD (years)																	
Factor	**0 to 18**		**≥18**		**0 to <2**		**≥2 to <7**		**≥7 to <12**		**≥12 to <18**		**≥18 to <41**		**≥41 to <61**		**≥61**	
Dirty neck	127	22.6	38	21.8	83	25.5	28	19.7	7	15.2	9	18.4	15	16.0	13	28.3	10	29.4
White dermographism	344	61.2	75	43.1	210	64.6	75	52.8	23	50.0	36	73.5	43	45.7	19	41.3	13	38.2
Periorbital darkening	352	62.6	92	52.9	220	67.7	83	58.5	19	41.3	30	61.2	53	56.4	25	54.3	14	41.2
Dennie-Morgan fold	320	56.9	66	37.9	199	61.2	77	54.2	22	47.8	22	44.9	42	44.7	14	30.4	10	29.4
Anterior neck fold	242	43.1	59	33.9	153	47.1	55	38.7	20	43.5	14	28.6	32	34.0	18	39.1	9	26.5
Ear rhagades	176	31.3	37	21.3	122	37.5	33	23.2	9	19.6	12	24.5	20	21.3	14	30.4	3	8.8
Keratosis pilaris	179	31.9	41	23.6	112	34.5	39	27.5	11	23.9	17	34.7	26	27.7	7	15.2	8	23.5
Nipple eczema	59	10.5	7	4.0	38	11.7	12	8.5	4	8.7	5	10.2	6	6.4	1	2.2	0	–
Cheilitis sicca	266	47.3	63	36.2	161	49.5	74	52.1	13	28.3	18	36.7	36	38.3	18	39.1	9	26.5
Perleche	170	30.2	35	20.1	110	33.8	36	25.4	12	26.1	12	24.5	20	21.3	9	19.6	6	17.6
Pityriasis alba	98	17.4	18	10.3	63	19.4	19	13.4	11	23.9	5	10.2	8	8.5	6	13.0	4	11.8
Palmar hyperlinearity	372	66.2	108	62.1	222	68.3	88	62.0	26	56.5	36	73.5	57	60.6	29	63.0	22	64.7
Xerosis cutis	499	88.8	161	92.5	299	92.0	119	83.8	38	82.6	43	87.8	87	92.6	42	91.3	32	94.1
Active smoking	**124**	**22.1**	**45**	**25.9**	**65**	**20.0**	**39**	**27.5**	**8**	**17.4**	**12**	**24.5**	**32**	**34.0**	**12**	**26.1**	**1**	**2.9**
Daily smoking	72	12.8	30	17.2	40	12.3	17	12.0	6	13.0	9	18.4	19	20.2	10	21.7	1	2.9
Never-smokers	318	56.6	76	43.7	191	58.8	75	52.8	29	63.0	23	46.9	41	43.6	22	47.8	13	38.2
Occasional smokers	52	9.3	15	8.6	25	7.7	22	15.5	2	4.3	3	6.1	13	13.8	2	4.3	0	–
Former smokers	120	21.4	53	30.5	69	21.2	28	19.7	9	19.6	14	28.6	21	22.3	12	26.1	20	58.8
Passive smoking	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Never	190	33.8	49	28.2	105	32.3	50	35.2	18	39.1	17	34.7	24	25.5	15	32.6	10	29.4
Occasional	160	28.5	36	20.7	99	30.5	37	26.1	11	23.9	13	26.5	23	24.5	9	19.6	4	11.8
Daily	104	18.5	45	25.9	60	18.5	26	18.3	10	21.7	8	16.3	26	27.7	13	28.3	6	17.6
Former	108	19.2	44	25.3	61	18.8	29	20.4	7	15.2	11	22.4	21	22.3	9	19.6	14	41.2
Lifestyle, other	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Never-doing-sports	81	14.4	53	30.5	51	15.7	16	11.3	5	10.9	9	18.4	24	25.5	14	30.4	15	44.1
Household-size ≥ 4 persons	139	24.7	30	17.2	80	24.6	42	29.6	9	19.6	8	16.3	18	19.1	10	21.7	2	5.9
Only child	67	11.9	25	14.4	38	11.7	15	10.6	6	13.0	8	16.3	13	13.8	6	13.0	6	17.6
Cat exposure	345	61.4	103	59.2	192	59.1	92	64.8	29	63.0	32	65.3	60	63.8	24	52.2	19	55.9

(Continues)

TABLE 1 (Continued)

	Age at onset of AD (years)																	
Factor	**0 to 18**		**≥18**		**0 to <2**		**≥2 to <7**		**≥7 to <12**		**≥12 to <18**		**≥18 to <41**		**≥41 to <61**		**≥61**	
Dog exposure	337	60.0	107	61.5	188	57.8	85	59.9	29	63.0	35	71.4	54	57.4	31	67.4	22	64.7
Mould exposition	292	52.0	61	35.1	175	53.8	71	50.0	18	39.1	28	57.1	43	45.7	15	32.6	3	8.8
Rural living	200	35.6	70	40.2	117	36.0	49	34.5	19	41.3	15	30.6	31	33.0	20	43.5	19	55.9
No, inhabitants	50,000	11,139–313,958	28,638	5024–299,145	46963	10,500–300,000	59,865	9000–318,000	65,405	16,072–321,500	47,000	14,731–320,820	36,763	5000–300,000	32,114	17,359–79,250	20500.0	3375–130,000
Body mass index [Median, Q1–Q3]	23.8	21.5–27.1	24.8	22.7–28.4	23.5	21.5–26.8	23.9	21.0–28.0	24.3	22.1–28.3	24.2	21.8–26.9	24.7	22.4–27.6	24.6	22.2–28.6	26.6	24.0–28.9
Obesity (BMI≥30)	80	14.2	28	16.1	41	12.6	24	16.9	8	17.4	7	14.3	12	12.8	8	17.4	8	23.5
Academic patient &/or parents	**434**	**77.2**	**94**	**54.0**	**253**	**77.8**	**114**	**80.3**	**37**	**80.4**	**30**	**61.2**	**58**	**61.7**	**21**	**45.7**	**15**	**44.1**
Patient academic	384	68.3	83	47.7	219	67.4	102	71.8	34	73.9	29	59.2	50	53.2	18	39.1	15	44.1
Mother academic	213	37.9	36	20.7	157	48.3	63	44.4	22	47.8	13	26.5	36	38.3	10	21.7	10	29.4
Father academic	255	45.4	56	32.2	122	37.5	56	39.4	24	52.2	11	22.4	24	25.5	6	13.0	6	17.6
Perinatal factors	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Cesarean section (ref vag)	71	12.6	9	5.2	49	15.1	14	9.9	5	10.9	3	6.1	7	7.4	1	2.2	1	2.9
Birth weight (median, Q1–Q3)	3.330	3.045–3.600	3.500	3.100–3.700	3300	3000–3625	3400	3100–3710	3400	3180–3600	3200	2975–3525	3500	3175–3660	3450	3050–3600	3925	3562–4400
Preterm birth (<37 week)	29	5.2	8	4.6	19	5.8	5	3.5	1	2.2	4	8.2	6	6.4	2	4.3	0	0.0
Breastfeeding	429	76.3	140	80.5	243	74.8	112	78.9	40	87.0	34	69.4	66	70.2	40	87.0	34	100.0
Breastfeeding >4 months[a]	191	73.5	23	69.7	117	73.1	45	70.3	18	81.8	11	78.6	17	70.8	3	60.0	3	75.0
Proneness to infections	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Herpes simplex	272	48.4	76	43.7	162	49.8	63	44.4	18	39.1	29	59.2	39	41.5	19	41.3	18	52.9
Eczema herpeticum	67	11.9	7	4.0	46	14.2	12	8.5	3	6.5	6	12.2	4	4.3	3	6.5	0	–
Verrucae	347	61.7	73	42.0	193	59.4	88	62.0	30	65.2	36	73.5	40	42.6	21	45.7	12	35.3
Bacterial	242	43.1	54	31.0	162	49.8	50	35.2	11	23.9	19	38.8	32	34.0	13	28.3	9	26.5
Family history	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Positive family history for allergies	356	63.3	57	32.8	216	66.5	96	67.6	24	52.2	20	40.8	43	45.7	9	19.6	5	14.7
No parental atopy	172	30.6	92	52.9	216	66.5	96	67.6	13	28.3	22	44.9	37	39.4	31	67.4	24	70.6

TABLE 1 (Continued)

	Age at onset of AD (years)																	
Factor	**0 to 18**		**≥18**		**0 to <2**		**≥2 to <7**		**≥7 to <12**		**≥12 to <18**		**≥18 to <41**		**≥41 to <61**		**≥61**	
1 parent atopic	280	49.8	70	40.2	89	27.4	48	33.8	26	56.5	23	46.9	48	51.1	12	26.1	10	29.4
Both parents atopic	110	19.6	12	6.9	164	50.5	67	47.2	7	15.2	4	8.2	9	9.6	3	6.5	0	–
Maternal atopy	**301**	**53.6**	**57**	**32.8**	**72**	**22.2**	**27**	**19.0**	**22**	**47.8**	**21**	**42.9**	**41**	**43.6**	**11**	**23.9**	**5**	**14.7**
Maternal AD	151	26.9	34	19.5	92	28.3	31	21.8	15	32.6	13	26.5	25	26.6	6	13.0	3	8.8
Maternal asthma	98	17.4	18	10.3	60	18.5	24	16.9	8	17.4	6	12.2	10	10.6	5	10.9	3	8.8
Maternal allergic rhinitis	192	34.2	35	20.1	114	35.1	52	36.6	13	28.3	13	26.5	27	28.7	7	15.2	1	2.9
Maternal food allergy	137	24.4	15	8.6	94	28.9	29	20.4	7	15.2	7	14.3	14	14.9	1	2.2	0	–
Paternal atopy	**199**	**35.4**	**37**	**21.3**	**119**	**36.6**	**52**	**36.6**	**18**	**39.1**	**10**	**20.4**	**25**	**26.6**	**7**	**15.2**	**5**	**14.7**
Paternal AD	80	14.2	15	8.6	50	15.4	21	14.8	7	15.2	2	4.1	10	10.6	2	4.3	3	8.8
Paternal asthma	56	10.0	16	9.2	29	8.9	16	11.3	7	15.2	4	8.2	12	12.8	3	6.5	1	2.9
Paternal allergic rhinitis	126	22.4	16	9.2	74	22.8	34	23.9	10	21.7	8	16.3	13	13.8	2	4.3	1	2.9
Paternal food allergy	45	8.0	7	4.0	29	8.9	13	9.2	2	4.3	1	2.0	6	6.4	0	–	1	2.9
Basic demographics	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Female (ref male)	342	60.9	85	48.9	199	61.2	92	64.8	25	54.3	26	53.1	49	52.1	25	54.3	11	32.4
Age (median, Q1– Q3)	35.1	26.4–49.4	56.5	44.0–64.9	33.7	25.3–48.8	36.0	27.1–48.3	37.5	28.8–52.1	40.2	30.1–54.1	49.2	36.7–58.9	55.7	50.7–62.5	75.0	67.1–79.3
AD Course	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Active AD	525	93.4	172	98.9	312	96.0	124	87.3	44	95.7	45	91.8	93	98.9	46	100.0	33	97.1
AD in remission	37	6.6	2	1.1	13	4.0	18	12.7	2	4.3	4	8.2	1	1.1	0	0.0	1	2.9
Seasonal flare	211	37.5	52	29.9	118	36.3	58	40.8	19	41.3	16	32.7	37	39.4	9	19.6	6	17.6
AD course	Med	Q1–Q3	Med	Q1–Q3	Med	Q1–Q3	Med	Q1–Q3	Med	Q1–Q3	Med	Q1–Q3	Med	Q1–Q3	Med	Q1–Q3	Med	Q1–Q3
AD onset [years]	1.0	0.2–4.0	40.0	27.0–58.8	0.2	0.1–0.6	3.0	2.3–5.0	8.0	7.0–10.0	14.0	13.0–16.0	28.0	22.0–35.0	50.5	47.0–57.8	70.0	64.2–76.0
EASI	5.8	1.8–14.9	8.4	3.0–21.8	7.6	2.4–17.4	3.9	1.3–8.6	3.3	1.2–12.3	5.0	1.0–12.8	7.8	1.9–22.3	7.8	2.9–20.6	12.5	6.2–21.9
BSA	15.5	4.0–35.9	22.2	5.6–49.3	21.0	6.1–41.5	8.0	2.0–24.2	10.0	2.1–28.2	13.5	3.5–32.0	20.8	4.1–50.4	19.0	5.1–40.8	34.0	13.6–50.1
oSCORAD	30.3	17.9–42.5	34.8	21.4–47.2	33.5	20.5–44.9	25.5	14.6–38.8	23.0	14.5–38.1	25.7	14.2–41.2	32.7	21.3–44.6	30.9	19.4–44.7	40.1	31.1–51.5
SCORAD	36.0	22.0–51.8	42.0	25.8–56.7	39.9	24.9–54.2	32.0	18.0–47.0	29.1	18.7–49.1	30.2	16.4–49.4	40.8	22.6–56.1	36.7	25.0–51.5	47.0	39.4–62.9
DLQI	7.0	2.2–14.8	9.0	3.0–16.0	8.0	4.0–16.0	6.0	1.0–11.0	7.0	3.0–12.8	6.0	2.0–13.0	9.5	3.0–17.0	8.0	4.2–17.5	9.0	3.0–14.8
Pruritus	4.0	2.0–7.0	5.0	2.0–7.0	4.0	2.0–6.0	4.0	1.0–7.0	4.0	2.0–6.8	3.0	1.0–6.0	4.0	1.2–7.0	5.0	2.0–6.8	5.0	3.2–8.0

(Continues)

TABLE 1 (Continued)

Factor	Age at onset of AD (years)																	
	0 to 18		≥18		0 to <2		≥2 to <7		≥7 to <12		≥12 to <18		≥18 to <41		≥41 to <61		≥61	
Distribution of eczema	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Head neck	431	76.7	135	77.6	269	82.8	97	68.3	29	63.0	36	73.5	71	75.5	37	80.4	27	79.4
Trunk	372	66.2	133	76.4	236	72.6	77	54.2	26	56.5	33	67.3	65	69.1	37	80.4	31	91.2
Arms	469	83.5	151	86.8	285	87.7	108	76.1	36	78.3	40	81.6	82	87.2	40	87.0	29	85.3
Legs	384	68.3	127	73.0	240	73.8	83	58.5	28	60.9	33	67.3	65	69.1	36	78.3	26	76.5
Hand eczema	355	63.2	113	64.9	218	67.1	79	55.6	25	54.3	33	67.3	61	64.9	29	63.0	23	67.6
Hands dorsal	302	53.7	101	58.0	187	57.5	69	48.6	18	39.1	28	57.1	53	56.4	27	58.7	21	61.8
Palmae	215	38.3	76	43.7	136	41.8	45	31.7	14	30.4	20	40.8	42	44.7	19	41.3	15	44.1

Note: Blue font: adult-onset, black font: childhood-onset AD. Atopic comorbidities = allergic conjunctivitis, allergic rhinitis (AR), asthma, Food allergy (FA), BSA = body surface area, DLQI = Dermatology Life Quality Index, EASI = Eczema Area and Severity Index, tIgE↑: increased total serum immunglobulinE levels, age-dependent cut-off points: age 12–15 y: 200 IU/mL, age ≥16 y: 100 IU/mL, IQR = interquartile range (Q1–Q3), NA = not applicable (outcome variable), (o)SCORAD = (objective) SCORing Atopic Dermatitis.

[a] No imputation because of ≥30% missing values. Effect sizes of the characteristics associated with different subgroups of AD stratified by AD onset are given in Figures 1–3, Tables 2 and 3 and Figures S2–S14.

[3.15–370.28] versus controls[atopic] (Figure 3 and Figures S2–S6, Table 2 and Table S2). Additionally, maternal FA increased the odds of childhood-onset AD compared to controls[non-atopic] (aOR = 9.43 [1.10–80.95]; Figure 2). Stratification revealed associations across all ages of childhood up to early-adult-onset AD with the strongest association in infancy-onset AD (aOR = 29.54 [4.04–215.87]; Figure S5, Table 2). We found no association of maternal AD or maternal FA with mode of delivery and breastfeeding as important factors contributing to immune interactions between children and mothers (Table S3). Paternal AD was associated with AD with onset in up to age 6, but with onset at later age only in univariate analyses (Table 2 and Table S2).

3.3 | Lifestyle factors

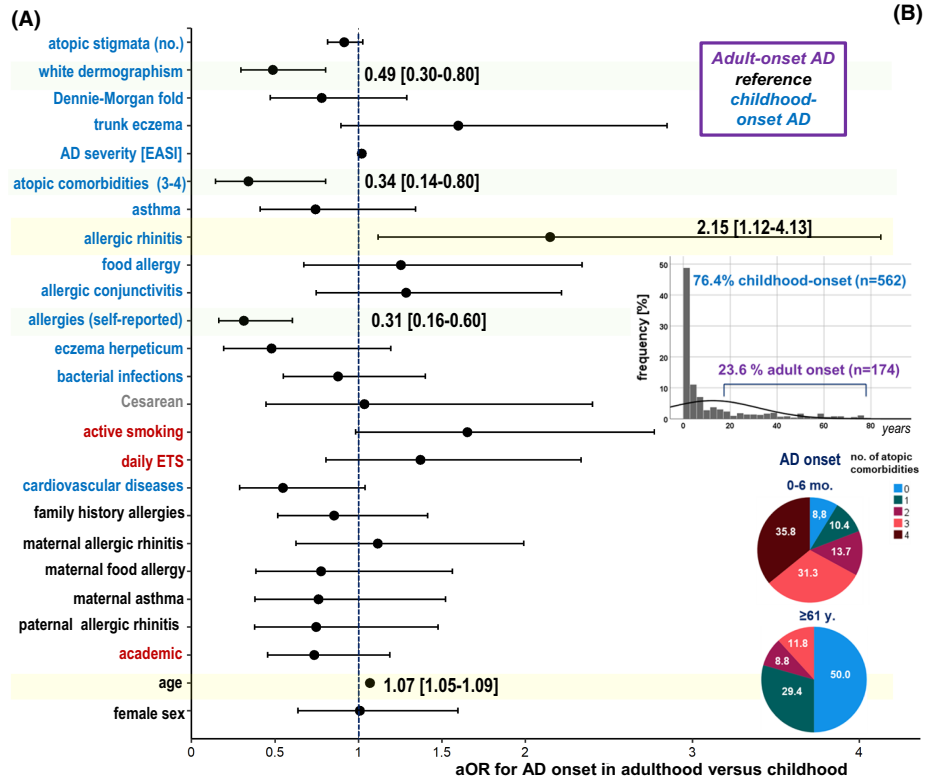
We investigated modifiable factors to assess their potential for AD prevention in different windows of life. Active smoking was the main lifestyle factor associated with adult-onset AD (aOR = 5.54 [1.06–29.01] vs. controls[non-atopic], aOR = 4.03 [1.20–13.45] vs. controls[atopic]; Figure 3). Daily passive exposure to environmental tobacco smoke (ETS) showed associations with childhood- and adult-onset AD in univariate analyses (Figures 2 and 3, Table S2) and MLR of subgroups (Table 2, Figures S2–S6).

Within AD, active smoking tended to increase the odds of adult-compared to childhood-onset AD overall (aOR = 1.65 [0.98–2.77]; Figure 1). Subgroup analysis revealed that active smoking (aOR = 2.08 [1.27–3.40]) and daily ETS (aOR = 1.68 [1.00–2.81]) increased the odds of AD onset in early-adulthood versus childhood (Figure S7) and halved the odds of infancy-onset versus adult-onset (Figure S8).

Never-doing sports compared to physical activity (PA) was associated with disease-onset in early- (aOR = 2.72 [1.13–6.55]), middle- (aOR = 3.61 [1.33–9.95]), and late-adulthood (aOR = 7.74 [2.17–27.63]) versus controls[non-atopic] (Table 2, Figures S2 and S3). Within AD, patients with onset in middle- (aOR = 2.19 [1.03–4.65]) and late- (aOR = 4.43 [1.48–13.23]) adulthood had higher odds of physical inactivity than adults with infancy-onset (Table 3, Figures S9 and S10).

A higher educational level of patients' and/or their parents doubled the odds of childhood-onset AD compared to controls[atopic] (aOR = 2.14 [1.00–4.54], Figure 2) and reduced the odds of AD with onset in middle- (aOR = 0.41 [0.21–0.79]) and late (aOR = 0.33 [0.12–0.86]) adulthood versus childhood (Figure S7), particularly versus infancy onset (Table 3; Figure S9). Analysis of a potential relationship between these factors revealed a higher frequency of smoking and of physical inactivity in subjects without compared to those with an academic background (Table S4).

A household size of at least four persons approximately halved the odds of AD onset before age 2 years (Figure S6) and between 7 and 40 years (Figure S4) compared to controls[atopic] (Table 2). Childhood- and adult-onset AD overall showed the same trend in univariate analyses (Figures 2 and 3). There was a small positive



(B)

Adult-onset	Ref. Childhood-onset AD	
Factor	OR [95% CI]	aOR [95% CI]
atopic stigma (no.)	**0.87 [0.82-0.93]**	0.91 [0.81-1.03]
white dermogr.	**0.48 [0.34-0.68]**	**0.49 [0.30-0.80]**
Dennie-Morgan	**0.46 [0.33-0.66]**	0.78 [0.47-1.29]
trunk eczema	**1.66 [1.12-2.45]**	1.60 [0.89-2.85]
EASI	**1.02 [1.01-1.03]**	1.02 [0.999-1.041]
0-2 atopic com.	Ref	
3-4 atopic com.	**0.28 [0.19-0.40]**	**0.34 [0.14-0.80]**
asthma	**0.35 [0.24-0.52]**	0.74 [0.41-1.34]
AR	**0.42 [0.30-0.61]**	**2.15 [1.12-4.13]**
Food allergy	**0.33 [0.23-0.48]**	1.25 [0.67-2.34]
conjunctivitis	**0.50 [0.36-0.71]**	1.29 [0.75-2.22]
allergies	**0.24 [0.16-0.35]**	**0.31 [0.16-0.60]**
CVD	**2.71 [1.75-4.21]**	0.55 [0.29-1.04]
EH	**0.31 [0.14-0.69]**	0.48 [0.19-1.19]
bacterial inf.	**0.60 [0.41-0.85]**	0.88 [0.55-1.40]
Cesarean	**0.38 [0.18-0.77]**	1.04 [0.45-2.40]
Active smoking	1.23 [0.83-1.83]	1.65 [0.98-2.77]
ETS (daily)	**1.54 [1.03-2.29]**	1.37 [0.80-2.33]
FH allergies	**0.28 [0.20-0.40]**	0.85 [0.52-1.41]
Maternal AR	**0.49 [0.32-0.73]**	1.12 [0.63-1.99]
Maternal FA	**0.29 [0.17-0.51]**	0.78 [0.38-1.56]
Mat.asthma	**0.55 [0.32-0.93]**	0.76 [0.38-1.52]
Paternal AR	**0.35 [0.20-0.61]**	0.75 [0.38-1.48]
academic	**0.35 [0.24-0.50]**	0.74 [0.46-1.19]
age	1.07 [1.06-1.09]	**1.07 [1.05-1.09]**
Female sex	**0.61 [0.44-0.86]**	1.01 [0.64-1.59]

FIGURE 1 Frequency and factors associated with adult-onset atopic dermatitis (AD) compared to childhood-onset AD. Allergic rhinitis was associated with adult-onset AD, multiple atopic comorbities, allergies, and white dermographism with childhood-onset AD. Forest plot (A) and Table (B) of associations of clinical and epidemiological factors with adult-onset AD ($n = 174$) versus childhood-onset AD ($n = 562$) obtained from a binary logistic regression model. Effect sizes are presented as adjusted odds ratios (aOR) with 95% confidence intervals (CI). Bold and yellow boxes: p-values < .05. Embedded in panel (A), the frequencies of age at onset of AD in child and adulthood are depicted in a histogram and number of atopic comorbidities [% of patients] depending on AD onset in pie charts (onset < 6 months: $n = 240$; ≥61 years: $n = 34$). Academic was defined as education at least A-level up to university degree of patients' and their parents. Allergies were self-reported. AR, allergic rhinitis; CVD, cardiovascular diseases; EASI, Eczema Area and Severity Index; EH, Eczema herpeticum; ETS, environmental tobacco smoke/passive smoking; FA, food allergy; FH, family history; no., number.

association between the patients' age at visit and adult-onset AD both versus controls and childhood-onset AD (Figures 2 and 3).

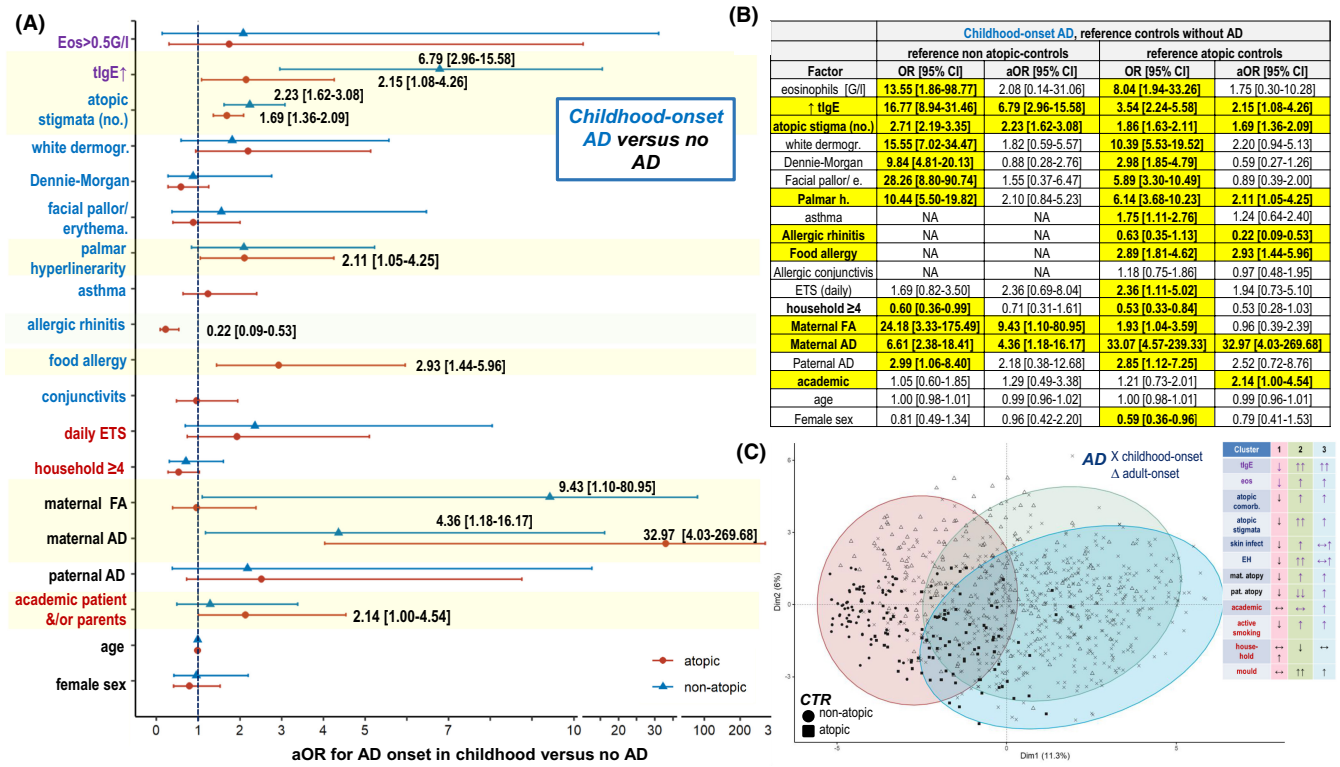
3.4 | Phenotype and atopic stigmata

We sought to investigate whether the phenotype of subjects is helpful in assessing the odds of AD with different ages of manifestation. Atopic stigmata are phenotypic traits described more frequently in patients with atopic comorbidities compared to the general population.[52,53] Patients with childhood-onset AD exhibited a median number of seven atopic stigmata, adult-onset-AD five, controls$^{non\text{-}atopic}$ two and controls$^{non\text{-}atopic}$ one (Table 1). Each additional atopic stigma approximately doubled the odds of AD compared to controls (Figures 2 and 3) with highest odds in infancy-onset (Table 2). All atopic stigmata were more frequent in both adult-onset and childhood-onset AD compared to controls with higher frequencies in atopic controls (Table 1) and associated factors in univariate LR (Table S2), most of them also in MLR (Table 2). Palmar hyperlinearity doubled the odds of childhood-onset AD versus controls^{atopic} (aOR = 2.11 [1.05–4.25], Figure 2).

Infancy-onset AD featured slightly increased odds of a higher number of atopic stigmata compared to later onsets (Table 3, Figures S8 and S11). Patients with childhood-onset overall exhibited a higher frequency of white dermographism, Dennie–Morgan fold, ear rhagades, pityriasis alba, perleche, cheilitis sicca, keratosis pilaris, nipple eczema, periorbital darkening, and anterior neck fold than those with adult-onset (Table 1 and Table S2). White dermographism was the stigma with the largest differences between groups, halved the odds of adult-compared to childhood-onset AD overall (Figure 1) with decreasing odds in later phases of adulthood (Figure S7).

3.5 | Severity and distribution of eczema

Adult-onset AD tended to be slightly more severe than childhood-onset (Figure 3), particularly versus onset between 2 and 12 years (Figure S8). Compared to infancy-onset, we found lower odds of (i) head–neck eczema in AD for onset between age 2 and 11 years as well as for early-adult-onset, and of (ii) trunk eczema with onset age ≥2–6 years in MLR adjusted for severity, sex, and age (Table 3,



	Childhood-onset AD, reference controls without AD			
	reference non atopic-controls		reference atopic controls	
Factor	OR [95% CI]	aOR [95% CI]	OR [95% CI]	aOR [95% CI]
eosinophils [G/l]	**13.55 [1.86-98.77]**	2.08 [0.14-31.06]	**8.04 [1.94-33.26]**	1.75 [0.30-10.28]
↑ tIgE	**16.77 [8.94-31.46]**	**6.79 [2.96-15.58]**	**3.54 [2.24-5.58]**	**2.15 [1.08-4.26]**
atopic stigma (no.)	**2.71 [2.19-3.35]**	**2.23 [1.62-3.08]**	**1.86 [1.63-2.11]**	**1.69 [1.36-2.09]**
white dermogr.	**15.55 [7.02-34.47]**	1.82 [0.59-5.57]	**10.39 [5.53-19.52]**	2.20 [0.94-5.13]
Dennie-Morgan	**9.84 [4.81-20.13]**	0.88 [0.28-2.76]	**2.98 [1.85-4.79]**	0.59 [0.27-1.26]
Facial pallor/ e.	**28.26 [8.80-90.74]**	1.55 [0.37-6.47]	**5.89 [3.30-10.49]**	0.89 [0.39-2.00]
Palmar h.	**10.44 [5.50-19.82]**	2.10 [0.84-5.23]	**6.14 [3.68-10.23]**	**2.11 [1.05-4.25]**
asthma	NA	NA	**1.75 [1.11-2.76]**	1.24 [0.64-2.40]
Allergic rhinitis	NA	NA	**0.63 [0.35-1.13]**	**0.22 [0.09-0.53]**
Food allergy	NA	NA	**2.89 [1.81-4.62]**	**2.93 [1.44-5.96]**
Allergic conjunctivis	NA	NA	1.18 [0.75-1.86]	0.97 [0.48-1.95]
ETS (daily)	1.69 [0.82-3.50]	2.36 [0.69-8.04]	**2.36 [1.11-5.02]**	1.94 [0.73-5.10]
household ≥4	**0.60 [0.36-0.99]**	0.71 [0.31-1.61]	**0.53 [0.33-0.84]**	0.53 [0.28-1.03]
Maternal FA	**24.18 [3.33-175.49]**	**9.43 [1.10-80.95]**	**1.93 [1.04-3.59]**	0.96 [0.39-2.39]
Maternal AD	**6.61 [2.38-18.41]**	**4.36 [1.18-16.17]**	**33.07 [4.57-239.33]**	**32.97 [4.03-269.68]**
Paternal AD	**2.99 [1.06-8.40]**	2.18 [0.38-12.68]	**2.85 [1.12-7.25]**	2.52 [0.72-8.76]
academic	1.05 [0.60-1.85]	1.29 [0.49-3.38]	1.21 [0.73-2.01]	**2.14 [1.00-4.54]**
age	1.00 [0.98-1.01]	0.99 [0.96-1.02]	1.00 [0.98-1.01]	0.99 [0.96-1.01]
Female sex	0.81 [0.49-1.34]	0.96 [0.42-2.20]	**0.59 [0.36-0.96]**	0.79 [0.41-1.53]

FIGURE 2 Main factors associated with childhood-onset atopic dermatitis (AD) compared to controls without AD and with clusters of all subjects. (A, B) Maternal atopic dermatitis (AD), maternal and patient's food allergy, increased total IgE and atopic stigmata were main factors associated with childhood-onset AD ($n = 562$) compared to controls ($n = 167$) without AD ($n = 76$ non-atopic (blue lines), $n = 91$ atopic (red lines)) obtained from a binary logistic regression model. Forest plot (A) and Table (B) of effect sizes presented as (adjusted) odds ratios (aOR) with 95% confidence intervals (CI). Bold and yellow boxes: p-values < .05. Violet: biomarker, Blue: visible phenotype, atopic stigmata and comorbidities, red: modifiable factors, black: unswayable factors. (C) Generation of three clusters of all subjects (AD ($n = 736$, childhood-onset: $n = 562$, adult-onset: $n = 174$), controls (non-atopic: $n = 76$, atopic: $n = 91$)) with hierarchical clustering using Ward's criterion of the 42 most important principal component of a factor analysis of mixed data (FAMD). Cluster 1: $n = 337$, Cluster 2: $n = 339$, Cluster 3: $n = 227$. Contribution of covariates are given in Table S7, exact numbers and other details of all clinical traits associated with the respective clusters in Table S8. Academic was defined as education at least A-level up to university degree. comorb., comorbidities; EH, eczema herpeticum; eos, eosinophils [G/L]; Eos > 0.5 G/L, eosinophilia; ETS, environmental tobacco smoke/passive smoking; household, household size (≥4 persons); mat, maternal; mold, mold exposition; no., number; pat., paternal; skin inf., proneness to skin infections (eczema herpeticum, other herpes simplex, bacterial and mycotic infections); tIgE, total-serum IgE [IU/mL]; tIgE↑, age-dependent increased tIgE.

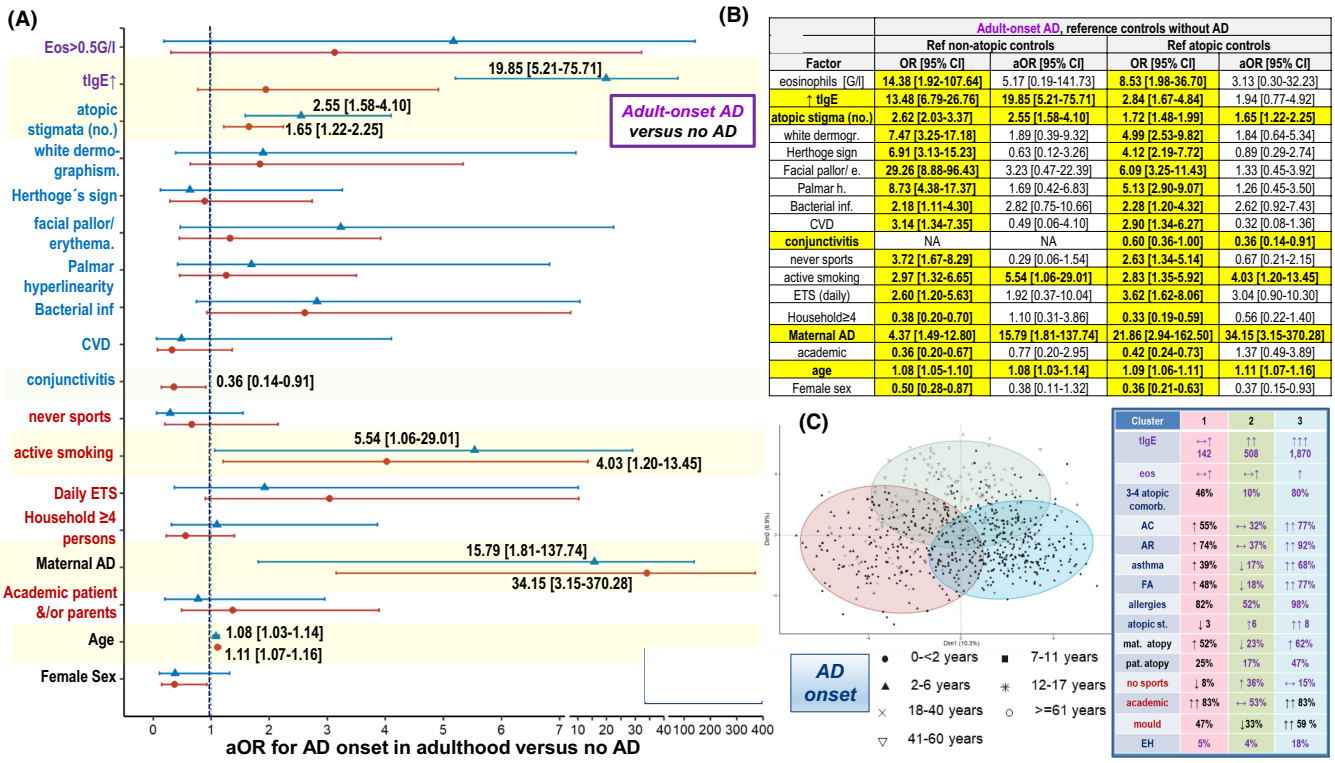
Figure S12). Adult-onset compared to childhood-onset AD overall tended to feature more trunk eczema, though no significant differences were found in the eczema-distribution of all body parts after adjustment for all covariates including severity (Figure 1).

3.6 | Increased total serum Immunoglobulin E (tIgE) associated with child- and adult-onset AD

Increased tIgE was associated with AD across all ages of AD onset with stronger effects versus non-atopic than versus atopic controls (adult-onset: aOR = 19.85 [5.21–75.71] vs. controls$^{non\text{-}atopic}$ (Figure 3) childhood-onset: aOR = 6.79 [2.96–15.58] vs. controls$^{non\text{-}atopic}$, aOR = 2.15 [1.08–4.26] vs. controls^{atopic}; Figure 2 and Figures S2–S6, Table 2). Levels of circulating eosinophils were associated with both childhood-and adult-onset AD overall compared to controls only in univariate analyses. Further stratification revealed strongest associations with late-adult-onset AD (aOR = 46.39/per G/L vs. controls$^{non\text{-}atopic}$, aOR = 25.44/per G/L vs. controls^{atopic}, Figures S4 and S5, Table 2). Eosinophil and tIgE levels did not differ significantly between adult- and childhood-onset AD (Table S2).

3.7 | Comorbidities

Atopic comorbidities of AD include FA, asthma, AR, and AC. Only 12.1% of patients with childhood-onset exhibited a "pure" AD, that is, without atopic comorbidities (Table 1, Figure S1). Conversely, adult-onset AD was purer (27.6%), especially in middle-(37.0%) and late-adulthood- (50.0%) onset (Figure 1 and Figure S1, Table 1). Patients with infancy-onset suffered most frequently (90.8%) from atopic comorbidities. Consistently, allergies (self-reported) showed the strongest associations with infancy-onset AD compared to adult-onset AD (aOR = 5.47 [3.18–9.41], Figure S8, Table 3). Compared to adult-onset AD overall, FA and asthma were associated with AD onset up to age 6 years, asthma also with adolescence-onset, AR and



	Adult-onset AD, reference controls without AD			
	Ref non-atopic controls		Ref atopic controls	
Factor	OR [95% CI]	aOR [95% CI]	OR [95% CI]	aOR [95% CI]
eosinophils [G/l]	**14.38 [1.92-107.64]**	5.17 [0.19-141.73]	**8.53 [1.98-36.70]**	3.13 [0.30-32.23]
↑ tIgE	**13.48 [6.79-26.76]**	**19.85 [5.21-75.71]**	**2.84 [1.67-4.84]**	1.94 [0.77-4.92]
atopic stigma (no.)	**2.62 [2.03-3.37]**	**2.55 [1.58-4.10]**	**1.72 [1.48-1.99]**	**1.65 [1.22-2.25]**
white dermogr.	**7.47 [3.25-17.18]**	1.89 [0.39-9.32]	**4.99 [2.53-9.82]**	1.84 [0.64-5.34]
Herthoge sign	**6.91 [3.13-15.23]**	0.63 [0.12-3.26]	**4.12 [2.19-7.72]**	0.89 [0.29-2.74]
Facial pallor/ e.	**29.26 [8.88-96.43]**	3.23 [0.47-22.39]	**6.09 [3.25-11.43]**	1.33 [0.45-3.92]
Palmar h.	**8.73 [4.38-17.37]**	1.69 [0.42-6.83]	**5.13 [2.90-9.07]**	1.26 [0.45-3.50]
Bacterial inf.	**2.18 [1.11-4.30]**	2.82 [0.75-10.66]	**2.28 [1.20-4.32]**	2.62 [0.92-7.43]
CVD	**3.14 [1.34-7.35]**	0.49 [0.06-4.10]	**2.90 [1.34-6.27]**	0.32 [0.08-1.36]
conjunctivitis	NA	NA	**0.60 [0.36-1.00]**	**0.36 [0.14-0.91]**
never sports	**3.72 [1.67-8.29]**	0.29 [0.06-1.54]	**2.63 [1.34-5.14]**	0.67 [0.21-2.15]
active smoking	**2.97 [1.32-6.65]**	**5.54 [1.06-29.01]**	**2.83 [1.35-5.92]**	**4.03 [1.20-13.45]**
ETS (daily)	**2.60 [1.20-5.63]**	1.92 [0.37-10.04]	**3.62 [1.62-8.06]**	3.04 [0.90-10.30]
Household≥4	**0.38 [0.20-0.70]**	1.10 [0.31-3.86]	**0.33 [0.19-0.59]**	0.56 [0.22-1.40]
Maternal AD	**4.37 [1.49-12.80]**	**15.79 [1.81-137.74]**	**21.86 [2.94-162.50]**	**34.15 [3.15-370.28]**
academic	**0.36 [0.20-0.67]**	0.77 [0.20-2.95]	**0.42 [0.24-0.73]**	1.37 [0.49-3.89]
age	**1.08 [1.05-1.10]**	**1.08 [1.03-1.14]**	**1.09 [1.06-1.11]**	**1.11 [1.07-1.16]**
Female sex	**0.50 [0.28-0.87]**	0.38 [0.11-1.32]	**0.36 [0.21-0.63]**	0.37 [0.15-0.93]

Cluster	1	2	3
tIgE	↔↑ 142	↑↑ 508	↑↑↑ 1,870
eos	↔↑	↔↑	↑
3-4 atopic comorb.	46%	10%	80%
AC	↑ 55%	↔ 32%	↑↑ 77%
AR	↑ 74%	↔ 37%	↑↑ 92%
asthma	↑ 39%	↓ 17%	↑↑ 68%
FA	↑ 48%	↓ 18%	↑↑ 77%
allergies	82%	52%	98%
atopic st.	↓ 3	↑ 6	↑↑ 8
mat. atopy	↑ 52%	↓ 23%	↑ 62%
pat. atopy	25%	17%	47%
no sports	↓ 8%	↑ 36%	↔ 15%
academic	↑↑ 83%	↔ 53%	↑↑ 83%
mould	47%	↓33%	↑↑ 59 %
EH	5%	4%	18%

FIGURE 3 Main factors associated with adult-onset atopic dermatitis (AD) compared to controls without AD and with clusters of AD patients. (A, B) Active smoking, maternal AD, increased total IgE, and atopic stigmata were main factors associated with adult-onset AD ($n = 174$) compared to controls ($n = 167$) without AD ($n = 76$ non-atopic (blue lines), $n = 91$ atopic (red lines)) obtained from a binary logistic regression model. Forest plot (A) and Table (B) of effect sizes presented as (adjusted) Odds Ratios (aOR) with 95% Confidence intervals (CI). Bold and yellow boxes: p-values < .05. Violet: biomarker, blue: visible phenotype, atopic stigmata and comorbidities, red: modifiable factors, black: unswayable factors. (C) Generation of three clusters of AD patients (AD ($n = 736$, childhood-onset: $n = 562$, adult-onset: $n = 174$)), with hierarchical clustering using Ward's criterion of the 42 most important principal component of a factor analysis of mixed data (FAMD). Cluster 1: $n = 288$, Cluster 2: $n = 196$, Cluster 3: $n = 312$. % refers to the number of patients with the respective trait within the respective cluster (e.g., AC in 46% of cluster 1 ($n = 104/288$)). Contribution of covariates are given in Table S7, exact numbers and other details of all clinical traits associated with the respective clusters in Table S8. AC, allergic conjunctivitis, academic defined as education at least A-level up to university degree of the patient and/or parents. AR, allergic rhinitis; atopic st., median number of atopic stigmata; CVD, cardiovascular diseases; eos, eosinophils [G/L]; Eos > 0.5 G/L, eosinophilia; comorb., comorbidities; EH, eczema herpeticum; ETS, environmental tobacco smoke/passive smoking; FA, food allergy; mat, maternal; pat., paternal; household, household size (≥4 persons); HSV, herpes simplex infection; mold, mold exposition; palmar h., palmar hyperlinearity; skin inf., proneness to skin infections (eczema herpeticum, other herpes simplex, bacterial and mycotic infections); tIgE, median total-serum IgE [IU/mL]; white derm., white dermographism; no., number; tIgE↑, age-dependent increased total serum IgE.

conjunctivitis only with infancy-onset (Figure S8). Adolescent-onset AD featured higher odds of asthma, herpes simplex virus, and verrucae than early-adulthood-onset AD (Tables S5 and S6).

Adult compared to childhood-onset AD overall featured doubled odds of AR (aOR = 2.15 [1.12–4.13]), but threefold-reduced odds of multiple (3–4) atopic comorbidities at once (aOR = 0.34 [0.14–0.80]) and allergies (aOR = 0.31 [0.16–0.60]; Figure 1). The odds of AD with 3–4 atopic comorbidities were highest with infancy onset (aOR = 5.38 [3.44–8.44] vs. adult onset, Figure S8), decreased with later manifestation (Figures S8 and S13, Table 3) and were 10-fold reduced for late-adult-onset-AD compared to childhood-onset (early-adult: aOR = 0.40 [0.25–0.63], middle-adult: aOR = 0.16 [0.07–0.35], and late-adult onset: aOR = 0.10 [0.03–0.37]; Figure S7, Table 3).

AR and AC were the most frequent comorbidities in atopic controls (Table 1). AR decreased the odds of childhood-onset AD (aOR = 0.22 [0.09–0.53]; Figure 2), AC the odds of adult-onset AD (aOR = 0.36 [0.14–0.91]; Figure 3) compared to controls^{atopic}. Conversely, FA nearly tripled the odds of childhood-onset AD versus controls^{atopic} (aOR = 2.94 [1.43–6.03]; Figure 2). Compared to controls^{atopic}, also asthma was associated with infancy-onset AD (aOR = 2.25 [1.39–3.65]), but not with later onsets (Figure S6, Table 2).

Patients with childhood-onset AD were more prone to eczema herpeticum (EH) and bacterial infections than adult-onset AD and both more susceptible to bacterial and mycotic infections than controls in univariate analyses (Figure 1, Table S2). Stratification revealed higher odds of EH in infancy-onset (aOR = 4.49 [1.89–10.67]) and adolescent-onset (aOR = 3.43 [1.08–10.91]) than in adult-onset AD (Figure S8), particularly versus early-adult onset (Table 3, Figures S7 and S14).

TABLE 2 Atopic dermatitis (AD) versus controls: associations with clinical and epidemiological factors from multinomial logistic regression models with stratification by age at onset of AD.

Age at AD onset	0 to <24 months	≥2 to <7 years	≥7 to <12 years	≥12 to <18 years	≥18 to <41 years	≥41 to <61 years	≥61 years
Ref. controls	**aOR [95% CI]**	**aOR [95% CI]**	**aOR [95% CI]**	**aOR [95% CI]**	**aOR [95% CI]**	**aOR [95% CI]**	**aOR [95% CI]**
Biomarkers							
Eosinophils [G/L]							
Non-atopic	**14.47 [1.97–106.44]**	**10.89 [1.42–83.35]**	**12.95 [1.54–109.26]**	**14.01 [1.69–116.17]**	7.57 [0.93–61.46]	**18.63 [2.23–155.35]**	**46.39 [4.78–450.19]**
Atopic	**8.35 [1.99–35.01]**	**6.29 [1.42–27.84]**	**7.53 [1.49–38.02]**	**8.16 [1.65–40.28]**	4.41 [0.92–21.17]	**10.72 [2.15–53.38]**	**25.44 [4.19–154.32]**
↑ tIgE							
Non-atopic	**18.91 [9.75–36.66]**	**13.94 [6.84–28.41]**	**22.83 [8.59–60.65]**	**14.50 [5.93–35.43]**	**15.04 [6.90–32.76]**	**10.14 [4.09–25.13]**	**9.86 [2.99–35.21]**
Atopic	**3.69 [2.24–6.08]**	**2.72 [1.55–4.79]**	**4.36 [1.81–10.49]**	**2.73 [1.25–6.00]**	**2.80 [1.46–5.36]**	1.83 [0.82–4.09]	1.59 [0.51–4.97]
Atopic stigmata							
Atopic stigma (no.)							
Non-atopic	**3.09 [2.48–3.86]**	**2.69 [2.16–3.36]**	**2.53 [2.00–3.20]**	**2.74 [2.16–3.46]**	**2.60 [2.08–3.26]**	**2.51 [1.97–3.19]**	**2.50 [1.89–3.32]**
Atopic	**2.02 [1.77–2.31]**	**1.76 [1.53–2.02]**	**1.65 [1.41–1.94]**	**1.79 [1.52–2.10]**	**1.70 [1.47–1.96]**	**1.63 [1.38–1.93]**	**1.59 [1.27–2.00]**
White dermogr.							
Non-atopic	**18.02 [8.01–40.53]**	**11.06 [4.75–25.75]**	**9.71 [3.68–25.60]**	**26.72 [9.78–72.97]**	**7.99 [3.31–19.32]**	**6.58 [2.43–17.80]**	**4.18 [1.21–14.45]**
Atopic	**12.07 [6.30–23.12]**	**7.39 [3.70–14.75]**	**6.55 [2.82–15.17]**	**18.00 [7.46–43.43]**	**5.34 [2.55–11.17]**	**4.22 [1.76–10.10]**	2.42 [0.76–7.71]
Dennie–Morgan fold							
Non-atopic	**11.61 [5.58–24.17]**	**8.79 [4.06–19.05]**	**7.16 [2.88–17.80]**	**6.55 [2.66–16.15]**	**7.06 [3.12–16.01]**	**4.74 [1.80–12.48]**	**12.97 [3.66–45.87]**
Atopic	**3.44 [2.08–5.68]**	**2.61 [1.49–4.56]**	**2.11 [1.01–4.42]**	1.93 [0.93–4.00]	**2.08 [1.12–3.86]**	1.39 [0.62–3.11]	**3.65 [1.16–11.46]**
Herthoge sign							
Non-atopic	**7.67 [3.55–16.57]**	**5.85 [2.60–13.19]**	**5.71 [2.22–14.70]**	**5.38 [2.11–13.70]**	**6.37 [2.74–14.83]**	**4.50 [1.72–11.74]**	**4.36 [1.35–14.05]**
Atopic	**4.47 [2.45–8.16]**	**3.40 [1.77–6.55]**	**3.33 [1.47–7.53]**	**3.13 [1.40–6.99]**	**3.67 [1.83–7.36]**	**2.49 [1.08–5.74]**	2.20 [0.74–6.48]
Facial pallor/erythema							
Non-atopic	**37.02 [11.41–120.18]**	**20.43 [6.14–67.99]**	**19.99 [5.48–72.93]**	**20.56 [5.68–74.39]**	**32.36 [9.47–110.65]**	**16.26 [4.40–60.10]**	**21.55 [4.95–93.83]**
Atopic	**7.53 [4.13–13.70]**	**4.17 [2.19–7.97]**	**4.05 [1.81–9.07]**	**4.16 [1.88–9.20]**	**6.53 [3.25–13.13]**	**3.22 [1.40–7.39]**	**3.94 [1.34–11.61]**
Palmar hyperlinearity							
Non-atopic	**13.28 [6.77–26.04]**	**9.73 [4.76–19.92]**	**7.13 [3.01–16.90]**	**14.88 [6.06–36.53]**	**7.16 [3.36–15.25]**	**6.03 [2.48–14.68]**	**3.33 [1.05–10.60]**
Atopic	**7.67 [4.44–13.26]**	**5.65 [3.10–10.28]**	**4.13 [1.91–8.92]**	**8.60 [3.83–19.32]**	**4.13 [2.16–7.92]**	**3.42 [1.53–7.65]**	1.63 [0.53–5.02]
Comorbidities							
Asthma							
Non-atopic	NA	NA	NA	NA	NA	NA	NA
Atopic	**2.25 [1.39–3.65]**	1.25 [0.72–2.15]	0.92 [0.44–1.94]	1.75 [0.86–3.55]	0.65 [0.35–1.21]	0.55 [0.25–1.23]	0.29 [0.08–1.00]

TABLE 2 (Continued)

Age at AD onset	0 to <24 months	≥2 to <7 years	≥7 to <12 years	≥12 to <18 years	≥18 to <41 years	≥41 to <61 years	≥61 years
Ref. controls	aOR [95% CI]	aOR [95% CI]	aOR [95% CI]	aOR [95% CI]	aOR [95% CI]	aOR [95% CI]	aOR [95% CI]
Allergic rhinitis							
Non-atopic	NA	NA	NA	NA	NA	NA	NA
Atopic	0.82 [0.44–1.53]	**0.50 [0.26–0.98]**	**0.33 [0.14–0.74]**	0.48 [0.21–1.10]	0.53 [0.25–1.09]	**0.18 [0.08–0.42]**	**0.09 [0.03–0.28]**
Food allergy							
Non-atopic	NA	NA	NA	NA	NA	NA	NA
Atopic	**4.85 [2.94–7.99]**	**1.85 [1.07–3.21]**	0.90 [0.42–1.94]	1.67 [0.82–3.42]	1.38 [0.75–2.54]	0.74 [0.33–1.67]	0.65 [0.20–2.14]
Allergic conjunctivis							
Non-atopic	NA	NA	NA	NA	NA	NA	NA
Atopic	1.39 [0.86–2.25]	1.13 [0.66–1.93]	0.80 [0.39–1.64]	0.98 [0.48–1.98]	1.03 [0.57–1.86]	**0.39 [0.18–0.84]**	**0.27 [0.09–0.81]**
Bacterial inf.							
Non-atopic	**5.03 [2.65–9.54]**	**2.72 [1.36–5.43]**	1.46 [0.59–3.61]	**2.89 [1.26–6.64]**	**2.29 [1.09–4.80]**	1.84 [0.75–4.52]	**3.71 [1.11–12.38]**
Atopic	**5.18 [2.84–9.43]**	**2.80 [1.45–5.40]**	1.50 [0.62–3.62]	**2.98 [1.34–6.66]**	**2.36 [1.16–4.78]**	1.89 [0.79–4.51]	**3.77 [1.14–12.46]**
CVD							
Non-atopic	1.58 [0.64–3.92]	0.83 [0.28–2.41]	0.97 [0.27–3.52]	1.18 [0.36–3.91]	0.50 [0.17–1.51]	1.05 [0.35–3.20]	1.70 [0.49–5.93]
Atopic	1.39 [0.61–3.17]	0.73 [0.27–1.98]	0.84 [0.25–2.91]	1.03 [0.33–3.20]	0.43 [0.15–1.23]	0.91 [0.32–2.60]	1.50 [0.45–4.99]
Lifestyle factors							
Active smoking							
Non-atopic	2.04 [0.93–4.46]	**3.18 [1.40–7.26]**	1.76 [0.61–5.10]	**2.79 [1.04–7.50]**	**4.82 [2.04–11.41]**	**4.09 [1.47–11.33]**	0.83 [0.09–7.85]
Atopic	1.87 [0.92–3.83]	**2.93 [1.37–6.25]**	1.62 [0.59–4.46]	**2.56 [1.01–6.53]**	**4.42 [1.99–9.39]**	**3.72 [1.41–9.82]**	0.71 [0.08–6.55]
ETS (daily)							
Non-atopic	1.68 [0.79–3.56]	1.68 [0.74–3.80]	2.00 [0.74–5.37]	1.40 [0.50–3.92]	**2.77 [1.20–6.41]**	**3.20 [1.21–8.49]**	**4.72 [1.22–18.22]**
Atopic	**2.29 [1.05–5.00]**	2.29 [0.99–5.32]	**2.74 [1.00–7.53]**	1.92 [0.67–5.50]	**3.83 [1.61–9.08]**	**4.48 [1.65–12.16]**	**6.86 [1.72–27.30]**
Never-sports							
Non-atopic	1.59 [0.72–3.51]	1.08 [0.44–2.67]	1.00 [0.31–3.28]	1.82 [0.65–5.13]	**2.72 [1.13–6.55]**	**3.61 [1.33–9.85]**	**7.74 [2.17–27.63]**
Atopic	1.12 [0.58–2.18]	0.76 [0.35–1.67]	0.70 [0.23–2.11]	1.27 [0.50–3.24]	1.87 [0.87–4.00]	2.41 [0.98–5.94]	**4.89 [1.47–16.26]**
Household ≥ 4 pers.							
Non-atopic	**0.56 [0.33–0.96]**	0.73 [0.40–1.34]	0.44 [0.18–1.07]	**0.37 [0.15–0.91]**	0.51 [0.25–1.04]	0.95 [0.38–2.36]	0.44 [0.06–2.99]
Atopic	**0.50 [0.30–0.82]**	0.65 [0.37–1.14]	**0.40 [0.17–0.92]**	**0.33 [0.14–0.79]**	**0.45 [0.23–0.90]**	0.87 [0.36–2.11]	0.46 [0.06–3.31]
Academic[a]							
Non-atopic	0.99 [0.54–1.83]	1.20 [0.60–2.39]	1.36 [0.54–3.43]	0.53 [0.24–1.87]	0.63 [0.31–1.26]	**0.42 [0.18–0.96]**	0.36 [0.12–1.04]
Atopic	1.15 [0.67–2.00]	1.39 [0.73–2.62]	1.58 [0.65–3.83]	0.62 [0.29–1.32]	0.72 [0.38–1.39]	0.47 [0.22–1.03]	0.37 [0.13–1.07]

(Continues)

TABLE 2 (Continued)

Age at AD onset	0 to <24 months	≥2 to <7 years	≥7 to <12 years	≥12 to <18 years	≥18 to <41 years	≥41 to <61 years	≥61 years
Ref. controls	**aOR [95% CI]**	**aOR [95% CI]**	**aOR [95% CI]**	**aOR [95% CI]**	**aOR [95% CI]**	**aOR [95% CI]**	**aOR [95% CI]**
Family history							
Maternal AD							
Non-atopic	**7.03 [2.50–19.79]**	**5.00 [1.69–14.75]**	**8.64 [2.65–28.14]**	**6.44 [1.96–21.21]**	**6.46 [2.13–19.63]**	2.71 [0.71–10.37]	2.21 [0.35–13.83]
Atopic	**34.93 [4.80–254.50]**	**24.84 [3.33–185.52]**	**42.78 [5.42–337.60]**	**31.82 [4.01–252.59]**	**31.56 [4.16–239.56]**	**12.85 [1.48–111.71]**	**11.77 [1.06–130.47]**
Paternal AD							
Non-atopic	**3.41 [1.19–9.78]**	**3.20 [1.05–9.71]**	3.25 [0.89–11.82]	0.75 [0.13–4.29]	2.03 [0.61–6.81]	0.76 [0.13–4.40]	1.29 [0.14–11.67]
Atopic	**3.28 [1.27–8.52]**	**3.08 [1.12–8.52]**	3.14 [0.94–10.57]	0.73 [0.14–3.94]	1.99 [0.65–6.14]	0.76 [0.14–4.18]	2.38 [0.39–14.66]
Maternal FA							
Non-atopic	**29.54 [4.04–215.87]**	**18.95 [2.52–142.34]**	**13.84 [1.64–117.04]**	**13.37 [1.58–112.92]**	**15.66 [2.00–122.75]**	2.54 [0.15–42.20]	-
Atopic	**2.28 [1.21–4.33]**	1.47 [0.71–3.01]	1.07 [0.39–2.92]	1.03 [0.38–2.81]	1.21 [0.53–2.78]	0.20 [0.02–1.59]	-

Note: Associations of clinical and epidemiological factors with AD ($n = 736$) versus controls ($n = 167$, non-atopic: $n = 76$, atopic: $n = 91$) from multinomial logistic regression models with strata of onset at age: (i) 0 to <2 years (infancy, $n = 325$ (44.17%)); (ii) ≥2 to <7 ($n = 142$ (19.3%)); (iii) ≥7 to <12 ($n = 142$ (11.5%)); (iv) ≥12 to <18 years ($n = 49$ (6.7%)); (v) ≥18 and <41 years: $n = 94$ (12.8%); (vi) ≥41 and <61 years: $n = 46$ (6.2%) and (vii) ≥61 years: $n = 34$ (4.6%). All effect sizes are adjusted (a) for age and sex and given in aOdds Ratios (aOR) with 95% Confidence intervals (CI). Bold and yellow shaded values: p-values < .05.

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; FA, food allergy.

[a]Academic defined as education at least A-level up to university degree.

TABLE 3 Atopic dermatitis (AD) with strata of childhood- and adult-onset versus infancy-onset: associations with clinical and epidemiological factors from multinomial logistic regression models.

Age at AD onset	AD onset strata with reference 0 to <2 years					
	≥2 to <7 years	≥7 to 12 years	≥12 to 18 years	≥18 to <41 years	≥41 to <61 years	≥61 years
	aOR [95% CI]	aOR [95% CI]	aOR [95% CI]	aOR [95% CI]	aOR [95% CI]	aOR [95% CI]
Biomarkers						
tIgE/100 IU/mL	0.99 [0.99–1.00]	0.99 [0.98–1.00]	1.00 [1.00–1.00]	1.00 [0.99–1.00]	1.00 [1.00–1.00]	0.99 [0.98–1.01]
↑ tIgE	0.74 [0.46–1.17]	1.18 [0.52–2.68]	0.74 [0.36–1.52]	0.76 [0.43–1.34]	0.50 [0.23–1.05]	0.43 [0.14–1.32]
Eosinophils [G/l]	0.74 [0.40–1.36]	0.88 [0.37–2.06]	1.34 [0.78–2.32]	0.50 [0.21–1.20]	1.33 [0.78–2.27]	1.46 [0.66–3.24]
eos > 0.5 G/L	0.75 [0.42–1.34]	0.90 [0.38–2.12]	0.97 [0.43–2.21]	0.53 [0.24–1.13]	1.29 [0.56–2.99]	3.15 [0.97–10.22]
Atopic stigmata						
Number of atopic stigmata	**0.87 [0.81–0.93]**	**0.82 [0.73–0.91]**	**0.88 [0.79–0.98**	**0.84 [0.77–0.92]**	**0.81 [0.71–0.92]**	**0.80 [0.65–0.97]**
White dermographism	**0.61 [0.41–0.91]**	**0.54 [0.29–1.01]**	1.48 [0.75–2.92]	**0.44 [0.27–0.72]**	**0.36 [0.19–0.71]**	**0.22 [0.08–0.61]**
Dennie–Morgan fold	0.76 [0.51–1.13]	0.61 [0.33–1.15]	0.56 [0.30–1.03]	**0.60 [0.37–0.97]**	**0.40 [0.20–0.82]**	1.07 [0.37–3.14]
Hertoghe sign	0.76 [0.51–1.15]	0.75 [0.40–1.42]	0.71 [0.38–1.33]	0.85 [0.53–1.37]	0.60 [0.31–1.18]	0.56 [0.21–1.46]
Facial pallor/erythema	0.55 [0.37–0.82]	0.54 [0.29–1.00]	0.55 [0.30–1.01]	0.86 [0.53–1.40]	**0.43 [0.22–0.84]**	0.55 [0.21–1.45]
Dirty neck	0.71 [0.44–1.16]	0.45 [0.19–1.06]	055 [0.27–1.09]	**0.43 [0.23–0.80]**	0.85 [0.41–1.77]	1.36 [0.47–3.97]
Periorbital darkening	0.68 [0.45–1.03]	0.45 [0.19–1.06]	0.55 [0.25–1.19]	0.81 [0.50–1.33]	0.94 [0.48–1.84]	1.14 [0.43–3.06]
Anterior neck fold	0.70 [0.46–1.04]	0.82 [0.44–1.53]	**0.41 [0.21–0.80]**	**0.50 [0.31–0.83]**	0.57 [0.29–1.12]	**0.32 [0.11–0.89]**
Ear rhagades	**0.51 [0.32–0.79]**	**0.41 [0.19–0.87]**	0.55 [0.27–1.09]	**0.46 [0.26–0.80]**	0.78 [0.38–1.59]	**0.19 [0.04–0.89]**
Keratosis pilaris	0.72 [0.46–1.11]	0.63 [0.31–1.30]	1.10 [0.58–2.09]	**0.83 [0.49–1.41]**	0.44 [0.18–1.04]	1.43 [0.48–4.28]
Nipple eczema	0.67 [0.34–1.34]	0.78 [0.26–2.34]	0.96 [0.35–2.63]	0.60 [0.24–1.51]	0.21 [0.03–1.65]	0.00 [0.00–0.00]
Cheilitis sicca	1.10 [0.74–1.64]	**0.43 [0.22–0.85]**	0.66 [0.35–1.23]	0.74 [0.45–1.21]	0.83 [0.42–1.64]	0.61 [0.21–1.74]
Perleche	0.65 [0.42–1.02]	0.75 [0.37–1.52]	0.71 [0.35–1.43]	0.63 [0.36–1.10]	0.64 [0.29–1.43]	0.79 [0.23–2.76]
Pityriasis alba	0.64 [0.36–1.11]	1.43 [0.68–2.99]	0.52 [0.20–1.39]	**0.45 [0.20–0.9966]**	0.78 [0.30–2.04]	0.97 [0.24–3.86]
Palmar hyperlinearity	0.73 [0.48–1.11]	0.53 [0.28–1.01]	1.11 [0.56–2.21]	**0.53 [0.32–0.88]**	**0.45 [0.22–0.91]**	**0.22 [0.08–0.65]**
Xerosis cutis	**0.45 [0.24–0.81]**	**0.36 [0.15–0.86]**	0.52 [0.20–1.34]	0.79 [0.32–1.91]	0.49 [0.15–1.59]	0.72 [0.07–7.07]
Distribution of eczema						
Trunk eczema	**0.59 [0.36–0.96]**	0.60 [028–1.28]	0.90 [0.42–1.90]	0.63 [0.34–1.15]	1.04 [0.42–2.54]	1.46 [0.30–7.19]
Hand eczema	0.79 [0.51–1.22]	0.68 [0.35–1.35]	1.12 [0.56–2.24]	0.75 [0.44–1.29]	0.62 [0.29–1.32]	0.54 [0.18–1.64]
Hands dorsal	0.95 [0.61–1.47]	0.54 [0.27–1.10]	1.12 [0.57–2.19]	0.78 [0.46–1.34]	0.79 [0.38–1.64]	0.58 [0.20–1.64]
Palmae	0.70 [0.46–1.08]	0.60 [0.30–1.20]	0.89 [0.47–1.68]	0.88 [0.54–1.43]	0.65 [0.33–1.28]	1.12 [0.40–3.15]
Head neck	**0.58 [0.36–0.95]**	**0.42 [0.20–0.86]**	0.63 [0.30–1.34]	**0.54 [0.29–0.99]**	0.68 [0.29–1.64]	0.99 [0.27–3.57]
Arms	0.61 [0.35–1.05]	0.67 [0.29–1.55]	0.74 [0.31–1.74]	0.91 [0.43–1.93]	0.91 [0.32–2.55]	0.78 [0.18–3.42]
Legs	0.69 [0.42–1.12]	0.72 [0.34–1.54]	0.87 [0.41–1.84]	0.66 [0.36–1.21]	1.13 [0.47–2.72]	0.66 [0.18–2.41]
Course and comorbidities						
Atopic com. (3–4, Ref 0–2)	**0.45 [0.30–0.67]**	**0.37 [0.20–0.69]**	**0.45 [0.24–0.83]**	**0.27 [0.16–0.44]**	**0.10 [0.05–0.23]**	**0.07 [0.02–0.24]**
Asthma	**0.55 [0.37–0.83]**	**0.41 [0.22–0.78]**	0.78 [0.42–1.43]	**0.29 [0.17–0.48]**	**0.24 [0.12–0.50]**	**0.13 [0.04–0.42]**
Allergic rhinitis	**0.61 [0.39–0.97]**	**0.40 [0.21–0.78]**	0.59 [0.30–1.18]	0.66 [0.38–1.15]	**0.23 [0.12–0.47]**	**0.11 [0.04–0.32]**
Food allergy	**0.38 [0.25–0.57]**	**0.19 [0.10–0.37]**	**0.35 [0.19–0.65]**	**0.29 [0.18–0.48]**	**0.16 [0.08–0.34]**	**0.15 [0.05–0.46]**
Allergic conjunctivitis	**0.81 [0.54–1.22]**	0.58 [0.31–1.09]	0.71 [0.39–1.32]	0.76 [0.47–1.23]	**0.29 [0.15–0.58]**	**0.20 [0.07–0.57]**
Allergies	**0.55 [0.31–1.00]**	**0.35 [0.16–0.79]**	**0.27 [0.13–0.57]**	**0.25 [0.14–0.47]**	**0.16 [0.07–0.34]**	**0.04 [0.01–0.12]**
Cardiovascular diseases	**0.53 [0.31–1.00]**	**0.35 [0.16–0.79]**	**0.27 [0.13–0.57]**	**0.33 [0.14–0.75]**	0.70 [0.30–1.63]	1.15 [0.41–3.24]
Eczema herpeticum	0.56 [0.28–1.09]	0.39 [0.11–1.30]	0.75 [0.30–1.89]	**0.23 [0.08–0.66]**	0.35 [0.10–1.23]	NA
Herpes simplex	0.76 [0.50–1.15]	0.53 [0.28–1.03]	1.20 [0.64–2.26]	**0.48 [0.29–0.79]**	**0.36 [0.18–0.72]**	0.39 [0.15–1.05]

(Continues)

TABLE 3 (Continued)

Age at AD onset	AD onset strata with reference 0 to <2 years					
	≥2 to <7 years	≥7 to 12 years	≥12 to 18 years	≥18 to <41 years	≥41 to <61 years	≥61 years
	aOR [95% CI]	aOR [95% CI]	aOR [95% CI]	aOR [95% CI]	aOR [95% CI]	aOR [95% CI]
Bacterial inf.	**0.54 [0.36–0.82]**	**0.29 [0.14–0.60]**	0.58 [0.31–1.08]	**0.46 [0.28–0.76]**	**0.37 [0.18–0.76]**	0.77 [0.26–2.31]
Verrucae	1.10 [0.73–1.65]	1.23 [0.64–2.35]	1.78 [0.90–3.51]	**0.45 [0.28–0.73]**	**0.46 [0.24–0.90]**	**0.24 [0.09–0.67]**
Lifestyle and perinatal factors						
Active smoking	1.56 [0.98–2.48]	0.87 [0.38–1.96]	1.38 [0.67–2.81]	**2.39 [1.40–4.06]**	2.04 [0.95–4.40]	0.40 [0.04–3.42]
ETS (daily)	**1.00 [0.60–1.67]**	1.19 [0.56–2.55]	0.84 [0.37–1.89]	1.67 [0.97–2.90]	1.98 [0.94–4.17]	3.05 [0.91–10.24]
Never-doing-sports	0.68 [0.37–1.24]	0.62 [0.23–1.66]	1.13 [0.51–2.49]	1.68 [0.95–2.98]	**2.19 [1.03–4.65]**	**4.43 [1.48–13.23]**
Mold exposition	0.85 [0.57–1.27]	0.58 [0.31–1.11]	1.26 [0.68–2.33]	0.85 [0.53–1.37]	0.57 [0.29–1.15]	**0.19 [0.05–0.82]**
Household-size ≥ 4 persons	1.32 [0.85–2.06]	0.80 [0.37–1.76]	0.67 [0.30–1.51]	0.95 [0.52–1.72]	1.85 [0.80–4.25]	0.92 [0.13–6.51]
Academic[a]	1.20 [0.73–1.98]	1.36 [0.62–3.01]	0.53 [0.28–1.02]	0.62 [0.37–1.04]	**0.41 [0.21–0.81]**	**0.32 [0.12–0.87]**
Cesarean	0.62 [0.33–1.18]	0.83 [0.31–2.27]	0.48 [0.14–1.63]	0.75 [0.32–1.77]	0.31 [0.04–2.48]	0.27 [0.01–7.47]
Birthweight	1.03 [0.99–1.08]	1.01 [0.93–1.09]	1.00 [0.91–1.01]	1.06 [0.9995–1.12]	1.02 [0.92–1.13]	1.06 [0.89–1.27]
Family history						
Family history positive for allergies	1.06 [0.69–1.64]	0.62 [0.33–1.18]	**0.41 [0.22–0.77]**	0.58 [0.36–0.95]	0.22 [0.10–0.48]	0.47 [0.14–1.58]
Maternal AD	0.71 [0.45–1.13]	1.23 [0.63–2.38]	0.91 [0.46–1.81]	0.92 [0.54–1.56]	**0.38 [0.15–0.97]**	0.36 [0.09–1.47]
Maternal FA	0.64 [0.40–1.03]	0.47 [0.20–1.09]	0.45 [0.19–1.05]	**0.53 [0.28–0.99]**	**0.09 [0.01–0.64]**	NA
Maternal AR	1.09 [0.72–1.65]	0.80 [0.40–1.60]	0.77 [0.39–1.53]	0.98 [0.58–1.66]	0.59 [0.24–1.41]	0.30 [0.04–2.52]
Mat. asthma	0.90 [0.54–1.52]	0.97 [0.43–2.20]	0.66 [0.27–1.62]	0.58 [0.28–1.20]	0.63 [0.23–1.74]	0.83 [0.19–3.64]
Paternal AR	1.08 [0.68–1.73]	1.04 [0.49–2.22]	0.76 [0.34–1.70]	0.69 [0.36–1.33]	0.23 [0.05–1.02]	0.33 [0.04–3.08]

Note: Associations of clinical and epidemiological factors with AD ($n = 736$) versus controls ($n = 167$, non-atopic: $n = 76$, atopic: $n = 91$) from multinomial logistic regression models with strata of onset at age: (i) 0 to <2 years (infancy, $n = 325$ (44.17%)); (ii) ≥2 to <7 ($n = 142$ (19.3%)); (iii) ≥7 to <12 ($n = 142$ (11.5%)); (iv) ≥12 to <18 years ($n = 49$ (6.7%)); (v) ≥18 and <41 years: $n = 94$ (12.8%); (vi) ≥41 and <61 years: $n = 46$ (6.2%) and (vii) ≥61 years: $n = 34$ (4.6%). All effect sizes are adjusted (a) for age and sex and given in aOdds Ratios (aOR) with 95% Confidence intervals (CI). Bold and yellow boxes: p-values < .05.

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; FA, food allergy.

[a]Academic defined as education at least A-level up to university degree.

3.8 | FAMD and cluster analyses

Analyses of (i) all subjects (Figure 2) and (ii) only AD patients (Figure 3) revealed three clusters each with distinct characteristics detailed in the Results S1, Tables S7 and S8. Patients with childhood-onset, particularly infancy-onset, were mainly represented in the most "atopic" clusters with highest numbers of atopic comorbidities, atopic stigmata, higher levels of tIgE, and eosinophils (Figures 2 and 3, Table S8). Adult-onset AD, especially onset ≥61 years, grouped mainly in clusters with lower contributions of personal and familial atopy and higher frequencies of physical inactivity (Figures 2 and 3, Table S8).

4 | DISCUSSION

The prevalence and incidence of AD overall are increasing,[1,6,54] as well as the evidence for AD with onset in adulthood in previously unaffected subjects or relapses of AD in adulthood after long remission phases.[1,2,9,12,13,20,30] Thus, a better understanding of factors associated with adult-versus childhood-onset AD is needed to design adequate preventive strategies. We found (i) maternal AD being the main familial RF for both onset-groups; (ii) maternal FA being an additional RF for childhood-onset AD; (iii) active smoking the main lifestyle factor associated with adult-onset AD versus controls; (iv) an academic background doubling the odds of childhood-onset AD versus controls; (v) each additional atopic stigma approximately doubling the odds of AD versus controls; (vi) palmar hyperlinearity associated with childhood-onset versus controls[atopic]; (vii) white dermographism associated with childhood-versus adult-onset AD; (viii) a "pure" AD without atopic comorbidities in only 12% of patients with childhood-onset, but in 28% of adult-onset AD overall with infancy-onset AD as the most atopic (9% pure), late-adult-onset (50% pure) the least atopic subgroup; (ix) adult-onset AD more prone to AR, but with reduced odds of multiple atopic comorbidities than childhood-onset AD; (x) FA nearly tripling the odds of childhood-onset AD versus

no-AD; (xi) increased tIgE levels associated with both childhood- and adult-onset AD versus controls; (xii) childhood-onset AD, particularly infant-onset, grouping mainly in "high-atopic"-clusters, middle- and late-adult-onset AD preferentially in clusters with lower contributions of personal and familial atopy and high frequencies of physical inactivity. Associated factors and their impact partly differed depending on AD onset in different phases of child- and adulthood.

Our observed proportion of adult-onset ≥18 years in 23.6% of patients aligns with other European countries.[12] The distribution and associated factors of adult-compared to childhood-onset of AD in the literature are varying depending on study design: longitudinal versus cross-sectional, self-reported versus physician-diagnosed AD, diagnostic criteria of AD, numbers of participants, cohorts from countries with different conditions potentially influencing the onset and phenotype of AD such as ethnicity, climatic conditions, sociodemographic factors, particulate matter, and others.

Here, we analyzed cross-sectional data of mainly Caucasian adults from Germany and Switzerland with the strengths of physician-diagnosed AD according to Hanifin and Rajka, a large age range from 18 to 89 years, detailed assessment of AD severity and phenotypic traits by experienced dermatologists plus self-reported information on the disease course and numerous other clinical and epidemiological factors not only for AD, but also controls.

We found active smoking to be the main modifiable factor for onset of AD in early and middle adulthood compared to controls. Also, daily ETS tended to be associated with AD compared to controls, especially with adult-onset AD. Both active smoking and daily ETS doubled the odds of AD with onset in early adulthood compared to childhood. Active smoking can exert multiple pathophysiological effects on cellular and humoral immunity[55] and also contribute to skin barrier dysfunction via reactive oxygen species.[56–58] Current and former active smoking as well as ETS have also been shown to be associated with physician-diagnosed adult-onset AD compared to controls in a Taiwanese study,[59] but not with self-reported adult-onset AD in US women.[60] The BCS associated adulthood smoking with adult-onset AD both versus controls and childhood-onset AD with slightly lower effect sizes than our study.[2] Conversely, an US study did not find differences between adult- and childhood-onset AD depending on the current smoking status.[15] Generally, passive and active smoking have been associated with an increased prevalence of AD,[56] active smoking also with both self-reported[61,62] and physician-assessed[8,62] AD severity. Besides biological effects, this might potentially be ascribed to a worse health behavior because of a higher psychological burden[6,63] in severe AD.

Regarding other lifestyle factors, we observed a trend towards protective effects of sports on adult-onset AD compared to controls. Broad anti-inflammatory effects have been reported for regular PA.[64] Our findings align with previously found protective effects of PA on atopic diseases overall,[65] on AD severity,[8] and less PA in AD in United States,[66] although not in Swedish[67] adults. Moderate-intensity aerobic exercise also improved dermatitis in allergic inflammation in mouse models.[68] We further found an academic background associated with childhood-onset AD versus controls^{atopic} and reduced odds of middle- and late-adult-onset AD versus childhood-onset. This concurs with the association of a lower childhood socioeconomic status with adult-onset AD found in the BCS.[2] Our analyses of a possible relationship between sociodemographic and lifestyle factors revealed a higher frequency of smokers and lack of PA in AD patients without compared to those with academic background. This aligns with the generally found association of smoking and nicotine dependence with a lower educational level and socio-economic status, single marital status, older age, higher stress, and BMI also irrespective of AD.[69,70] Our findings further support previously reported associations of a small household size and mold exposition with increased probability of AD.[1]

We found maternal AD being the main familial RF associated with both adult- and childhood-onset AD versus controls, childhood-onset AD additionally with maternal FA. Consistently, several epidemiological studies have suggested a preferential transmission of allergy risk through mothers.[71,72]

Regarding the phenotype, a higher number of atopic stigmata was associated with higher odds of both childhood- and adult-onset AD compared to controls in our study. However, adult-onset AD featured less atopic stigmata and comorbidities than childhood-onset AD with varying effect sizes depending on type of comorbidities and life period. Patients with adult-onset AD had reduced odds of multiple atopic comorbidities at once, especially in late adulthood. The association to multiple type 2 (T2) related atopic comorbidities might indicate a more pronounced T2-inflammation in childhood compared to adult-onset AD where other factors might have a higher impact. Accordingly, we also observed two third lower odds of self-reported allergies in adult compared to childhood-onset AD. Also, other studies reported adult-versus childhood-onset to be associated with lower proportions of allergies and personal or familial allergic diseases[2,9,12,15] with AR as the most frequent atopic comorbidity[2,12] and asthma with lower[2,15,33] or similar[12] proportions in adult-versus childhood-onset AD.

In our cohort, AR was associated with adult-onset AD and with atopic controls versus childhood-onset AD. We further found FA increasing the odds of childhood-onset AD threefold compared to atopic controls consistent with multiple studies associating food sensitization with AD onset in early infancy.[10,73,74]

We found nearly all atopic stigmata more frequent in childhood- than in adult-onset AD than in controls consistent with other studies.[9,15] White dermographism showed the highest differences and doubled the odds of childhood-onset AD compared to adult-onset AD with the lowest odds of late-adult-onset AD. Palmar hyperlinearity has been associated with filaggrin loss-of-function mutations,[1,53,75] of which at least some have been previously linked only to AD with childhood-onset before age 8, but not in later child- or adulthood.[76] Herein, palmar hyperlinearity doubled the odds of childhood-onset AD overall versus controls^{atopic} and was less likely with disease onset in adulthood than in infancy. Our findings are consistent with higher frequencies of cheilitis,[9,15] Dennie–Morgan fold,[9,15] pityriasis alba,[9,15] anterior neck fold,[15] perleche,[9] dirty neck,[9] periorbital darkening[9] in childhood versus adult-onset

reported in the United States,[15] and/or another German[9] cohort. The German,[9] but not the United States[15] cohort also found higher frequencies of white dermographism. None of the upper-mentioned atopic stigmata was found to differ by AD onset in an Korean cohort,[33] suggesting a large variation of adult-onset phenotypes among ethnicities.

We did not find systemic differences in severity and localization of eczema between adult- and childhood-onset AD overall. Similarly, clinician-[9,15,33] or patient-reported[15] AD severity,[9,15,33] pruritus,[15] or xerosis[15,33] did not differ in other cohorts by AD onset. Herein, trunk eczema tended to be associated with adult-onset versus childhood-onset AD consistent with a Korean study.[33] However, after adjustment for all covariates including severity, we did not find significant differences between adult- and childhood-onset overall in any body region in contrast to other studies reporting a higher probability of hand and/or head–neck dermatitis,[12,15] potentially due to differences in ethnicity and study design.

The susceptibility of AD to cutaneous infections is well-known.[1,6] Herein, adult-onset AD tended to be less prone to bacterial infections than childhood-onset AD consistent with a Korean study.[33] We further found a higher proneness to EH in patients with onset in infancy and adolescence while being less likely in early-adult-onset. Besides the association with tIgE with both childhood- and adult-onset AD, we also observed a trend towards stronger associations of circulating eosinophils with middle- and late-adult-onset-AD providing an interesting link to the eosinophilic endotype in adult-onset asthma.[77] Due to the explorative approach with a focus on the evaluation of factors associated with age of AD onset in different life periods, no corrections for multiple testing were applied in the LR models, only in the cluster analyses. Other limitations of our study include lack of genotyping, no measurement of specific IgE and biomarkers other than tIgE and eosinophils, and the cross-sectional design with a potential recall-bias of the self-reported age of AD onset, especially in older patients. However, this recall bias applies to nearly all studies about adult-onset AD, which are mostly cross-sectional. A longitudinal follow-up of birth cohorts up to late adulthood with physician-assessed AD would be highly desirable, but is unfortunately difficult due to economic reasons and drop-out-rates. Most longitudinal birth cohort studies on AD cover the childhood, some also adolescence, but data from early and middle adulthood are sparse and longitudinal data on AD up to late-adulthood to our knowledge non-existent. Further, our number of participants was lower than those from survey-or insurance-data-based studies, yet more detailed and with physician-based diagnosis, assessment of AD severity and atopic stigmata. The herein identified partly common, but also different associated factors (i) suggest varying endo- and exogeneous mechanisms underlying adult-versus childhood-onset AD, (ii) might contribute to a deeper understanding and better assessment of the individual risk to develop AD in different life periods with (iii) potential for prevention of modifiable factors. Further studies are warranted to investigate the underlying differences in the endotype and genotype of adult-versus childhood-onset of AD.

AUTHOR CONTRIBUTIONS

Study concept and design: LM, MTS, NH, ER, EB, PSG, CTH, CA, RL, MCB, TB. Acquisition of data: LM, MTS, NH, JB, SM, RH, AD, EB, DF, GH, DL, CL, ER, PSG, MCB, CTH, TB. Recruitment of patients: LM, JB, RH, SM, EB, DF, GH, DL, CL, ER, MCB, PSG, CTH, TB. Analysis and interpretation of data: LM, MTS, MS, TB. Drafting of the manuscript: LM, MTS, MS, TB. Critical revision of the manuscript for important intellectual content: NH, SM, RH, JB, DF, CR, AD, AN, EB, GH, MR, DL, CL, ER, PSG, CTH, CA, MCB, RL, TB. Obtained funding: PSG, CTH, CA, MCB, RL, TB.

ACKNOWLEDGEMENTS

We are very grateful to all our study participants, and to Matthias Möhrenschlager, Anna Sophie Wesselmann, Nina Evertz, Lisa Braun, Veronika Ralser-Isselstein for their help in recruitment of participants in this study and Sylvia Schnautz, Helene Kirins, Yassin Chabane, Said Benfadal, Jolien Oosterveer, Simone Willms, and Anja Heider for excellent technical assistance. We are thankful to Beate Rückert for her work with the CK-CARE biobank, and all other co-workers of the prospective longitudinal study investigating the remission phase in patients with atopic dermatitis and other allergy-associated diseases (ProRaD). Open Access funding enabled and organized by Projekt DEAL.

FUNDING INFORMATION

We thank the Christine Kühne-Center for Allergy Research and Education (CK-CARE), Davos, Switzerland for funding of the study. Laura Maintz, Marie-Therese Schmitz, Juliette Brauer, Svenja Müller, Regina Havenith, Claudio Rhyner, Anita Dreher, Eugen Bersuch, Daria Luschkova and Ellen D Renner were or are supported by, or were or are employees of CK-CARE. Marie-Charlotte Brüggen is supported by CK-CARE. The funding sources did not participate in the study design and conduct, nor in the data collection, management, analysis, and interpretation, nor in preparation, review or approval of the manuscript nor in the decision to submit the article for publication.

CONFLICT OF INTEREST STATEMENT

Thomas Bieber was speaker, and/or consultant and/or investigator for: AbbVie, Allmiral, AnaptysBio, Arena, Asana Biosciences, ASLAN pharma Bayer Health, BioVerSys, Böhringer-Ingelheim, Connect Pharma, Dermavant/Roivant, Domain Therapeutics, Eli Lilly, Galderma, Glenmark, GSK, Incyte, Innovaderm, IQVIA, Janssen, Kirin, Kymab, LEO Pharma, LG Chem, L'Oréal, MSD, Novartis, Numab, OM Pharma, Pfizer, Pierre Fabre, Q32bio, RAPT, Sanofi/Regeneron, UCB. Thomas Bieber is founder and chairman of the non-profit biotech company "Davos Biosciences". Laura Maintz is or was investigator for AbbVie, Allmirall, Bristol-Myers Squibb, Eli Lilly, Galderma, LEO Pharma, OM Pharma, Pfizer, Sanofi/Regeneron, was advisor for Eli Lilly, speaker for AbbVie and LEO Pharma and received research funding from Eli Lilly, LEO Pharma and Sanofi Genzyme. M.C. Brüggen has received grants and research funding from the Swiss National Science foundation (SNF), Freenovation foundation, LEO

foundation, Olga Mayenfisch foundation, the University of Zurich, LEO Pharma and the Eczema Foundation of Pierre Farbre; consultation fees from Eli Lilly, LEO Pharma, AbbVie, and AstraZeneca. C. A. Akdis has received research grants from the Swiss National Science Foundation, European Union (EU CURE, EU Syn-Air-G), European Union, Novartis Research Institutes, Stanford University and SciBase; is on the Advisory Boards of Sanofi/Regeneron, Stanford University Sean Parker Asthma Allergy Center, Novartis, GlaxoSmithKline, Bristol-Myers Squibb (London) and SciBase; and is the Editor-in-Chief of Allergy. Claudia Lang is or was speaker, advisor or investigator for AbbVie, EliLilly, LEO, Novartis, Pfizer, and SanofiGenzyme. Peter Schmid-Grendelmeier was speaker, advisor or investigator for AbbVie, Astra Zeneca, Biomed, EliLilly, Galderma, Glaxo Smith Kline, LEO, L'Oreal, Novartis, Pfizer, Pierre Fabre and SanofiGenzyme. Claudia Traidl-Hoffmann was speaker, and/or consultant and/or investigator for: Asana Biosciences, Eli Lilly, Bencard, Stallergenes, Hal Allergy, ALK Abello, Galderma, L'Oréal, LaRochePosay, Novartis, Sanofi/Regeneron, Sebapharma, Töpfer, Beiersdorf, Siemens Health Care, Reviderm, Nutriummun, Berlin Chemie. All other authors have no conflict of interest to declare within the scope of the submitted work.

ORCID

Laura Maintz https://orcid.org/0000-0001-6053-1530
Marie-Therese Schmitz https://orcid.org/0000-0003-2940-647X
Nadine Herrmann https://orcid.org/0000-0003-4924-2281
Svenja Müller https://orcid.org/0000-0002-2118-959X
Regina Havenith https://orcid.org/0000-0003-0148-7159
Juliette Brauer https://orcid.org/0000-0001-6975-2559
Claudio Rhyner https://orcid.org/0000-0003-3339-3923
Anita Dreher https://orcid.org/0000-0001-8823-6621
Eugen Bersuch https://orcid.org/0000-0003-1409-1786
Danielle Fehr https://orcid.org/0000-0001-6361-3662
Gertrud Hammel https://orcid.org/0000-0002-1800-7679
Matthias Reiger https://orcid.org/0000-0002-6173-2104
Daria Luschkova https://orcid.org/0000-0003-3354-4277
Avidan Neumann https://orcid.org/0000-0002-2149-5917
Claudia C. V. Lang https://orcid.org/0000-0003-0469-7661
Ellen D. Renner https://orcid.org/0000-0001-9816-8538
Peter Schmid-Grendelmeier https://orcid.org/0000-0003-3215-3370
Claudia Traidl-Hoffmann https://orcid.org/0000-0001-5085-5179
Cezmi A. Akdis https://orcid.org/0000-0001-8020-019X
Roger Lauener https://orcid.org/0000-0002-8412-606X
Marie-Charlotte Brüggen https://orcid.org/0000-0002-8607-6254
Matthias Schmid https://orcid.org/0000-0002-0788-0317
Thomas Bieber https://orcid.org/0000-0002-8800-3817

REFERENCES

1. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Primers*. 2018;4:1.
2. Abuabara K, Ye M, McCulloch CE, et al. Clinical onset of atopic eczema: results from 2 nationally representative British birth cohorts followed through midlife. *J Allergy Clin Immunol*. 2019;144:710-719.
3. Czarnowicki T, He H, Krueger JG, Guttman-Yassky E. Atopic dermatitis endotypes and implications for targeted therapeutics. *J Allergy Clin Immunol*. 2019;143:1-11.
4. Thorsteinsdottir S, Stokholm J, Thyssen JP, et al. Genetic, clinical, and environmental factors associated with persistent atopic dermatitis in childhood. *JAMA Dermatol*. 2019;155:50-57.
5. Reiger M, Traidl-Hoffmann C, Neumann AU. The skin microbiome as a clinical biomarker in atopic eczema: promises, navigation, and pitfalls. *J Allergy Clin Immunol*. 2020;145:93-96.
6. Ständer S. Atopic dermatitis. *N Engl J Med*. 2021;384:1136-1143.
7. Klaeschen AS, Nümm TJ, Herrmann N, et al. JAK1/2 inhibition impairs the development and function of inflammatory dendritic epidermal cells in atopic dermatitis. *J Allergy Clin Immunol*. 2020;147:2202-2212.e8.
8. Maintz L, Welchowski T, Herrmann N, et al. Machine learning-based deep phenotyping of atopic dermatitis: severity-associated factors in adolescent and adult patients. *JAMA Dermatol*. 2021;157:1414-1424.
9. Garmhausen D, Hagemann T, Bieber T, et al. Characterization of different courses of atopic dermatitis in adolescent and adult patients. *Allergy*. 2013;68:498-506.
10. Roduit C, Frei R, Depner M, et al. Phenotypes of atopic dermatitis depending on the timing of onset and progression in childhood. *JAMA Pediatr*. 2017;171:655-662.
11. Paternoster L, Savenije OEM, Heron J, et al. Identification of atopic dermatitis subgroups in children from 2 longitudinal birth cohorts. *J Allergy Clin Immunol*. 2018;141:964-971.
12. Lee HH, Patel KR, Singam V, Rastogi S, Silverberg JI. A systematic review and meta-analysis of the prevalence and phenotype of adult-onset atopic dermatitis. *J Am Acad Dermatol*. 2019;80:1526-1532.e7.
13. Silverberg JI. Adult-onset atopic dermatitis. *J Allergy Clin Immunol Pract*. 2019;7:28-33.
14. Ingordo V, Cazzaniga S, Naldi L, et al. Atopic dermatitis in young adult italian males: persistent and adult-onset varieties did not differ clinically and as for allergological variables. *G Ital Dermatol Venereol*. 2019;155:724-732.
15. Silverberg JI, Vakharia PP, Chopra R, et al. Phenotypical differences of childhood- and adult-onset atopic dermatitis. *J Allergy Clin Immunol Pract*. 2018;6:1306-1312.
16. Silverberg JI. Atopic dermatitis in adults. *Med Clin North Am*. 2020;104:157-176.
17. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults. Results from an International Survey. *Allergy*. 2018;73:1284-1293.
18. Abuabara K, Langan SM, Yu AM. Conclusions about atopic dermatitis persistence might be premature. *J Am Acad Dermatol*. 2017;76:e177-e178.
19. Wan J, Mitra N, Hoffstad OJ, Yan AC, Margolis DJ. Longitudinal atopic dermatitis control and persistence vary with timing of disease onset in children: a cohort study. *J Am Acad Dermatol*. 2019;81:1292-1299.
20. Kim JP, Chao LX, Simpson EL, Silverberg JI. Persistence of atopic dermatitis (AD). A systematic review and meta-analysis. *J Am Acad Dermatol*. 2016;75:681-687.e11.
21. Silverberg JI. Persistence of childhood eczema into adulthood. *JAMA Dermatol*. 2014;150:591-592.
22. Kim Y, Blomberg M, Rifas-Shiman SL, et al. Racial/ethnic differences in incidence and persistence of childhood atopic dermatitis. *J Invest Dermatol*. 2019;139:827-834.
23. Abuabara K, Yu AM, Okhovat J-P, Allen IE, Langan SM. The prevalence of atopic dermatitis beyond childhood: a

systematic review and meta-analysis of longitudinal studies. *Allergy*. 2018;73:696-704.
24. Abuabara K, Margolis DJ, Langan SM. The long-term course of atopic dermatitis. *Dermatol Clin*. 2017;35:291-297.
25. Mulick AR, Mansfield KE, Silverwood RJ, et al. Four childhood atopic dermatitis subtypes identified from trajectory and severity of disease and internally validated in a large UK birth cohort. *Br J Dermatol*. 2021;185:526-536.
26. Abuabara K, Hoffstad O, Troxel AB, Gelfand JM, McCulloch CE, Margolis DJ. Patterns and predictors of atopic dermatitis disease control past childhood: an observational cohort study. *J Allergy Clin Immunol*. 2018;141:778-780.e6.
27. Margolis JS, Abuabara K, Bilker W, Hoffstad O, Margolis DJ. Persistence of mild to moderate atopic dermatitis. *JAMA Dermatol*. 2014;150:593-600.
28. Silverwood RJ, Forbes HJ, Abuabara K, et al. Severe and predominantly active atopic eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. *BMJ*. 2018;361:k1786.
29. Zhou L, Leonard A, Pavel AB, et al. Age-specific changes in the molecular phenotype of patients with moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol*. 2019;144:144-156.
30. Ozkaya E. Adult-onset atopic dermatitis. *J Am Acad Dermatol*. 2005;52:579-582.
31. Wang X, Shi X-D, Li L-F, Zhou P, Shen Y-W, Song Q-K. Prevalence and clinical features of adult atopic dermatitis in tertiary hospitals of China. *Medicine*. 2017;96:e6317.
32. Wang S, Zhu R, Gu C, et al. Distinct clinical features and serum cytokine pattern of elderly atopic dermatitis in China. *J Eur Acad Dermatol Venereol*. 2020;34:2346-2352.
33. Son JH, Chung BY, Kim HO, Park CW. Clinical features of atopic dermatitis in adults are different according to onset. *J Korean Med Sci*. 2017;32:1360-1366.
34. Bieber T, Traidl-Hoffmann C, Schäppi G, Lauener R, Akdis C, Schmid-Grendlmeier P. *Unraveling the Complexity of Atopic Dermatitis: the CK-CARE Approach toward Precision Medicine*. Universität Augsburg; Wiley; 2020.
35. Husson F, Lê S, Pagès J. *Exploratory Multivariate Analysis by Example Using R*. CRC Press; 2017.
36. Pagès J. Analyse factorielle de donnees mixtes. *Rev Stat Appl*. 2004;52:93-111.
37. R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing; 2019 https://www.R-project.org/
38. Schauberger P, Walker A. openxlsx: Read, Write and Edit xlsx Files. R package version 4.1.4. 2019 https://CRAN.R-project.org/package=openxlsx
39. Dowle M, Srinivasan A. Data.Table: extension of 'data.Frame'. R package version 1.12.8. 2019 https://CRAN.R-project.org/package=data.table
40. Kuhn M. Classification and regression training. R package version 6.0–86. https://CRAN.R-project.org/package=caret
41. Wickham H, Bryan J. readxl: Read Excel Files. R package version 1.3.1. 2019 https://CRAN.R-project.org/package=readxl
42. Fox J, Weisberg S. *An {R} Companion to Applied Regression*. 3rd ed. Sage; 2019 https://socialsciences.mcmaster.ca/jfox/Books/Companion/index.html
43. Dragulescu A, Arendt C. xlsx: Read, Write, Format Excel 2007 and Excel 97/2000/XP/2003 Files. R package version 0.6.3. 2020 https://CRAN.R-project.org/package=xlsx
44. Hothorn T, Hornik K, van de Wiel MA, Zeileis A. A Lego system for conditional inference. *Am Stat*. 2006;60:257-263.
45. Wickham H. *ggplot2: Elegant Graphics for Data Analysis*. Springer-Verlag; 2016.
46. Auguie B. gridExtra: Miscellaneous Functions for "Grid" Graphics. R package version 2.3. 2017 https://CRAN.R-project.org/package=gridExtra
47. Harrell F Jr, with contributions from Charles Dupont and many others. Hmisc: Harrell Miscellaneous. R package version 4.4-0. 2020 https://CRAN.R-project.org/package=Hmisc
48. Kuhn M, Johnson K. *Applied Predictive Modelling*. Springer Science+Business Media; 2013.
49. Zhang T, Yu B. Boosting with early stopping: convergence and consistency. *Ann Stat*. 2005;33:1538-1579.
50. Chen T, He T, Benesty M, et al. xgboost: Extreme Gradient Boosting. R package version 0.90.0.2. 2019 https://CRAN.R-project.org/package=xgboost
51. Friedman JH. Greedy function approximation: a gradient boosting machine. *Ann Stat*. 2001;29:1189-1232.
52. Diepgen TL, Fartasch M, Hornstein OP. Evaluation and relevance of atopic basic and minor features in patients with atopic dermatitis and in the general population. *Acta Derm Venereol Suppl*. 1989;144:50-54.
53. Bradshaw LE, Haines RH, Thomas KS, et al. Clinical examination for hyperlinear palms to determine filaggrin genotype: a diagnostic test accuracy study. *Clin Exp Allergy*. 2021;51:1421-1428.
54. Nutten S. Atopic dermatitis: global epidemiology and risk factors. *Ann Nutr Metab*. 2015;66(Suppl 1):8-16.
55. Sopori M. Effects of cigarette smoke on the immune system. *Nat Rev Immunol*. 2002;2:372-377.
56. Kantor R, Kim A, Thyssen JP, Silverberg JI. Association of atopic dermatitis with smoking: a systematic review and meta-analysis. *J Am Acad Dermatol*. 2016;75:1119-1125.e1.
57. Sticozzi C, Belmonte G, Pecorelli A, et al. Cigarette smoke affects keratinocytes SRB1 expression and localization via H_2O_2 production and HNE protein adducts formation. *PLoS ONE*. 2012;7:e33592.
58. Sticozzi C, Belmonte G, Frosini M, Pessina F. Correction to: nitric oxide/cyclic GMP-dependent calcium signalling mediates IL-6- and TNF-α-induced expression of glial fibrillary acid protein. *J Mol Neurosci*. 2021;71:867-868.
59. Lee CH, Chuang HY, Hong CH, et al. Lifetime exposure to cigarette smoking and the development of adult-onset atopic dermatitis. *Br J Dermatol*. 2011;164:483-489.
60. Morra DE, Cho E, Li T, Camargo CA, Qureshi AA, Drucker AM. Smoking and risk of adult-onset atopic dermatitis in US women. *J Am Acad Dermatol*. 2021;84:561-563.
61. Smirnova J, Montgomery S, Lindberg M, Svensson Å, von Kobyletzki L. Associations of self-reported atopic dermatitis with comorbid conditions in adults: a population-based cross-sectional study. *BMC Dermatol*. 2020;20:23.
62. Pilz AC, Schielein MC, Schuster B, et al. Atopic dermatitis: disease characteristics and comorbidities in smoking and non-smoking patients from the TREATgermany registry. *J Eur Acad Dermatol Venereol*. 2022;36:413-421.
63. Davis DMR, Drucker AM, Alikhan A, et al. AAD guidelines: awareness of comorbidities associated with atopic dermatitis in adults. *J Am Acad Dermatol*. 2022;86:1335-1336.e18.
64. Salimans L, Liberman K, Njemini R, Kortekaas Krohn I, Gutermuth J, Bautmans I. The effect of resistance exercise on the immune cell function in humans: a systematic review. *Exp Gerontol*. 2022;164:111822.
65. Morales E, Strachan D, Asher I, Ellwood P, Pearce N, Garcia-Marcos L. Combined impact of healthy lifestyle factors on risk of asthma, rhinoconjunctivitis and eczema in school children: ISAAC phase III. *Thorax*. 2019;74:531-538.
66. Strom MA, Silverberg JI. Associations of physical activity and sedentary behavior with atopic disease in United States children. *J Pediatr*. 2016;174:247-253.e3.
67. Lonne-Rahm S-B, Sundström I, Nordlind K, Engström L-M. Adult atopic dermatitis patients and physical exercise: a Swedish questionnaire study. *Acta Derm Venereol*. 2014;94:185-187.
68. Son WK, Yoon W, Kim S, et al. Can moderate-intensity aerobic exercise ameliorate atopic dermatitis. *Exp Dermatol*. 2020;29:699-702.

69. Pennanen M, Broms U, Korhonen T, et al. Smoking, nicotine dependence and nicotine intake by socio-economic status and marital status. *Addict Behav*. 2014;39:1145-1151.
70. Sim YS, Yoo S, Lee K-S, Rhee CK, Kim YK. Associations of clinical, psychological, and socioeconomic characteristics with nicotine dependence in smokers. *Sci Rep*. 2021;11:18544.
71. Esparza-Gordillo J, Matanovic A, Marenholz I, et al. Maternal filaggrin mutations increase the risk of atopic dermatitis in children: an effect independent of mutation inheritance. *PLoS Genet*. 2015;11:e1005076.
72. Cookson W. Genetics and genomics of asthma and allergic diseases. *Immunol Rev*. 2002;190:195-206.
73. Alduraywish SA, Lodge CJ, Campbell B, et al. The march from early life food sensitization to allergic disease: a systematic review and meta-analyses of birth cohort studies. *Allergy*. 2016;71:77-89.
74. Paller AS, Spergel JM, Mina-Osorio P, Irvine AD. The atopic march and atopic multimorbidity: many trajectories, many pathways. *J Allergy Clin Immunol*. 2019;143:46-55.
75. Fukuie T, Yasuoka R, Fujiyama T, Sakabe J-I, Taguchi T, Tokura Y. Palmar hyperlinearity in early childhood atopic dermatitis is associated with filaggrin mutation and sensitization to egg. *Pediatr Dermatol*. 2019;36:213-218.
76. Rupnik H, Rijavec M, Korošec P. Filaggrin loss-of-function mutations are not associated with atopic dermatitis that develops in late childhood or adulthood. *Br J Dermatol*. 2015;172:455-461.
77. Lommatzsch M, Klein M, Stoll P, Virchow JC. Type 2 biomarker expression (FeNO and blood eosinophils) is higher in severe adult-onset than in severe early-onset asthma. *Allergy*. 2021;76:3199-3202.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Maintz L, Schmitz M-T, Herrmann N, et al. Atopic dermatitis: Correlation of distinct risk factors with age of onset in adulthood compared to childhood. *Allergy*. 2023;78:2181-2201. doi:10.1111/all.15721