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ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

IL-13, periostin and dipeptidyl-peptidase-4 reveal endotype-phenotype associations in atopic dermatitis

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Abstract

Background: The heterogeneous (endo)phenotypes of atopic dermatitis (AD) require precision medicine. Currently, systemic therapy is recommended to patients with an Eczema Area and Severity Index (EASI) ≥ 16. Previous studies have demonstrated an improved treatment response to the anti-interleukin (IL)-13 antibody tralokinumab in AD subgroups with elevated levels of the IL-13-related biomarkers dipeptidyl-peptidase (DPP)-4 and periostin.

Methods: Herein, 373 AD patients aged ≥12 years were stratified by IL-13^{high}, periostin^{high} and DPP-4^{high} endotypes using cross-sectional data from the ProRaD cohort Bonn. "High" was defined as >80th quantile of 47 non-atopic controls. We analyzed endotype-phenotype associations using machine-learning gradient boosting compared to logistic regression.

Results: Atopic dermatitis severity and eosinophils correlated with IL-13 and periostin levels. Correlations of IL-13 with EASI were stronger in patients with increased (rs = 0.482) than with normal (rs = 0.342) periostin levels. We identified eosinophilia >6% and an EASI range of 5.5–17 dependent on the biomarker combination to be associated with increasing probabilities of biomarker^{high} endotypes. Also patients with mild-to-low-moderate severity (EASI < 16) featured increased biomarkers (IL-13^{high}: 41%, periostin^{high}: 48.4%, DPP-4^{high}: 22.3%). Herthoge sign (adjusted Odds Ratio (aOR) = 1.89, 95% Confidence Interval (CI) [1.14–3.14]) and maternal allergic rhinitis (aOR = 2.79–4.47) increased the probability of an IL-13^{high}-endotype, "dirty neck" (aOR = 2.83 [1.32–6.07]), orbital darkening (aOR = 2.43 [1.08–5.50]),

Abbreviations: Ab, Antibody; AD, Atopic Dermatitis; ALE, Accumulated Local Effect; AR, Allergic Rhinitis; AUC, Area Under the Curve; BM, Biomarker; BMI, Body Mass Index; BSA, Body Surface Area; CBM, Combined-Biomarker Profile model; CCL17, Chemokine (C-C motif) Ligand (CCL)17/Thymus and Activation-Regulated Chemokine (TARC); ClinRO, Clinician-Reported Outcome; DLQI, Dermatology Life Quality Index; DPP-4, Dipeptidyl Peptidase 4; EASI, Eczema Area and Severity Index; FA, Food Allergy; IGA, Investigator's Global Assessment; IL, Interleukin; ITT, Intention-to-treat; JAKi, Janus Kinase Inhibitors; LOD, Limit of Detection; LR, Logistic Regression; MLGB, Machine Learning Gradient Boosting; MLR, Multinomial Logistic Regression; NPX, Normalized Protein eXpression; OR, Odds Ratio; PRO, Patient-Reported Outcome; ProRaD, Prospective longitudinal study investigating the Remission phase in patients with Atopic Dermatitis and other allergy-associated diseases; QoL, Quality of Life; RCT, Randomized Clinical Trial; rs, Correlation Coefficient (Spearman's rho); SBM, Single-Biomarker Profile model; SCORAD, SCORing Atopic Dermatitis; T2, Type 2; tIgE, Total Serum Immunoglobulin E.

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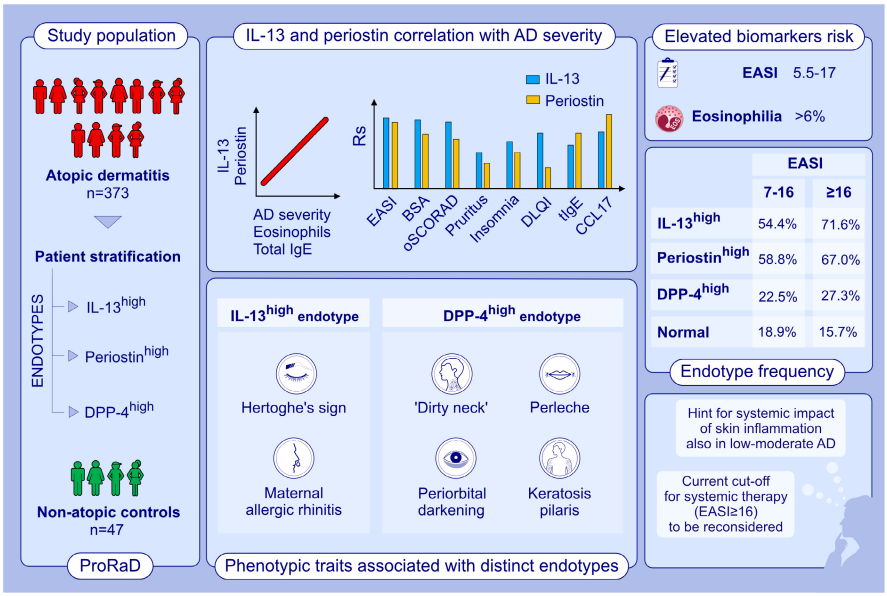
keratosis pilaris (aOR = 2.21 [1.1–4.42]) and perleche (aOR = 3.44 [1.72–6.86]) of a DPP-4^{high}-endotype.

Conclusions: A substantial proportion of patients with EASI < 16 featured high biomarker levels suggesting systemic impact of skin inflammation already below the current cut-off for systemic therapy. Our findings facilitate the identification of patients with distinct endotypes potentially linked to response to IL-13-targeted therapy.

KEYWORDS
atopic dermatitis, biomarker, endotype, interleukin-13, tralokinumab



GRAPHICAL ABSTRACT
IL-13 and periostin correlate with AD disease severity and eosinophils. The substantial portion of biomarker^{high} patients with EASI < 16 and machine-learning-based increasing probabilities of biomarker^{high} AD within EASI = 5.5–17 dependent on the biomarker combination suggest systemic impact of skin inflammation also in mild-to-moderate AD and question the current *cut-off* EASI 16 for systemic therapy. Several phenotypic traits (i.e. Hertoghe's sign, periorbital darkening, 'dirty neck', keratosis pilaris, perleche) are associated with distinct endotypes. Abbreviations: AD, atopic dermatitis; BSA, affected body surface area; CCL17, C-C motif chemokine ligand 17; DLQI, dermatology life quality index; DPP-4, dipeptidyl peptidase-4; EASI, eczema area and severity index; Eos, eosinophils; IL, interleukin; (o)SCORAD, (objective) scoring atopic dermatitis; ProRaD, prospective longitudinal study investigating the remission phase in patients with atopic dermatitis and other allergy-associated diseases; Rs, correlation coefficient; tIgE, total serum Immunoglobulin E

1 | INTRODUCTION

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease with highly heterogeneous clinical phenotypes reflecting the complex pathophysiology and endotypes.[1–8] Recently, various promising targeted therapies have been developed.[1] Interleukin (IL)-4 and IL-13 are key cytokines of the type 2 (T2) immune response driving the pathophysiology of AD. Dupilumab[9,10] targeting the IL-4Rα subunit of the IL-4 and IL-13 receptors was the first biologic approved for moderate-to-severe AD. Recently, the Janus kinase inhibitors (JAKi) baricitinib,[11–16] upadacitinib,[17–22] abrocitinib[23–31] and the anti-IL-13 antibody tralokinumab[32–36] have also been approved in Europe. Lebrikizumab, targeting the IL-13-receptor assembly, is in advanced clinical development.[37,38] Results from phase 3 dupilumab studies and real-world data clearly show that there is no "one-size-fits-all" treatment, as only one third of patients are fully responsive to monotherapy. These studies support the need for a precision medicine approach with biomarker-based stratification strategies to define optimal target populations.[1,6,7,39–41]

IL-13 is a key driver of underlying T2 inflammation in AD aggravating the genetically-inherited skin barrier dysfunction, immune dysregulation, inducing itch and contributing to microbiome dysbiosis.[34,37] IL-13 is upregulated in both acute and chronic lesions,[37,38,42,43] non-lesional skin[32,37,44,45] and associated with AD severity.[32] Reductions in IL-13 have been shown to correlate with treatment response and improved clinical outcomes.[32,37,44,45] IL-13 upregulates dipeptidyl peptidase-4 (DPP-4) and periostin expression, both regarded as biomarkers of IL-13 activity.[32,46,47] Treatment with dupilumab has been shown to reduce T2 inflammatory markers, including gene expression of IL-13 and DPP-4 in the skin and periostin serum levels.[10] Most interestingly, a phase 2b study investigating the efficacy and safety of tralokinumab for the treatment of AD showed improved responses

in subgroups with increased circulating levels of DPP-4 and periostin compared to those with low levels.[32] Asthmatic patients with elevated levels of DPP-4, periostin (blood) and IL-13 (sputum), responded better to tralokinumab.[48] An Eczema Area and Severity Index (EASI) ≥ 16 is a typically used severity cut-off for inclusion in AD clinical trials and indication for systemic therapy.[49–51]

In this study, using a machine-learning-based approach, we explore possible endotype-phenotype associations based on IL-13 and its related biomarkers periostin and DPP-4 in AD overall and stratified by EASI16 and asthma. This may facilitate the identification of AD patients that will benefit from targeted therapy against IL-13 and its' receptors.

2 | METHODS

2.1 | Study design and participants

We analyzed cross-sectional baseline data of 420 subjects ≥12 years enrolled in the ProRAD[52,53] study after written informed consent: 373 AD patients fulfilling the Hanifin and Rajka criteria with only topical treatment and 47 non-atopic controls. Exclusion criteria were systemic treatment of AD ≤30 days and remission. Patients' characteristics and further details are outlined in Table 1, Methods S1. All study methods followed the Declaration of Helsinki and have been approved by the local ethics committee (ProRaD, 232/15).

2.2 | Circulating serum biomarkers

Protein biomarkers were analyzed with multiplex immunoassays from Olink (IL-13: #95302, Olink proteomics, Uppsala, Sweden) and MesoScale (CCL17, periostin (#K1506M), DPP4, R-PLEX (#F21YC-8), MesoScaleDiscovery, Rockville, USA). Further details are outlined in Methods S2.

2.3 | Statistical analysis

2.3.1 | Analysis of endotype-phenotype associations in AD by multivariable Machine Learning Gradient Boosting (MLGB) compared to multivariable Logistic Regression (LR) models

AD patients were stratified by IL-13^{high}-, periostin^{high}-, and DPP-4^{high}-endotypes. The 80th quantile of non-atopic controls was set as cut-off for normal levels of IL-13 (1.66 NPX), periostin (10.06 ng/mL) and DPP-4 (1.95 μg/mL). Values above were defined as "high". This study is based on a Randomized Clinical Trial (RCT) showing improved treatment responses to tralokinumab in AD subgroups with at least (i) periostin^{high} and (ii) DPP-4^{high} levels,[32] but does not discuss mixed endotypes of IL-13, periostin and DPP-4. We fitted single-biomarker profile models (=SBM) with binary outcome variables of at least (i) IL-13^{high} versus IL-13^{normal}, (ii) periostin^{high} versus periostin^{normal}, and (iii) DPP-4^{high} versus DPP-4^{normal}, to have endotype outcomes comparable to this RCT. Additionally, we fitted combined-biomarker profile models (CBM) with multicategorial outcomes allowing for all combinations of IL-13, periostin and DPP-4 levels (reference: IL-13^{normal}/periostin^{normal}/DPP-4^{normal}) to provide a more precise characterisation of the endotypes. We analyzed the associations of the respective biomarker profiles with 67 clinical and epidemiological factors (covariates Table S1). Each profile was analyzed using two different multivariable approaches: (i) MLGB with tree base-learners,[54,55] (ii) main-effects logistic regression (LR) and multinomial LR (MLR) for the single and combined outcomes, respectively. We further performed subgroup analysis of patients (i) with and (ii) without asthma (iii) low-moderate AD (EASI>7 < 16), (iv) moderate-to-severe AD (EASI≥16). This specification of severity was chosen for critical appraisal of EASI16 as cut-off for systemic therapy. The contributions of variables to the prediction models were evaluated by permutation-based variable importance[56] with respect to differences in multinomial log-likelihood. Each importance value represents the average decrease in model fit if the values of the variable were permuted randomly. In the regression models, variables were selected by forward selection based on corrected AIC.[57] Statistical analysis and visualization of data was conducted using R version 3.5.3[58] and SPSS version 25.0. Further details such as data pre-processing,[59] add-on packages,[60–73] handling of missing data and model performance[74] are provided in the Appendix S1 (Methods S3).

3 | RESULTS

3.1 | Factors associated with increased biomarker levels

IL-13^{high}- and periostin^{high}-endotypes showed the strongest associations with AD severity, circulating eosinophil levels, total serum Immunoglobulin E (tIgE) and several atopic stigmata in MLGB (Figures 1 and 2, Figures S1 and S2, Tables S1–S3). Only 27.9% of AD patients had normal levels of all three target markers, 49.3% featured IL-13^{high}-, 56.1% periostin^{high}-, and 23.8% DPP-4^{high}-endotypes with distinct associated phenotypic characteristics in SBM (Figure 2, Table 1, Tables S2, S3 and S6). CBM revealed IL-13^{high}/periostin^{normal}/DPP-4^{normal} as the most (19.3%), IL-13^{normal}/periostin^{normal}/DPP-4^{high} the least (3.2%) frequent combined-biomarker signature (Table S2). Analysis of CBM using the more conservative MLR also indicated associations of EASI and eosinophils with elevated biomarker levels, albeit with weaker effects in certain endotype combinations (Table S5).

3.2 | Correlation of IL-13 and periostin with disease severity

IL-13 and periostin serum levels correlated with disease severity as evaluated by clinician-reported (EASI,[50] Scoring Atopic Dermatitis,[75] affected body surface area) and patient-reported outcomes (Pruritus, Sleeplessness, Dermatology Life Quality Index (DLQI)[76]) in our cohort encompassing the entire severity spectrum. IL-13 correlated with periostin (rs = 0.242, 95% Confidence Interval (CI)

TABLE 1 Characteristics of patients with active atopic dermatitis≥12 years stratified by the single-biomarker profiles (1) at least IL-13^{high}, reference IL-13^{normal} (2) at least periostin^{high}, reference periostin^{normal} and (3) at least dipeptidyl dipeptidase-4 (DPP-4)^{high}, reference DPP-4^{normal}.

	All patients		IL-13^{normal} 189/373 (50.7%)		IL-13^{high} 184/373 (49.3%)		Periostin^{normal} 133/303 (43.9%)		Periostin^{high} 170/373 (56.1%)		DPP-4^{normal} 231/303 (76.2%)		DPP-4^{high} 72/303 (23.8%)	
Biomarker	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Factor														
Female	212/373	56.8	111/189	58.7	101/184	54.9	88/133	66.2	86/170	50.6	134/231	58.0	40/72	55.6
Eosinophilia > 0.5 G/L	80/362	22.1	18/183	9.8	62/179	34.6	15/133	11.3	57/169	33.7	49/231	21.2	23/71	32.4
Increased total serum IgE[a]	272/365	74.5	125/185	67.6	147/180	81.7	89/133	66.9	139/170	81.8	171/231	74.0	57/72	79.2
EASI < 16	271/373	72.7	160/271	59.0	111/271	41.0	104/215	48.4	111/215	51.6	167/215	77.7	48/215	22.3
EASI ≥ 7 < 16	90/373	24.1	41/90	45.6	49/90	54.4	33/80	41.3	47/80	58.8	62/80	77.5	18/80	22.5
EASI ≥ 16	102/373	27.3	29/102	28.4	73/102	71.6	29/88	33.0	59/88	67.0	64/88	72.7	24/88	27.3
↓ Life quality: DLQI ≥ 11	148/371	39.9	57/187	30.5	91/184	49.5	53/132	40.2	67/170	39.4	86/230	37.4	34/72	47.2
Previous dupilumab therapy (stopped >4 mo. before study inclusion)[b]	1/373	0.27	0/1	0.0	1/1	100.0	0/1	0.0	1/1	100.0	0/1	0.0	1/1	100.0
Atopic comorbidities														
Asthma	171/373	45.8	79/189	41.8	92/184	50.0	62/133	46.6	82/170	48.2	108/231	46.8	36/72	50.0
Allergic rhinitis	260/373	69.7	130/189	68.8	130/184	70.7	93/133	69.9	120/170	70.6	164/231	71.0	49/72	68.1
Food allergy	195/373	52.3	96/189	50.8	99/184	53.8	68/133	51.1	99/170	58.2	122/231	52.8	45/72	62.5
	All		**IL-13^{normal}**		**IL-13^{high}**		**Periostin^{normal}**		**Periostin^{high}**		**DPP-4^{normal}**		**DPP-4^{high}**	
Biomarker profile	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Atopic stigmata														
Hertoghe's sign	181/373	48.5	76/189	40.2	105/184	57.1	57/133	42.9	43/170	54.7	116/231	50.2	34/72	47.2
Facial pallor/erythema	199/373	53.4	82/189	43.4	117/184	63.6	66/133	49.6	97/170	57.1	119/231	51.5	44/72	61.1
Dirty neck	98/372	26.3	37/189	19.6	61/184	33.2	27/133	20.3	56/170	32.9	59/231	25.5	24/72	33.3
White dermographism	249/373	66.8	113/189	59.8	136/184	73.8	86/133	64.7	118/170	69.4	156/231	67.5	48/72	66.7
Periorbital darkening	265/373	71.0	123/189	65.1	142/184	77.2	96/133	72.2	120/170	70.6	155/231	67.1	61/72	84.7
Dennie-Morgan fold	189/373	50.7	85/189	45.0	104/184	56.5	64/133	48.1	90/170	52.9	114/231	49.4	40/72	55.6
Anterior neck fold	186/373	49.9	81/189	42.9	105/184	57.1	62/133	46.6	90/170	52.9	115/231	49.8	37/72	51.4
Xerosis cutis	342/373	91.7	165/189	87.3	177/184	96.2	118/133	88.7	158/170	92.9	211/231	91.3	65/72	90.3
Ear rhagades	136/373	36.5	64/189	33.9	72/184	39.1	38/133	28.6	69/170	40.6	76/231	32.9	31/72	43.1

(Continues)

TABLE 1 (Continued)

Biomarker profile	All		IL-13^{normal}		IL-13^{high}		Periostin^{normal}		Periostin^{high}		DPP-4^{normal}		DPP-4^{high}	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Keratosis pilaris	88/373	23.6	37/189	19.6	51/184	27.7	36/133	27.1	37/170	21.8	49/231	21.2	24/72	33.3
Nipple eczema	43/373	11.5	15/189	7.9	28/184	15.2	12/133	9.0	24/170	14.1	23/231	10.0	13/72	18.1
Perleche	129/373	34.6	59/189	31.2	70/184	38.0	38/133	28.6	63/170	37.1	67/231	29.0	34/72	47.2
Pityriasis alba	58/372	15.6	32/188	17.0	26/184	14.1	17/133	12.8	26/169	15.4	31/230	13.5	12/72	16.7
Palmar hyperlinearity	280/373	75.1	137/189	72.5	143/184	77.7	108/133	81.2	126/170	74.1	181/231	78.4	53/72	73.6
Proneness to infections														
Herpes simplex	157/349	45.0	82/181	45.3	75/168	44.6	54/125	43.2	77/157	49.0	97/213	45.5	34/69	49.3
Eczema herpeticum	43/349	12.3	19/178	10.7	24/171	14.0	15/124	12.1	18/158	11.4	20/213	9.4	13/69	18.8
Verrucae	203/353	57.5	109/181	60.2	94/172	54.7	80/126	63.5	78/159	49.1	113/215	52.6	45/70	64.3
Bacterial	126/316	39.9	58/159	36.5	68/157	43.3	43/109	39.4	62/146	42.5	73/190	38.4	32/65	49.2
Mycotic	121/313	38.7	67/163	41.1	54/150	36.0	44/111	39.6	57/141	40.4	75/192	39.1	26/60	43.3

Biomarker profile	All patients		IL-13^{normal}		IL-13^{high}		Periostin^{normal}		Periostin^{high}		DPP-4^{normal}		DPP-4^{high}	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Factor														
Age	38.5	25.9–53.9	37.3	21.8–27.6	40.3	28.1–54.7	39.0	28.1–50.8	41.2	27.8–55.6	41.1	29.0–54.8	35.2	25.5–51.4
BMI	24.2	21.7–28.0	24.1	21.8–27.6	24.2	21.5–28.1	24.9	21.7–28.7	23.8	21.7–27.1	24.3	21.9–28.4	23.2	21.2–26.9
tIgE [IU/mL]	540	95.6–2711.5	314	65.1–1164.0	1253.5	188.5–4395.0	231	63.1–1385.0	1071.0	177.3–4650.0	620.0	84.2–2971.0	442.5	130.8–2879.5
Eos [%]	3.9	2.1–6.5	3.4	1.8–5.2	4.6	2.6–9.1	3.5	1.7–5.8	4.8	2.7–8.8	4.2	2.0–6.5	4.2	2.6–9.3
AD duration [years]	26.7	17.6–40.8	25.4	17.2–39.4	28.5	17.2–39.4	28.5	10.8–40.2	28.9	19.7–42.1	29.9	19.6–42.6	25.4	20.8–37.5
Age of AD onset [years]	2.0	0.2–13.8	2.0	0.25–12.0	2.0	0.17–16.0	2.0	0.2–11.0	2.0	0.3–16.5	2.0	0.2–14.0	2.0	0.3–13.0
EASI	7.4	2.5, 6.8	4.6	1.8–10.2	12.8	4.9–22.4	5.3	1.9–13.9	10.9	4.1–22.5	7.8	2.5–17.5	8.7	3.4–19.9
BSA	17.5	5.5–37.0	10.0	3.3–25.8	29.2	12.0–45.9	12	3.0–33.5	26.0	10.0–45.3	20.0	5.5–39.0	20.6	7.8–39.4
ObjectiveSCORAD	33.4	21.3–44.8	26.5	15.2–38.1	38.9	27.1–49.4	29.7	18.3–40.5	37.3	25.0–48.8	34.6	21.5–45.5	33.7	21.5–48.0
SCORAD	39.2	25.4–53.3	32.5	20.4–45.8	48.4	32.2–59.4	33.3	23.6–49.5	46.2	30.4–58.8	40.7	27.5–54.6	41.5	24.9–56.7
DLQI	7.0	3.0–16.0	6.0	2.0–12.0	10.0	5.0–18.0	7.0	2.3–15.0	8.0	4.0–16.0	7.0	3.0–16.0	8.5	5.0–15.8

Note: Blue: characteristics of biomarker^{high} patients, EASI = Eczema Area and Severity Score.

[a]IgE↑: increased total serum immunglobulinE levels, age-dependent cut-off points: age 12–15 years: 200 IU/mL, age ≥16 years: 100 IU/mL (Immulite 2000 immunoassay, DPC Biermann, Germany), IQR = interquartile range (Q1–Q3), SCORAD = SCORing Atopic Dermatitis.

[b]Patients with systemic therapy ≤last 30 days before the study were excluded. Previous therapies >30 days: systemic corticosteroids: $n = 23$, dupilumab: $n = 1$, other biologicals, janus kinase inhibitors, cyclosporine A, methotrexate or azathioprine: all $n = 0$.

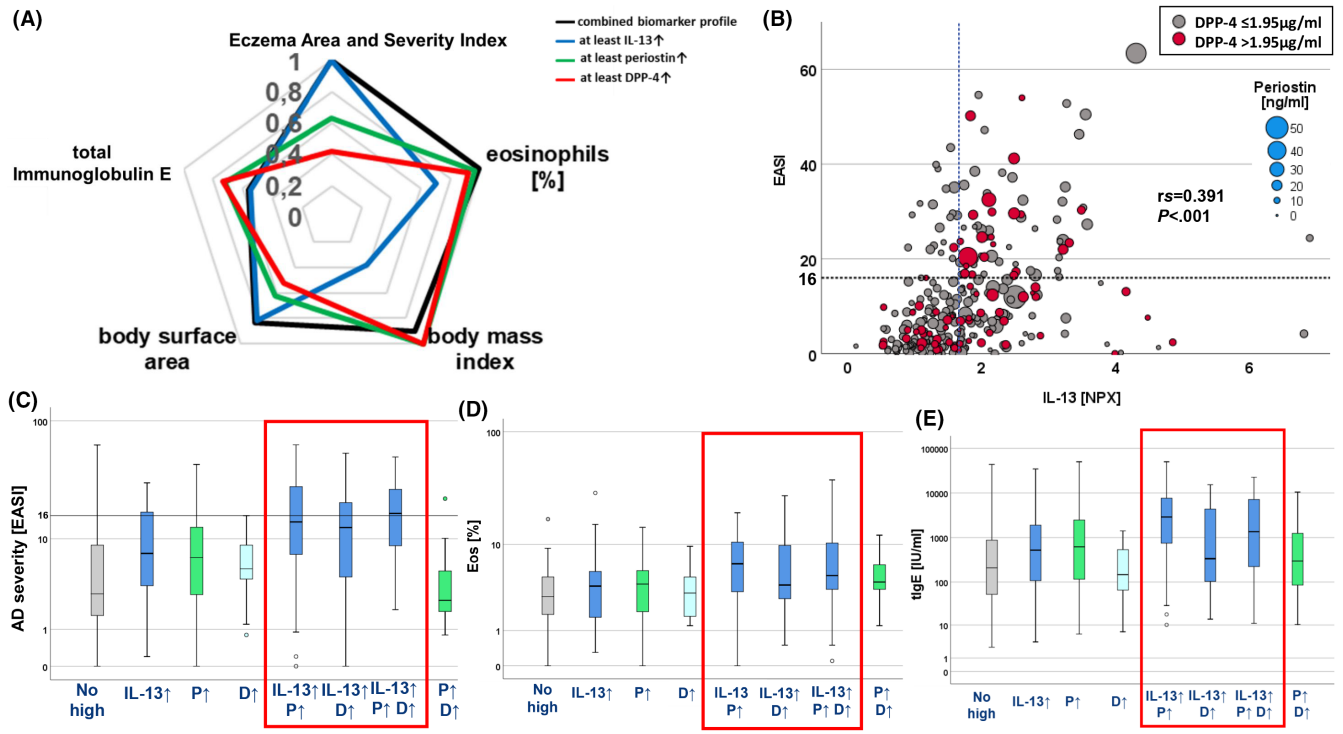


FIGURE 1 Association of circulating Interleukin-13 levels and periostin levels with disease severity, eosinophils and total serum Immunoglobulin E. (A) Disease severity, eosinophils, total IgE, body mass index were the most important factors for the prediction of atopic dermatitis endotypes with increased levels of Interleukin-13, periostin and/ or dipeptidyl-peptidase-4 alone or in combination identified by machine-learning gradient boosting models. Combined-biomarker profile model: black; single-biomarker profile models of at least: (i) IL-13^{high}, reference IL-13^{normal} (blue), (ii) periostin^{high}, reference periostin^{normal} (green); (iii) dipeptidyl-peptidase (DPP)-4^{high}, reference DPP-4^{normal} (red). Numbers refer to the value of the importance normalized to 100. The importance shows the average change of goodness on fit, with respect to one variable, if the values are randomly permuted (no relationship between variable and outcome groups). (B) Correlation of IL-13 with disease severity [Eczema Area and Severity Index = EASI]. The horizontal dotted line at EASI 16 refers to a the typically used *cut-off* for disease severity as inclusion criterion for clinical trials as well as indication for systemic therapy. The vertical dotted line at 1.66 NPX refers to the cut-off for normal levels of IL-13 (80th quantile of non-atopic controls). Periostin levels are visualized by bubble size [increased >10.06 ng/mL], increased levels of at least DPP-4 (D) by red color. (C–E) Patients with increased levels of IL-13, periostin (P) alone and in combination exhibit higher EASI scores (C), levels of eosinophils (D) and tIgE (E) compared to patients with normal levels of IL-13 and periostin.

[0.133–0.345]) and both with eosinophils, tIgE, and CCL17[41] levels (Figures 1 and 2, Tables S5 and S7). Correlations of IL-13 with disease severity were stronger in patients with increased (rs = 0.482) than with normal (rs = 0.342) periostin levels (Figure S3). Accordingly, patients with elevated levels of IL-13 and periostin alone, but especially with the combined endotype, tended to exhibit higher severity scores (Figure 1, Figures S1 and S3; Table 1, Table S2). Periostin increased EASI-levels by 0.566 ± 0.12/ng/ml after adjustment for IL-13 and DPP-4 ($p < .0001$). Conversely, DPP-4 levels correlated only weakly with CCL-17 and eosinophils, but not with other scores or biomarkers (Figure 2, Figures S2 and S4, Table S7).

3.3 | Clinical phenotypes associated with biomarker^{high} endotypes revealed by single biomarker profile models

3.3.1 | IL-13^{high}-(endo)phenotypes

Machine learning approaches allowed us to estimate cut-offs for AD severity scores and identify biomarkers associated with increased probability of specific endotypes. The probability of IL-13^{high}-endotypes increased with EASI > 10.6, eosinophils > 6.9% and tIgE > 1300 IU/mL (Figure 3).

Several atopic stigmata were associated with distinct endotypes. IL-13^{high}-endotypes were associated with thinning of the lateral eyebrow (Hertoghe sign) (adjusted Odds Ratio (aOR) = 1.89 [1.14–3.14]), and maternal AR (symptoms in adulthood: aOR = 3.19 [1.50–6.79], in both child-and adulthood: aOR = 2.79 [1.17–6.63]) (Figure 2 and 4, Tables S2 and S3). Conversely, parental atopy overall (aOR = 0.64 [0.43–0.95]/per affected parent) and the viral skin infection with the molluscum contagiosum virus were associated with reduced probabilities of elevated IL-13 levels (aOR = 0.29 [0.11–0.74]).

Atopic dermatitis patients with asthma did not exhibit statistically different biomarker levels, but partly varying phenotype-endotype associations (Figure 4, Tables S3 and S8). High IL-13 levels in asthma patients were associated with Herthoghe sign, keratosis pilaris (follicular hyperkeratosis), xerosis, pruritus, maternal food allergy (FA). The odds of IL-13^{high}-AD without concomitant asthma increased with maternal AR, high eosinophil levels, "dirty neck" and decreased with FA, no-siblings, ear rhagades and mollusca contagiosa.

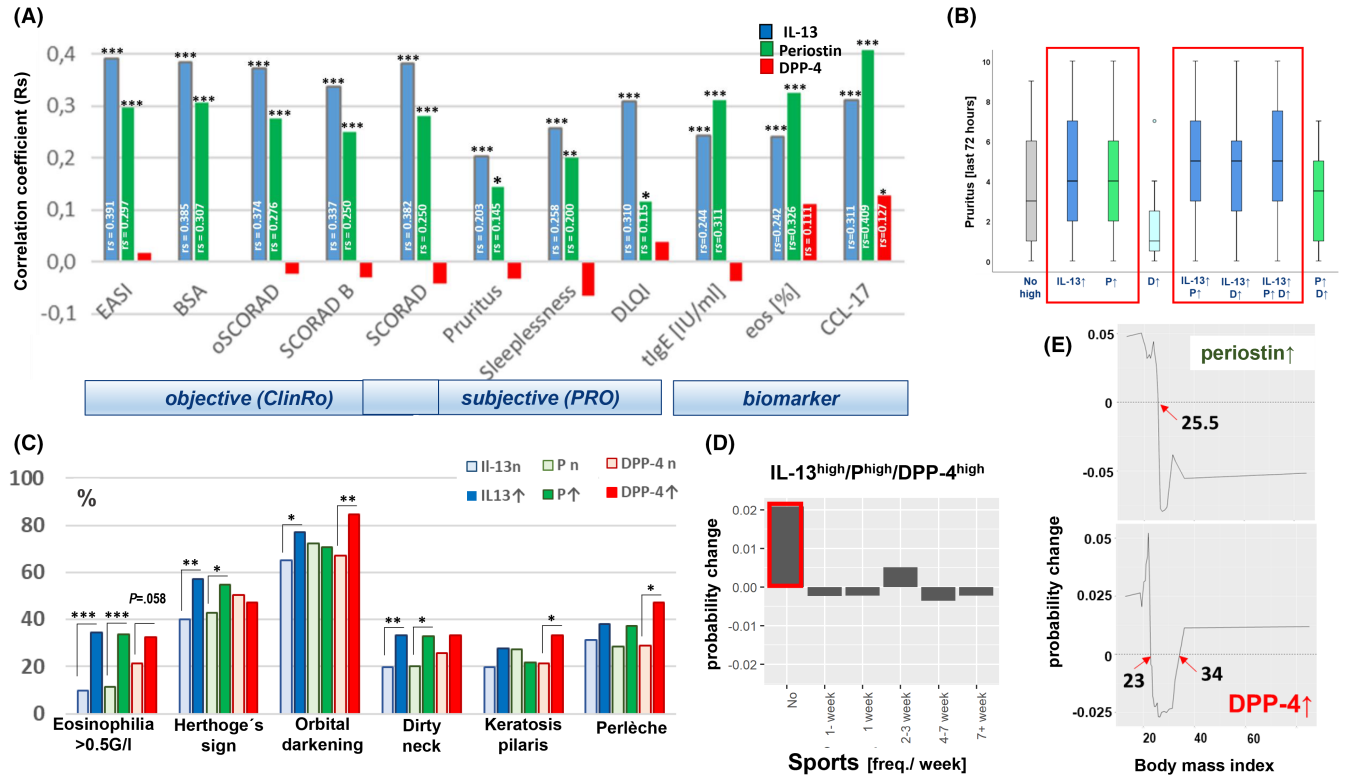


FIGURE 2 Correlations of signs and symptoms of AD, atopic stigmata, sports and body mass index with different endotypes. (A) Correlation of circulating IL-13 and periostin levels with AD with disease severity (evaluated by clinician-reported (ClinROs) and patient-reported outcome measures (PRO)), total serum IgE (tIgE), eosinophils (eos) and Chemokine ligand 17 (=CCL17)/thymus and activation-regulated chemokine. ClinROs: Eczema Area and Severity Index (EASI), affected body surface area (BSA), SCORing Atopic Dermatitis (total SCORAD, SCORAD B (= intensity of eczema), objective SCORAD (extent and intensity of eczema). PROs pruritus (last 72 h), sleeplessness (last 72 h) and Dermatology Life Quality Index (DLQI). Rs = correlation coefficient (Spearman-Rho). *$p < .05$, **$p < .01$, ***$p < .001$. (B) Patients with increased levels of IL-13 and periostin, but not DPP-4 alone reported higher pruritus levels. (C) Frequency of main phenotypic traits associated with the single-biomarker profiles of at least (i) IL-13^{high} versus (vs.) reference category IL-13^{normal} (blue); (ii) periostin^{high} vs. periostin^{normal} (green); (iii) dipeptidyl-peptidase (DPP)-4^{high} vs. DPP-4^{normal} (red). (D) Sport abstinence increased the probability of a IL-13^{high}P^{high}DPP-4^{high}-endotype. (E) Accumulated Local Effect (=ALE) plots of the body mass index visualize the expected change in probability for the grouping into the single biomarker profiles (A2) at least periostin^{high} vs. periostin^{normal} and (A3) DPP-4^{high} vs. DPP-4^{normal} compared to the average prediction in the complete data set.

Patients with EASI<16 (mild and mild–moderate) also featured increased circulating biomarkers (IL-13^{high} [41%], periostin^{high} [48.4%], DPP-4^{high}: [22.3%], Table 1, Tables S5 and S9, Figure 5). A severely impaired QoL (DLQI ≥ 11) indicating insufficient disease control was reported by 50.6% (45/89) of patients with low-moderate severity (EASI > 7 < 16). In low-moderate AD, high IL-13 levels were associated with eosinophilia >0.5 G/L, Hertoghe sign, and maternal AR. In moderate-to-severe AD (EASI ≥ 16), the odds of IL13^{high}-endotypes increased with eosinophilia, history of frequent mycotic infections and decreased with parental atopy and never-having-a-cat (Figure 5, Table S6).

3.3.2 | Periostin^{high}-(endo)phenotypes

The probabilities of periostin^{high}-endotypes increased with eosinophils >6.1%, tIgE > 859 IU/mL and EASI > 17 (Figure 3). However, AD subgroups with alopecia areata (AA) (OR = 2.68 [1.16–6.29]) and cardiovascular diseases (CVD) (OR = 2.15 [1.20–3.84]) had an increased risk of high periostin levels starting at EASI > 5.9 (Figure 3A2). Term and post-term gestational age reduced the odds of periostin^{high}-AD (aOR = 0.06 [0.007–0.56] for week 37–41 [term], aOR = 0.06 [0.007–0.64]) for week ≥42 (post-term) versus pre-term birth. Periostin^{high}-AD with concomitant asthma was associated with male sex, higher numbers of eosinophils and of atopic comorbidities and periostin^{high}-AD without concomitant asthma with increased tIgE and caesarean (Figure 4, Table S3).

In low-moderate AD, perleche (rhagades at the corners of the mouth) increased and never-having-a-dog reduced the odds of periostin^{high}-endotypes.

In moderate-to-severe AD, Hertoghe sign, eosinophilia and increased tIgE increased the odds of periostin^{high}-endotypes with add-on effects of combinations of these traits (Figure 5, Table S6).

3.3.3 | DPP-4^{high}-(endo)phenotypes

The probability of DPP-4^{high}-AD increased with an EASI > 6.6 and eosinophils >7% (Figure 3). Main associated atopic stigmata were dirty neck (aOR = 2.83 [1.32–6.07]), periorbital darkening

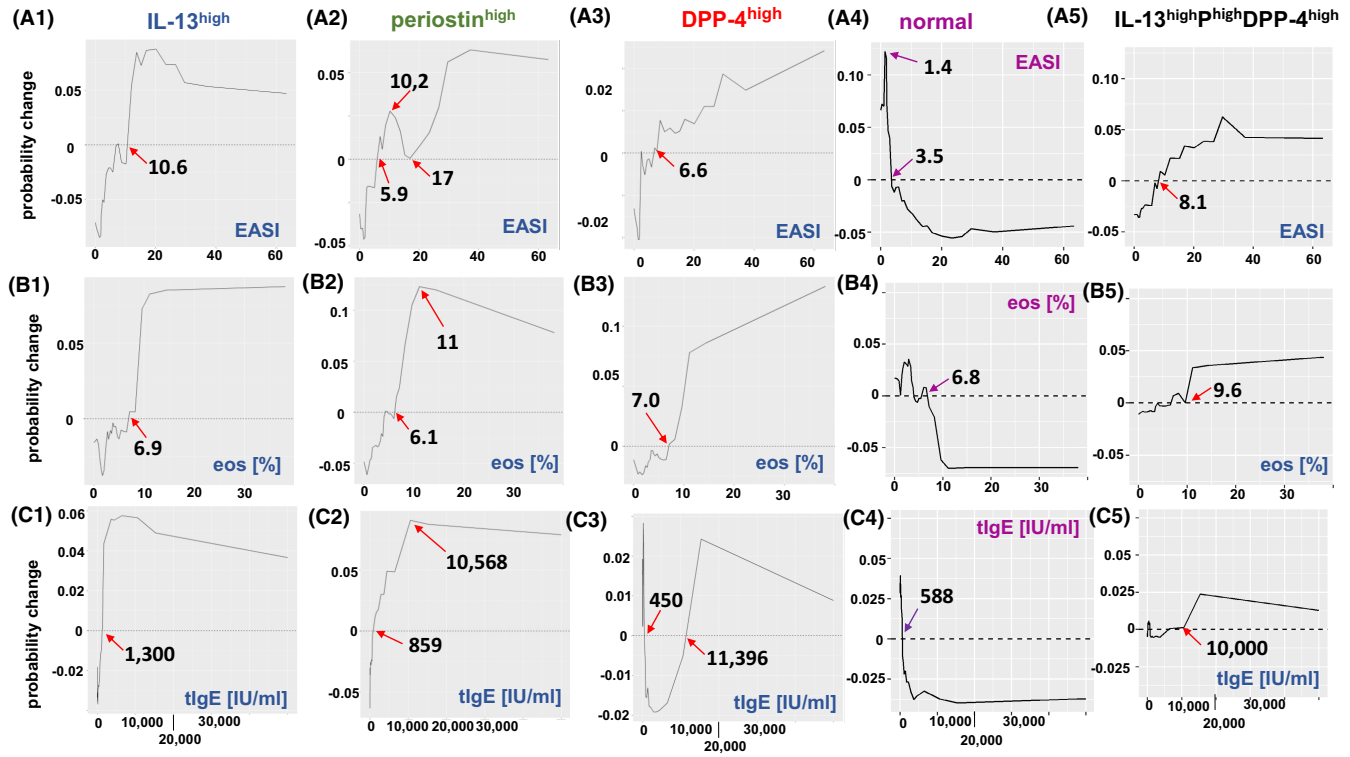


FIGURE 3 Probability of different biomarker profiles dependent on AD severity, eosinophils and total IgE. 1–3: single-biomarker profile: (1) at least IL-13^{high} versus (vs.) reference category IL-13^{normal}; (2) at least periostin^{high} vs. periostin^{normal}; (3) at least dipeptidyl peptidase (DPP)-4^{high} vs. DPP-4^{normal}. 4, 5: combined-biomarker profile: (4) normal = IL-13^{normal}/periostin^{normal}/DPP-4^{normal}; (5) IL-13^{high}/P (=periostin)^{high}/DPP-4^{high}. Accumulated Local Effect (=ALE) plots of AD severity (Eczema Area and Severity Index = EASI) (A), eosinophil (eos) (B) and total serum IgE levels (tIgE) (C) visualize the expected change in probability for the grouping into the different biomarker profiles compared to the average prediction in the complete data set. Lines above Zero show an increased probability, below reduced probability of high biomarker profiles dependent on the variable. e.g. Figure 2A1: Patients with EASI values (*x*-axis) higher than 10.6 (point of probability change crossing zero, marked with a red arrow) have an increased probability of an endotype with at least high levels of IL-13 (single-biomarker profile).

(aOR = 2.43 [1.08–5.50]), keratosis pilaris (aOR = 2.21 [1.1–4.42]) and perleche (aOR = 3.44 [1.72–6.86]). Eosinophils had slight effects on DPP-4^{high}-endotypes. Factors reducing the odds of DPP-4^{high}-endotypes were parental atopy (aOR = 0.57 [0.34–0.95]), higher number of siblings (aOR = 0.66/per sibling [0.48–0.92]) and pruritus (aOR = 0.87 [0.77–0.98]) (Figure 4, Table S3). Stratification by asthma linked the associations of DPP-4^{high}-endotypes with orbital darkening and lower number of siblings to AD with asthma. The odds of DPP-4^{high}-AD without asthma increased with dirty neck, perleche, parental non-atopy, impetigo and high eosinophil levels.

The subgroup analysis of low-moderate AD revealed increased odds of high DPP-4 levels in patients with dirty neck, facial pallor/erythema and nipple eczema, whilst age and female sex reduced the odds (Figure 5, Table S6).

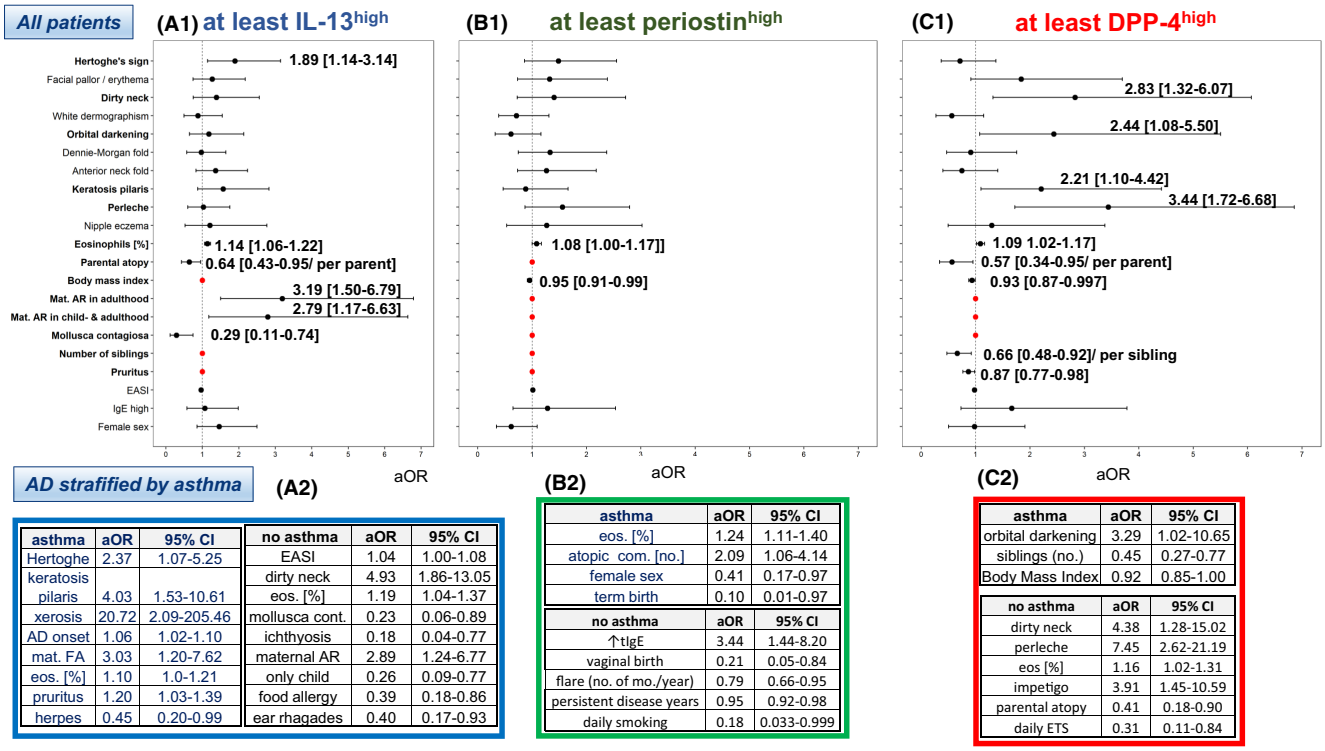
3.3.4 | Phenotypes associated with combined-biomarker profiles

The probability of "normal" levels of all three target biomarkers was highest in patients with an EASI < 3.5, eosinophils < 6.8% and with tIgE < 588 IU/mL (Figure 3).

The probabilities of high biomarkers increased in the severity range between EASI 5.5 (IL-13^{high}/periostin^{high}/DPP-4^{normal}) and 8.1 (IL-13^{high}/periostin^{high}/DPP-4^{high}) and with eosinophilia>6%, cut-offs depending on the biomarker pattern: >6.1: IL-13^{high}/periostin^{high}/DPP-4^{normal}-, >7.6%: IL-13^{high}/periostin^{normal}/DPP-4^{high}-, >9.6%: IL-13^{high}/periostin^{high}/DPP-4^{high}-AD. Total IgE levels>1120 IU/mL increased the probability of IL-13^{high}/periostin^{high}/DPP-4^{normal}-, >10,000 IU/mL of IL-13^{high}/periostin^{high}/DPP-4^{high}-AD.

Accordingly, levels of eosinophils, tIgE, frequencies of eosinophilia and age-dependent increased tIgE were higher in IL-13^{high}/periostin^{high}/DPP-4^{normal}-AD (48.5% eosinophilia, 84.8% tIgE^{high}) and IL-13^{high}/periostin^{high}/DPP-4^{high}-AD (45.2% eosinophilia, 90.3% tIgE^{high}) than in IL-13^{normal}/periostin^{normal}/DPP-4^{normal}-AD (19.3% eosinophilia, 74.5% tIgE^{high}) (Figures 1 and 4, Figure S10, Table S2).

Hertoghe sign, facial pallor/erythema and dirty neck were main atopic stigmata associated with IL-13^{high}/periostin^{high}/DPP-4^{high}-AD (Figure S5, Table S2). However, partially opposing effects of each biomarker on a specific trait were observed in CBM. The main associated factors with IL-13^{high}-, periostin^{high}- or DPP-4^{high}-AD were more evident in SBM with a higher number of cases in each group (Figures 3 and 4, Table S3). Lack of exercise was associated with an increased probability of IL-13^{high}/periostin^{high}/DPP-4^{high}-AD, but not of single biomarkers (Figure 2).



asthma	aOR	95% CI
Hertoghe	2.37	1.07-5.25
keratosis pilaris	4.03	1.53-10.61
xerosis	20.72	2.09-205.46
AD onset	1.06	1.02-1.10
mat. FA	3.03	1.20-7.62
eos. [%]	1.10	1.0-1.21
pruritus	1.20	1.03-1.39
herpes	0.45	0.20-0.99

no asthma	aOR	95% CI
EASI	1.04	1.00-1.08
dirty neck	4.93	1.86-13.05
eos. [%]	1.19	1.04-1.37
mollusca cont.	0.23	0.06-0.89
ichthyosis	0.18	0.04-0.77
maternal AR	2.89	1.24-6.77
only child	0.26	0.09-0.77
food allergy	0.39	0.18-0.86
ear rhagades	0.40	0.17-0.93

asthma	aOR	95% CI
eos. [%]	1.24	1.11-1.40
atopic com. [no.]	2.09	1.06-4.14
female sex	0.41	0.17-0.97
term birth	0.10	0.01-0.97

no asthma	aOR	95% CI
↑tIgE	3.44	1.44-8.20
vaginal birth	0.21	0.05-0.84
flare (no. of mo./year)	0.79	0.66-0.95
persistent disease years	0.95	0.92-0.98
daily smoking	0.18	0.033-0.999

asthma	aOR	95% CI
orbital darkening	3.29	1.02-10.65
siblings (no.)	0.45	0.27-0.77
Body Mass Index	0.92	0.85-1.00

no asthma	aOR	95% CI
dirty neck	4.38	1.28-15.02
perleche	7.45	2.62-21.19
eos [%]	1.16	1.02-1.31
impetigo	3.91	1.45-10.59
parental atopy	0.41	0.18-0.90
daily ETS	0.31	0.11-0.84

FIGURE 4 Association of clinical and epidemiological factors with the endotypes IL-13^{high}, periostin^{high} and DPP-4^{high} in multivariable single-biomarker logistic regression models in AD patients with all severity grades with and without asthma. Individual effect estimates (adjusted Odds Ratio [aOR] and 95% Confidence Interval [CI]) refer to the single-biomarker logistic regression models with binary outcome variables: (A) at least IL-13^{high} versus (vs.) reference category IL-13^{normal} (B) at least periostin^{high} vs. periostin^{normal} (C) at least dipeptidyl-peptidase (DPP)-4^{high} vs. DPP-4^{normal}. (A–C1) Analysis of all AD patients. (A–C2) Separate analysis of AD subsets with and without asthma with depiction of main associations. All aORs with 95% CI are given in Table S3. Bold: $p < .05$. red point: not applicable (variable not selected in the model based on corrected AIC). All aORs with 95% CI are given in Table S3.

3.4 | Other factors

Body mass index (BMI) was an important determinant factor for the single-biomarker profiles periostin^{high} and DPP-4^{high} with non-linear effects (U-curve) in MLGB. The highest probability of normal biomarker levels were estimated in a BMI range between 23–34 for DPP-4 and higher than 25.5 for periostin (Figure 2). In contrast, linear effects of BMI levels were small and showed negative correlations with periostin (rs: −0.138 [−0.246−−0.027]) and DPP-4 levels (rs: −0.139 [−0.247−−0.027]), fitting to the effect sizes of the single outcomes in LR (periostin^{high}: aOR = 0.95 [0.91–0.99], DPP-4^{high}: aOR = 0.93 [0.87–1.0]) and without statistically significant differences between different endotype groups. Age correlated weakly with periostin (rs = 0.126 [0.011–0.231]), and inversely with DPP-4 (rs = −0.169 [−0.169−−0.276]). Factors associated with normal levels of at least IL-13, periostin or DPP-4 potentially associated with a worse response to IL-13-targeted therapies are depicted in Table S10.

4 | DISCUSSION

The search for predictive biomarkers of AD treatment response is imperative for a personalized medicine approach.[1,35] Using machine learning-based deep phenotyping[77–79] with endotype stratification by IL-13, periostin and DPP-4, we found that (i) AD severity and eosinophilia were the most important factors for the combined biomarker profile and correlated with both IL-13 and periostin; (ii) the risk of elevated biomarkers increased with eosinophilia > 6% and in an EASI range between 5.5–17 depending on the biomarker combination pattern; (iii) many patients with EASI < 16 featured elevated levels of T2 biomarkers suggesting that systemic impact of skin inflammation is also present in mild-to-moderate AD which questions a current cut-off for systemic therapy and (iv) several phenotypic traits were associated with distinct endotypes at various extents contingent on combination of traits, AD severity and concomitant asthma.

These findings support the development of anti-IL-13-therapies, thus ameliorating the initiation and maintenance of T2 chronic inflammation in AD.[1,33,34,37,80–82]

Periostin and DPP-4 are both induced by IL-4 and IL-13, have an increased expression in asthma[46] and AD lesional skin.[83–85] They are considered as surrogate markers of IL-13 activity.[32,46,47,86] Therefore, anti-IL-13 targeted therapy is regarded to also affect downstream pathways mediated by periostin[87] and DPP-4, both of which contribute to inflammation and chronicity in T2 diseases.[83,88] Periostin is an extracellular matrix and matricellular protein[89] which links T2 inflammation with airway remodeling,[86,87] keratinocyte

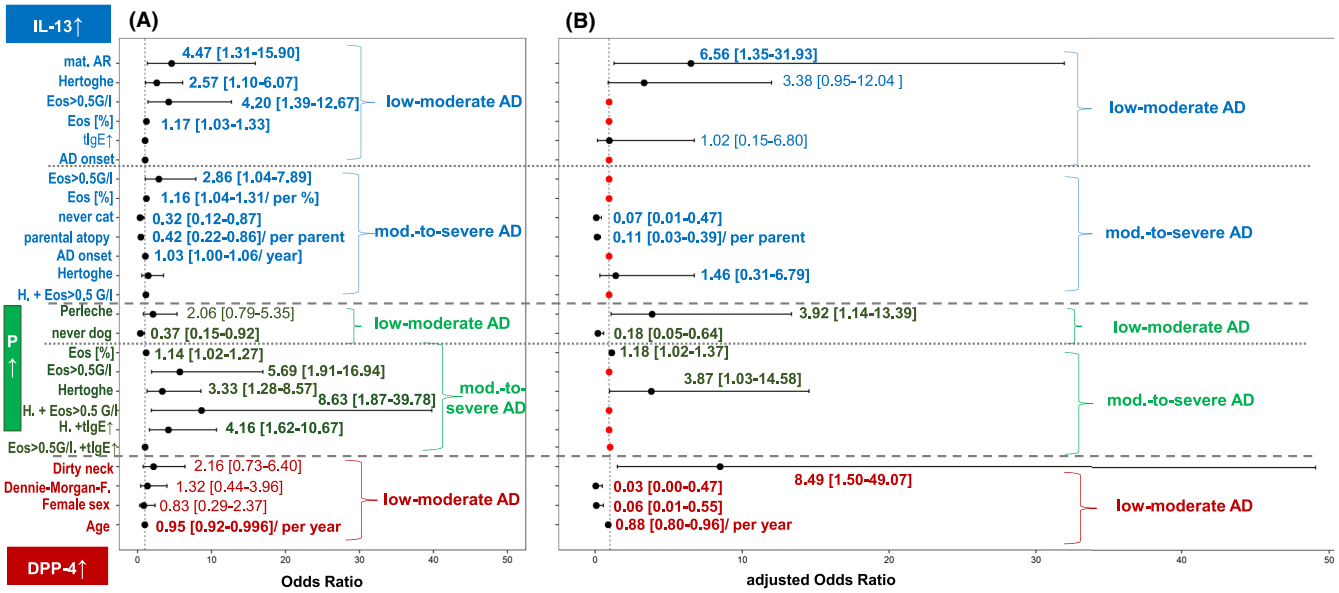


FIGURE 5 Associations of clinical and epidemiological factors with the endotypes Interleukin (IL)-13^{high}, periostin^{high}, and dipeptidyl dipeptidase-4 (DPP-4)^{high} in single-biomarker logistic regression models in AD patients stratified by severity in low-moderate AD (EASI > 7 < 16) and moderate-to-severe AD (EASI ≥ 16). (A) univariate LR, (B) multivariable LR. AD onset = age at onset of AD, AR = allergic rhinitis, Dennie-Morgen-F. = Dennie-Morgan-fold, EASI = Eczema Area and Severity Score, H./Hertoghe = Hertoghe sign, Eos = eosinophils, Eos > 0.5 G/L = Eosinophilia, IgE↑: increased total serum immunoglobulin E (tIgE) levels, age-dependent cut-off points: age 12–15 years: 200 IU/mL, age ≥ 16 years: 100 IU/mL, IQR = interquartile range (Q1–Q3). Mat. AR = maternal AR with symptoms in adulthood, parental atopy: affect size per affected parent, reference category: no parental atopy. Individual effect estimates ((Odds Ratio = OR) and adjusted OR (B) and 95% Confidence Interval (CI)) refer to the single biomarker logistic regression models with binary outcome variables: (1) at least IL-13^{high} versus (vs.) reference category IL-13^{normal} (blue script), (2) at least periostin^{high} vs. periostin^{normal} (green script) (3) at least DPP-4^{high} vs. DPP-4^{normal} (red script) in AD patients stratified by severity. Only the most important associations are depicted. All covariates and effect estimates of the adjusted models are specified in Table S6. Bold: $p < .05$. red dot: not applicable (variable not selected in the model based on corrected AIC).

activation including production of proinflammatory cytokines such as TSLP[83,88] and correlates with AD severity.[10,83] It contributes to itch by direct stimulation of sensory neurons via integrin receptors[90] and indirectly by stimulation of immune and/or non-immune cells to secrete pruritogens.[89] Interestingly, our AD patients with AA or CVD were already at higher risk of elevated periostin levels with lower AD severity compared to AD without these comorbidities. This might be attributed to the pathophysiological effects of periostin not only in AD, but also in AA[91,92] and CVD.[93,94] AA is a frequent comorbidity of AD.[53,92,95,96] In lesional AA scalps, an upregulation of periostin and IL-13 was demonstrated along with other differentially expressed genes.[91] In the heart, periostin contributes to cardiac development and remodeling in CVD such as heart failure or myocardial infarction.[93,94] The serine protease DPP-4 is involved in various immune and neuroendocrine functions,[46] glucose metabolism,[46] cell proliferation and differentiation.[97] Of special interest for AD might be its contribution to T-cell activation and regulation[46,85] and to chemotaxis.[97,98] DPP-4 expression has been shown to be upregulated in AD compared to control skin.[84,85] However, another study found significantly higher DPP-4 serum levels in AD compared to psoriasis and cutaneous T cell lymphoma, but not to healthy controls.[99]

Levels of eosinophils and tIgE are established biomarkers for allergic inflammation and sensitization in AD.[53] The here found correlations of IL-13 and periostin with AD severity and eosinophils align with previous studies,[37,41,46,47,83] as well as the correlation of IL-13 with tIgE.[37] In our German AD cohort, also periostin correlated with tIgE, consistent with reports for Czech patients with asthma,[100] but not for Japanese AD patients.[46,83]

Using machine learning models, we derived new cut-off points for the risk of elevated biomarker levels, which started increasing with eosinophilia > 6% and within EASI 5.5–17. An EASI ≥ 16 is a typically used cut-off defining defining a ("high"-) moderate-to-severe AD population with recommendation for systemic therapy in RCTs and treatment guidelines.[49] However, a substantial subpopulation of our patients with EASI < 16 ("low-moderate" and mild population) featured increased serum biomarkers. As IL-13,[37] periostin[83] and DPP-4[84] are cytokines overexpressed in AD lesional skin,[46,83] the skin might represent a source of increased circulating biomarkers measured in our study. This indicates a higher systemic impact of skin inflammation than suspected from the visible lesional skin surface. These findings question the "arbitrary" indication of the need for systemic therapy only in patients with (high)-moderate-to-severe AD, especially considering that >50% of patients with low-moderate severity reported a severely impaired QoL. Therefore, deep phenotyping and the identification of biomarker^{high} AD patients with ideally simple clinical measures might have high translational relevance.

Biomarker^{high} AD patients with EASI > 7 < 16 might also benefit from systemic therapy. The risk of high biomarkers in low-moderate AD increased for (i) IL-13 in patients with eosinophilia, Hertoghe sign and a history of maternal AR, (ii) periostin in patients with perleche, and (iii) DPP-4 in patients with dirty neck, facial pallor/erythema, nipple eczema and male sex.

Patients with moderate-to-severe AD and EASI > 16 fulfil a current criterion for objective disease severity with indication for systemic therapy. However, patients in this severity range with low-to-normal biomarkers might benefit less from the therapy as indicated by an improved response to tralokinumab in periostin^{high}- and DPP-4^{high}-AD.[32] The poorer response to anti-IL-13 antibodies in asthma patients with low periostin levels[47,101] has been attributed to the activation of alternative pathogenic pathways that are not downstream of IL-13 and periostin.[87] Conversely, patients with very high IL-13 levels might need stronger doses for effective treatment. In our patients with EASI > 16, the probability of biomarker^{high} AD increased for (i) IL-13 in patients with eosinophilia, (ii) periostin with eosinophilia, increased tIgE and/or Hertoghe sign and synergistic effects of a combination of these traits.

Overall, we identified several traits which may facilitate identification of biomarker^{high}-patients as potential responders to IL-13-targeted therapy. Analysis of all AD patients irrespective of disease severity revealed Hertoghe sign and maternal AR, but not paternal atopy, as main IL-13^{high}-associated factors. Stratification by asthma linked maternal FA and Hertoghe sign to IL-13^{high}-AD and concomitant asthma, and maternal AR to IL-13^{high}-AD without asthma. A preferential genetic transmission of allergy through mothers has been suggested by most epidemiological studies.[102,103] Considering also other factors important for maternal transfer of immunity,[103] we found increased odds of periostin^{high}-AD in preterm birth compared to term or post-term birth. The odds of periostin^{high}-AD decreased tenfold with term birth in subsets with concomitant asthma, and increased fivefold with caesarean in AD without concomitant asthma. In contrast to other reports investigating maternal factors in AD, we did not perform genotyping and used biomarkers as a readout, limiting direct comparisons between studies.

Primary DPP-4^{high}-associated traits in AD overall were dirty neck, orbital darkening, keratosis pilaris and perleche. Subgroup analysis linked dirty neck and perleche with DPP-4^{high}-AD without asthma, and orbital darkening with DPP-4^{high}-AD plus asthma. Regarding lifestyle factors, lack of exercise increased the probability of a IL-13^{high}/periostin^{high}/DPP-4^{high}-endotype. Interestingly, BMI exhibited a non-linear association with periostin and DPP-4. However, this might be a bystander phenomenon as DPP-4 is involved in glucose metabolism.[46] We found only a weak correlation of DPP-4 with CCL17 and eosinophils with subgroup analysis linking eosinophils primarily to DPP-4^{high}-AD without asthma. Overall, we observed a distinct phenotype in DPP-4^{high}-patients with a (non)association to severity-associated scores, IgE or IL-13 and a different pattern of atopic stigmata. Also other studies did not find an association between serum DPP-4 and AD severity,[99] IgE[46] and varied regarding a correlation with eosinophils.[46] Thus, opposing DPP-4 trends might confound associations observed in the combined endotype IL-13 and/or periostin with DPP-4. The dominating cytokine of an endotype combination might differ between distinct phenotypic traits dependent on the impact of each single cytokine on the respective trait. Overall, phenotypes seem to differ between the various endotype combinations, with IL-13 and periostin having a synergistic effect in one direction and DPP-4 in the opposite direction. Our study does not support DPP-4 as a predictive biomarker for AD severity. However, the endotype combinations in real-life are even more complex and include additional mediators with potentially opposing effects.

Increased biomarker levels do not necessarily indicate that targeting that particular cytokine will improve treatment response. In asthma, patients with elevated IL-13 sputum concentrations demonstrated better response to tralokinumab.[48] Higher IL-13 baseline levels in the skin have been suggested to predict improved responses to dupilumab.[10] Conversely, a recent skin transcriptome study showed lower baseline levels of IL4RA and IL-13 in 7 high-responders to dupilumab.[104] Thus, data comparison from responder-endotype levels collected from different body compartments (e.g., skin, sputum, and blood) and to different therapies targeting the T2-axis (e.g., dupilumab, tralokinumab, and lebrikizumab) should be interpreted with caution and validated in larger cohorts. An improved response to tralokinumab was reported in DPP-4^{high}- and periostin^{high}-AD, but not in CCL17^{high}- and IgE^{high}- subgroups.[32] Note that single-biomarker profiles of this RCT were reported, but no endotype combinations nor IL-13 levels.[32] Differences in the study design impede a direct comparison with our study.

Herein, we identified epidemiological and clinical hallmarks for the different endotypes IL-13^{high}-, periostin^{high}- and/or DPP-4^{high}-AD within a broad spectrum of active AD in adolescent and adult patients covering all severity grades. To our knowledge, this is the first study performing deep phenotyping based on stratification by these therapeutically relevant biomarkers with further subgroup analysis considering low-moderate versus moderate-to-severe AD and asthma.

The identified endotype-associated factors such as atopic stigmata, eosinophil and tIgE levels might serve as simple and economic predictors of AD endotypes readily available in workaday life. This might facilitate the identification of treatment responders (periostin^{high}, arguably DPP-4^{high}) or patients (IL-13^{high}) that might benefit from administration of a stronger dose to saturate and counteract their increased IL-13 baseline levels.

Clinical trials and real-world data are warranted to validate the associations between the (endo)phenotypes and response to treatments aimed at blocking IL-13 pathways, such as dupilumab, tralokinumab and/ or lebrikizumab. Ideally, the analysis of circulating and tissue biomarkers obtained in clinical trials combined with the characterization of the phenotype of therapy-responders will further improve the patient's stratification and identification of the most promising candidates for the different targeted therapies.

AUTHOR CONTRIBUTIONS

Study concept and design: LM, TW, NH, CTH, CK-CARE study group, TB. Acquisition of data: LM, TW, NH, JB, AD, CR, TB. Recruitment of patients: LM, JB, RH, SM. Analysis and interpretation of data: LM, TW, MS, TB. Drafting of the manuscript: LM, TW, MS, TB. Critical revision of the manuscript. for important intellectual content: NH, AD, CR, RH, SM, JB, CTH, MS, TB, CK-CARE study group. Obtained funding: TB.

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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, Almirall, Bristol-Myers Squibb, Eli Lilly, Galderma, LEO Pharma, OM Pharma, Pfizer, Sanofi/Regeneron, was advisor for Eli Lilly and speaker for AbbVie and LEO Pharma. 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, (Basel, Switzerland), Stanford University (Redwood City, Calif), and SciBase (Stockholm, Sweden); is the Co-Chair for EAACI Guidelines on Environmental Science in Allergic diseases and Asthma; 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.

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SUPPORTING INFORMATION

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

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APPENDIX A

CK-CARE study group

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